Report on the Deliberation Results

February 6, 2023
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	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
	Wegovy Subcutaneous Injection 2.4 mg SD
Non-proprietary Name	Semaglutide (Genetical Recombination) (JAN*)
Applicant	Novo Nordisk Pharma Ltd.
Date of Application	August 25, 2021

Results of Deliberation

In its meeting held on January 27, 2023, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 4 years. 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

December 27, 2022
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	(a) Wegovy Subcutaneous Injection 0.25 mg SD Wegovy Subcutaneous Injection 0.5 mg SD Wegovy Subcutaneous Injection 1.0 mg SD (b) Wegovy Subcutaneous Injection 1.7 mg SD Wegovy Subcutaneous Injection 2.4 mg SD
Non-proprietary Name	Semaglutide (Genetical Recombination)
Applicant	Novo Nordisk Pharma Ltd.
Date of Application	August 25, 2021
Dosage Form/Strength	(a) Injection: Each pre-filled pen (0.5 mL) contains 0.25, 0.5 or 1.0 mg of semaglutide (genetical recombination). (b) Injection: Each pre-filled pen (0.75 mL) contains 1.7 or 2.4 mg of semaglutide (genetical recombination).
Application Classification	(a) Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage, (10) Other drugs (during the re-examination period) (b) Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage, (8) Drug in an additional dosage form (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 disease, 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 condition.

Indication

Obesity

Wegovy should only be used in patients with hypertension, dyslipidemia, or type 2 diabetes mellitus who have not responded adequately to dietary and exercise therapy and have:

- a BMI of ≥27 kg/m^2 and ≥2 obesity-related health disorders, or
- a BMI of ≥35 kg/m^2

Dosage and Administration

The usual adult initial dosage is 0.25 mg of semaglutide (genetical recombination) injected subcutaneously once weekly. Then the dose should be escalated every 4 weeks to 0.5, 1.0, and 1.7 mg once weekly until a dose of 2.4 mg is reached. The maintenance dose is 2.4 mg once weekly. The dose should be reduced as appropriate according to the patient's condition.

Approval Condition

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

Attachment

Review Report (1)

June 17, 2022

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	(a) Wegovy Subcutaneous Injection 0.25 mg SD Wegovy Subcutaneous Injection 0.5 mg SD Wegovy Subcutaneous Injection 1.0 mg SD (b) Wegovy Subcutaneous Injection 1.7 mg SD Wegovy Subcutaneous Injection 2.4 mg SD
Non-proprietary Name	Semaglutide (Genetical Recombination)
Applicant	Novo Nordisk Pharma Ltd.
Date of Application	August 25, 2021
Dosage Form/Strength	(a) Aqueous injection: Each pre-filled pen (0.5 mL) contains 0.25, 0.5 or 1.0 mg of semaglutide (genetical recombination). (b) Aqueous injection: Each pre-filled pen (0.75 mL) contains 1.7 or 2.4 mg of semaglutide (genetical recombination).

Proposed Indication

Obesity

Wegovy should only be used in patients with hypertension, dyslipidemia, or type 2 diabetes mellitus who have:
a BMI of ≥27 kg/m^2 and ≥2 obesity-related health disorders, or
a BMI of ≥35 kg/m^2 and ≥1 obesity-related health disorder

Proposed Dosage and Administration

The usual adult dosage is 2.4 mg of semaglutide (genetical recombination) injected subcutaneously once weekly. However, treatment should be initiated at 0.25 mg once weekly, and the dose should be escalated every 4 weeks to 0.5, 1.0, and 1.7 mg once weekly until a dose of 2.4 mg is reached. The dose should be adjusted according to the patient's condition, but should not exceed 2.4 mg once weekly.

Table of Contents

List of Abbreviations

See Appendix.

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

Wegovy is an injectable medicine containing semaglutide (genetical recombination), a glucagon-like peptide-1 (GLP-1) analog, as the active ingredient. In Japan, Ozempic Subcutaneous Injection 2 mg and Rybelsus 3 mg tablets etc., which contain the same active ingredient as Wegovy, were approved for the indication of type 2 diabetes mellitus in March 2018 and June 2020, respectively.

Obesity is known to cause various health disorders, and the major international organizations such as World Health Organization (WHO) define obesity as a disease (*Obesity*. 2019;27:7-9). Lifestyle intervention in the form of diet and exercise is first-line treatment for obesity, but most people with obesity struggle to achieve and maintain their weight loss. Thus, foreign clinical practice guidelines recommend that pharmacotherapy should be considered if weight reduction by lifestyle modifications is not adequate (*Obes Facts*. 2015;8:166-74, *J Clin Endocrinol Metab*. 2015;100:342-62). The Japanese guidelines for the management of obesity disease define "obesity" as a body mass index (BMI) of ≥25 kg/m^2 and "obesity disease" as a medical condition that is accompanied by obesity-related health disorders and thus medically requires weight loss. For the treatment of obesity disease in Japan, as in foreign countries, pharmacotherapy should be considered if lifestyle intervention consisting of dietary, exercise, and behavioral therapy does not produce effective weight loss or improvement of comorbidities, but there are limited options for pharmacotherapy. Although bariatric surgery offers an alternative, it is indicated for patients with a BMI of ≥35 kg/m^2 with a comorbidity such as diabetes, hypertension, and dyslipidemia who have not responded adequately to medical treatment, and a limited number of health facilities perform bariatric surgery due to facility standards/the qualifications of physicians, etc.

Wegovy is expected to induce weight loss in patients with obesity disease by activating areas of the brain involved in appetite regulation through the GLP-1 receptor, etc. Claiming that global phase III trials etc. demonstrated the efficacy and safety of semaglutide in patients with obesity disease, the applicant has filed a marketing application.

Wegovy was approved for the following indications in the US in June 2021 and in the EU in January 2022. As of June 2022, it has been approved in 6 countries or regions.

[Indication in the US]
WEGOVY is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of

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

[Indication in the EU]
Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

- ≥30 kg/m^2 (obesity), or
- ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.

2. Quality and Outline of the Review Conducted by PMDA

The present application is intended for an additional dosage form etc. as well as a new indication and a new dosage, and quality data have been submitted. As a result of its review for the additional dosage form etc., PMDA found no major problems.

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

The results of non-clinical pharmacology studies, which were submitted for the initial approval of Ozempic Subcutaneous Injection 2 mg, showed that semaglutide lowers body weight and suggested that this effect of semaglutide may be mainly associated with its effects on the hypothalamus (see "Review Report on Ozempic Subcutaneous Injection 2 mg as of November 16, 2017"]. Given these findings, for the present application, primary pharmacodynamic studies investigated cFos expression in neurons in the mouse brain and the access of semaglutide to the mouse brain following subcutaneous administration of semaglutide or fluorescently labeled semaglutide. No secondary pharmacodynamic, safety pharmacology, or pharmacodynamic drug interaction studies were conducted. The study results are described below.

3.1 Primary pharmacodynamics

3.1.1 *In vivo* studies

3.1.1.1 The access of semaglutide to the mouse brain following subcutaneous administration of semaglutide (CTD4.2.1.1-2)

Male C57BL/6J mice (9 weeks of age, 4-5/group) were subcutaneously given fluorescently labelled semaglutide (0.04 mg/kg on Day 1, 0.07 mg/kg on Day 2, 0.15 mg/kg on Days 3-5) or vehicle[1)] for 5 days, and the brains were collected 6 hours after the last dose for imaging by laser sheet fluorescence microscopy. In the semaglutide group, a fluorescent signal was detected in the median eminence, the hypothalamus (the arcuate nucleus, the dorsomedial nucleus, the paraventricular nucleus), the area postrema, the nucleus of the solitary tract, the dorsal motor nucleus of the vagus nerve, the septum (the triangular nucleus, the caudal part of the lateral septal nucleus, the septofimbrial nucleus), etc.

[1)] PBS (pH 7.4)

3.1.1.2 Neuronal activation in mouse brain following semaglutide administration (CTD4.2.1.1-1)

Following a single subcutaneous administration of semaglutide (0.1 mg/kg) or vehicle[2)] in male diet induced obese (DIO) C57BL/6J mice (20 weeks of age, 8/group), the brains were collected 4 hours following administration and immunohistochemically stained for the immediate early gene and transcription factor cFos to evaluate cFos immunoreactivity by laser sheet fluorescence microscopy. In the semaglutide group, cFos positive signal was detected in the nucleus of the solitary tract, the dorsal motor nucleus of the vagus nerve, the area postrema, the bed nuclei of the stria terminalis, the central amygdala nucleus, the parabrachial nucleus, the midline group of the dorsal thalamus, etc.

Following a single subcutaneous administration of semaglutide (0.1 mg/kg) or vehicle[2)] in male DIO C57BL/6J mice (27 weeks of age, 1-2/group), the brains were collected 4 hours following administration and immunohistochemically co-stained for cFos and calcitonin gene-related peptide (CGRP) to evaluate the co-localization of cFos and CGRP positive cells. Co-localization was not observed in the vehicle group, whereas in the parabrachial nucleus, cFos immunoreactivity co-localized with CGRP-positive neurons, in the semaglutide group.

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of semaglutide

The applicant's explanation about the mechanism of action of semaglutide for obesity disease:

In satiety regulation, satiation is induced by nutrient intake, stomach distension, and circulating hormones such as leptin, GLP-1, and cholecystokinin (CCK), which is known to involve the nucleus of the solitary tract in the brain stem, pro-opiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript (CART) neurons and neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons in the arcuate nucleus in the hypothalamus, the paraventricular nucleus of the hypothalamus, CGRP neurons in the parabrachial nucleus, etc. Following subcutaneous administration of fluorescently labelled semaglutide in mice, a fluorescent signal was detected in the hypothalamus, brain stem, and septum known to express the GLP-1 receptor (*Endcrinology*. 2018;159:665-75) (CTD4.2.1.1-2). Thus, semaglutide is considered to have direct access to these brain regions from the circulation. Following administration of semaglutide in mice, the collected brains were immunohistochemically stained for cFos, and cFos positive signal was detected in the midline group of the dorsal thalamus including the paraventricular nucleus of the thalamus. Following administration of semaglutide in mice, the collected brains were immunohistochemically co-stained for cFos and CGRP, and cFos immunoreactivity co-localized with CGRP positive neurons in the parabrachial nucleus (CTD4.2.1.1-1). Given the above findings, semaglutide is considered to induce weight loss by activating areas of the brain involved in appetite regulation through the GLP-1 receptor.

PMDA's view:

Taking also account of the results of studies for the initial approval of Ozempic Subcutaneous Injection 2 mg, etc., semaglutide is considered to have a pharmacological effect of weight loss. Regarding the mechanism of

[2)] Phosphate buffer (pH 7.4, 50 mmol/L phosphate, 70 mmol/L sodium chloride, 0.05% polysorbate 80)

body weight loss, given the primary pharmacodynamic studies conducted for the present application, as explained by the applicant, the central effects of semaglutide on the mechanisms of appetite regulation through the GLP-1 receptor expressed in the hypothalamus, brain stem, etc., may partly be involved. However, as GLP-1 receptor agonists including semaglutide stimulate insulin secretion and slow digestion, mechanisms other than the above central effects of semaglutide may also contribute to semaglutide-induced weight loss. These mechanisms of action are an issue for future investigation. The efficacy of semaglutide in humans will be evaluated in the subsequent sections.

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 Ozempic Subcutaneous Injection 2 mg, and no new study data have been submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is intended for a new indication and a new dosage, no new study data 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 1 shows drug products of semaglutide used in the clinical trials. In the sections below, trial numbers are abbreviated, e.g., Trial NN9536-4373 is Trial 4373.

Table 1. Semaglutide dug products used in clinical trials

Type of drug product	Phase of development (Trial ID)	
	Global trials	Foreign trials
Drug product A	Phase III trials (4382, 4373, 4374)	Phase I trials (4455, 4590) Phase II trial (4153) Phase III trials (4375, 4376)
Drug product B	Phase III trial (4374)	Phase I trial (4588)
To-be-marketed drug product	—	Phase I trials (4588, 4590)

—, Not applicable

Semaglutide concentrations in human biomaterials were quantified using liquid chromatography-tandem mass spectrometry (LC-MS/MS), and the lower limit of quantification in plasma was 0.250 to 0.729 nmol/L. Anti-semaglutide antibodies in human serum were measured using a radioimmunoassay (RIA), and neutralizing antibodies were detected using a cell-based assay.

The applicant submitted the results from bioequivalence trials (Trials 4590 and 4588) as the evaluation data on biopharmaceutics. The trial results are described below.

6.1.1 Bioequivalence trial (CTD5.3.1.2-1, Trial 4590 [December 2019 to September 2020])

A randomized, open-label, parallel-group trial was conducted to assess bioequivalence between semaglutide drug products with different formulations in non-Japanese adults with obesity[3)] (target sample size, 68 subjects).

Drug product A[4)] or the to-be-marketed drug product[5)] was to be administered subcutaneously once weekly for 21 weeks. The starting dose was 0.25 mg, and the dose was to be escalated every 4 weeks to 0.5, 1.0, and 1.7 mg until the maintenance dose of 2.4 mg was reached.

All of 68 randomized subjects (34 in the Drug product A group, 34 in the to-be-marketed drug product group) were included in the safety analysis set, and 64 subjects after excluding 4 subjects who did not receive the last 3 doses of 1.0 or 2.4 mg semaglutide were included in the full analysis set (FAS). The FAS was used for pharmacokinetic analysis etc.

Table 2 shows the pharmacokinetic parameters of semaglutide following multiple subcutaneous administration. The $C_{max, ss}$ and $AUC_{0\text{-}168\ h, ss}$ geometric mean ratios for the to-be-marketed drug product vs. Drug product A (to-be-marketed drug product/Drug product A) and their 90% confidence intervals (CIs) were 1.10 [1.02, 1.19] and 1.04 [0.99, 1.09], respectively, for semaglutide 1.0 mg and 1.16 [1.08, 1.24] and 1.05 [1.00, 1.11], respectively, for semaglutide 2.4 mg.

Table 2. Pharmacokinetic parameters of semaglutide following multiple subcutaneous administration

Dose	Drug product	N	C_{max} (nmol/L)	$AUC_{0\text{-}168\ h}$ (nmol·h/L)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_{ss}/F (L)
1.0 mg	Drug product A	31	41.5 (19.1)	5477 (16.9)	24 [6, 82]	—	0.044 (16.9)	—
	To-be-marketed drug product	33	46.8 (29.1)	5783 (20.7)	18 [6, 42]	—	0.042 (20.7)	—
2.4 mg	Drug product A	30	101 (21.3)	13712 (17.6)	24 [6, 81]	151 (7.3)	0.043 (17.6)	11.0 (20.6)
	To-be-marketed drug product	29	119 (26.3)	14698 (22.6)	24 [3, 48]	155 (9.8)	0.040 (22.6)	9.8 (23.4)

Geometric mean (CV%), Median [Range] for t_{max}; —, Not calculated

C_{max}, maximum plasma concentration; $AUC_{0\text{-}168\ h}$, area under the plasma concentration-time curve from time 0 to 168 hours; t_{max}, time to maximum plasma concentration; $t_{1/2}$, elimination half-life; CL/F, apparent clearance; V_{ss}/F, apparent volume of distribution

Table 3 shows the percent changes in body weight from baseline to different time points.

Table 3. Percent changes in body weight from baseline to different time points (%)

Treatment group	Body weight at baseline (kg)	Percent change in body weight at Week 4	Percent change in body weight at Week 8	Percent change in body weight at Week 12	Percent change in body weight at Week 16	Percent change in body weight at Week 21
Drug product A	97.4 ± 10.0 (N = 31)	−1.7 ± 1.8 (N = 31)	−3.6 ± 2.4 (N = 30)	−4.9 ± 3.7 (N = 31)	−6.7 ± 4.8 (N = 31)	−9.0 ± 5.2 (N = 30)
To-be-marketed drug product	96.3 ± 12.8 (N = 33)	−1.5 ± 1.7 (N = 33)	−3.1 ± 2.8 (N = 33)	−5.1 ± 3.5 (N = 33)	−6.7 ± 4.2 (N = 33)	−8.8 ± 4.5 (N = 30)

Mean ± SD (Number of evaluable subjects)

[3)] Body weight (kg) of ≥70.0 and ≤130.0, and BMI (kg/m^2) of ≥27.0 and ≤34.9

[4)] Semaglutide 1.0 or 3.0 mg/mL solution in a prefilled, multi-dose pen-injector that provides different injection volumes. The 0.25 and 0.5 mg doses were delivered using the 1.0 mg/mL strength, and the 1.0, 1.7, and 2.4 mg doses were delivered using the 3.0 mg/mL strength. It contains the following excipients: disodium phosphate dihydrate, propylene glycol, phenol, sodium hydroxide, hydrochloric acid, and water for injection (the same composition as Ozempic Subcutaneous Injection 2 mg, except for semaglutide concentration).

[5)] Semaglutide 0.5, 1.0, 2.0, 2.27, or 3.2 mg/mL solution in a pre-filled, single-dose pen-injector that delivers doses of 0.25, 0.5, 1.0, 1.7, or 2.4 mg. It contains the following excipients: disodium phosphate dihydrate, sodium chloride, sodium hydroxide, hydrochloric acid, and water for injection.

The incidences of adverse events and adverse drug reactions were 91.2% (31 of 34) of subjects and 88.2% (30 of 34) of subjects, respectively, in the Drug product A group and 82.4% (28 of 34) of subjects and 76.5% (26 of 34) of subjects, respectively, in the to-be-marketed drug product group. A serious adverse event occurred in 1 subject (arrhythmia supraventricular) in the to-be-marketed drug product group, but its causal relationship to trial drug was denied. There were no deaths or adverse events leading to treatment discontinuation. Injection site reactions occurred in 2 subjects (injection site pruritus; and injection site pain) in the to-be-marketed drug product group, and both events were mild in severity. The event of injection site pruritus was classified as an adverse drug reaction, but both events had an outcome of "resolved."

6.1.2 Bioequivalence trial (CTD5.3.1.2-2, Trial 4588 [November 2019 to May 2020])

A randomized, open-label, parallel-group trial was conducted to assess bioequivalence between semaglutide drug products with different formulations in non-Japanese adults with obesity[6)] (target sample size, 68 subjects).

Drug product B[7)] or the to-be-marketed drug product[5)] was to be administered subcutaneously once weekly for 7 weeks. The starting dose was 0.25 mg, and the dose was to be escalated to 0.5 mg after 4 weeks and then to 1.0 mg after 2 weeks.

All of 68 randomized subjects (33 in the Drug product B group, 35 in the to-be-marketed drug product group) were included in the safety analysis set, and 66 subjects after excluding 2 subjects who were withdrawn from the trial due to the investigator's decision were included in the FAS. The FAS was used for pharmacokinetic analysis.

As to the pharmacokinetics of semaglutide, the C_{max} and AUC[8)] geometric mean ratios for the to-be-marketed drug product vs. Drug product B (to-be-marketed drug product/Drug product B) and their 90% confidence intervals were 1.10 [1.05, 1.15] and 1.08 [1.03, 1.13], respectively, for semaglutide 0.25 mg and 1.27 [1.20, 1.34] and 1.10 [1.04, 1.17], respectively, for semaglutide 1.0 mg.

The incidences of adverse events and adverse drug reactions were 90.9% (30 of 33) of subjects and 78.8% (26 of 33) of subjects, respectively, in the Drug product B group and 91.4% (32 of 35) of subjects and 85.7% (30 of 35) of subjects, respectively, in the to-be-marketed drug product group. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation. Injection site reactions occurred in 3 subjects (injection site reaction [3 subjects]) in the to-be-marketed drug product group, which were mild or moderate in severity. All those events were classified as adverse drug reactions, but had an outcome of "resolved."

[6)] Body weight (kg) of ≥65.0 and ≤130.0, and BMI (kg/m^2) of ≥25.0 and ≤34.9

[7)] Semaglutide 1.34 mg/mL solution in a prefilled, multi-dose pen-injector that provides different injection volumes. It contains the following excipients: disodium phosphate dihydrate, propylene glycol, phenol, sodium hydroxide, hydrochloric acid, and water for injection (the same composition as Ozempic Subcutaneous Injection 2 mg).

[8)] $AUC_{0\text{-}168\ h}$ for semaglutide 0.25 mg and $AUC_{0\text{-}840\ h}$ for semaglutide 1.0 mg were used to calculate AUC.

6.2 Clinical pharmacology

The applicant submitted the results from 4 trials (Trials 4590, 4382, 4373, and 4374) as evaluation data. The applicant also submitted the results of a population pharmacokinetic analysis of Trials 4382, 4373, and 4374 and the results from 6 foreign trials (Trials 4455, 4153, 3652, 3616, 3651, and 3685) and 1 Japanese trial (Trial 3634) as reference data.

The results from the main trials are described below.

6.2.1 Patient studies

6.2.1.1 Global phase III trial in patients with obesity and hypertension, dyslipidemia, or type 2 diabetes (CTD5.3.5.1-2, Trial 4382 [January 2019 to November 2020])

A placebo-controlled, randomized, double-blind, parallel-group trial was conducted to investigate the efficacy and safety of semaglutide as an adjunct to dietary and exercise therapy in Japanese or Korean patients with obesity and hypertension, dyslipidemia, or type 2 diabetes (target sample size, 400 subjects [100 in the placebo group, 100 in the semaglutide 1.7 mg group, 200 in the semaglutide 2.4 mg group]) [for the details of the trial design and efficacy and safety results, see Section "7.1 Global phase III trial in patients with obesity and hypertension, dyslipidemia, or type 2 diabetes"].

As to the pharmacokinetics of semaglutide, Table 4 shows plasma semaglutide trough concentrations at different time points following once weekly subcutaneous administration of semaglutide.

Table 4. Plasma semaglutide trough concentrations at different time points following once weekly subcutaneous administration of semaglutide

Treatment group	Week 4[a)]	Week 8[b)]	Week 12[c)]	Week 16[d)]	Week 28	Week 52	Week 68
Semaglutide 1.7 mg	7 (21) (N = 60)	15 (20) (N = 50)	29 (20) (N = 57)	46 (31) (N = 53)	51 (47) (N = 45)	52 (28) (N = 52)	52 (50) (N = 49)
Semaglutide 2.4 mg	7 (35) (N = 118)	15 (22) (N = 110)	27 (38) (N = 102)	45 (41) (N = 112)	60 (90) (N = 103)	64 (57) (N = 85)	68 (56) (N = 92)

Geometric mean (CV%) (Number of evaluable subjects); Unit, nmol/L
a) at the 0.25 mg dose level, b) at the 0.5 mg dose level, c) at the 1.0 mg dose level, d) at the 1.7 mg dose level

6.2.1.2 Global phase III trial in patients with overweight or obesity (CTD5.3.5.1-3, Trial 4373 [June 2018 to April 2020])

A placebo-controlled, randomized, double-blind, parallel-group trial was conducted to investigate the efficacy and safety of semaglutide as an adjunct to dietary and exercise therapy in patients with overweight or obesity including Japanese patients (target sample size, 1950 subjects [650 in the placebo group, 1300 in the semaglutide 2.4 mg group]) [for the details of trial design and efficacy and safety results, see Section "7.2 Global phase III trial in patients with overweight or obesity"].

As to the pharmacokinetics of semaglutide, Table 5 shows plasma semaglutide trough concentrations at different time points following once weekly subcutaneous administration of semaglutide.

Table 5. Plasma semaglutide trough concentrations at different time points following once weekly subcutaneous administration of semaglutide

Treatment group	Week 2[a)]	Week 4 [a)]	Week 8[b)]	Week 12[c)]	Week 28	Week 52	Week 68
Semaglutide 2.4 mg	5 (39) (N = 734)	6 (41) (N = 695)	12 (45) (N = 672)	24 (47) (N = 637)	58 (53) (N = 502)	61 (58) (N = 451)	62 (63) (N = 359)

Geometric mean (CV%) (Number of evaluable subjects); Unit, nmol/L
a) at the 0.25 mg dose level, b) at the 0.5 mg dose level, c) at the 1.0 mg dose level

6.2.1.3 Global phase III trial in patients with overweight or obesity and type 2 diabetes (CTD5.3.5.1-4, Trial 4374 [June 2018 to May 2020])

A placebo-controlled, randomized, double-blind, parallel-group trial was conducted to investigate the efficacy and safety of semaglutide as an adjunct to dietary and exercise therapy in patients with overweight or obesity and type 2 diabetes including Japanese patients (target sample size, 1200 subjects [400 each in the placebo, semaglutide 1.0 mg, and semaglutide 2.4 mg groups]) [for the details of trial design and efficacy and safety results, see Section "7.3 Global phase III trial in patients with overweight or obesity and type 2 diabetes"].

As to the pharmacokinetics of semaglutide, Table 6 shows plasma semaglutide trough concentrations at different time points following once weekly subcutaneous administration of semaglutide.

Table 6. Plasma semaglutide trough concentrations at different time points following once weekly subcutaneous administration of semaglutide

Treatment group	Week 4[a)]	Week 8[b)]	Week 12[c)]	Week 28	Week 52	Week 68
Semaglutide 1.0 mg	5 (37) (N = 201)	11 (40) (N = 193)	20 (48) (N = 181)	23 (38) (N = 157)	23 (45) (N = 149)	23 (45) (N = 135)
Semaglutide 2.4 mg	5 (48) (N = 192)	10 (60) (N = 182)	22 (56) (N = 180)	47 (73) (N = 146)	51 (71) (N = 132)	52 (69) (N = 119)

Geometric mean (CV%) (Number of evaluable subjects); Unit, nmol/L
a) at the 0.25 mg dose level, b) at the 0.5 mg dose level, c) at the 1.0 mg dose level

6.2.2 Pharmacodynamics

6.2.2.1 Effect of semaglutide on gastric emptying (CTD5.3.4.2-1, Trial 4455]February to November 2019] Reference data)

A placebo-controlled, randomized, double-blind, parallel-group trial was conducted using acetaminophen to investigate the effect of semaglutide on gastric emptying in non-Japanese subjects with obesity[9)] (target sample size, 72 subjects [36 per group]).

Placebo or Drug product A[4)] was to be administered subcutaneously once weekly for 21 weeks. The starting dose was 0.25 mg, and the dose was to be escalated every 4 weeks to 0.5, 1.0, and 1.7 mg to reach the 2.4 mg dose. A single oral dose of acetaminophen 1.5 g was to be administered 1 day after the last dose of placebo or Drug product A (2.4 mg).

All of 72 randomized subjects (36 in the placebo group, 36 in the semaglutide group) were included in the safety analysis set and in the FAS. The FAS was used for pharmacokinetic analysis.

9) BMI of ≥30.0 and ≤45.0 kg/m^2

Table 7 shows the pharmacokinetics parameters of acetaminophen in plasma following multiple subcutaneous administration of placebo or semaglutide 2.4 mg. The plasma acetaminophen C_{max}, $AUC_{0\text{-}1\ h}$, and $AUC_{0\text{-}5\ h}$ geometric mean ratios for semaglutide 2.4 mg vs. placebo (semaglutide/placebo) and their 95% confidence intervals were 0.94 [0.82, 1.07], 0.99 [0.87, 1.12], and 1.08 [1.02, 1.14], respectively.

Table 7. Pharmacokinetic parameters of acetaminophen in plasma following multiple subcutaneous administration of placebo or semaglutide 2.4 mg

Treatment group	C_{max} (μg/mL)	$AUC_{0\text{-}1\ h}$ (μg·h/mL)	$AUC_{0\text{-}5\ h}$ (μg·h/mL)	t_{max} (h)
Placebo (N = 35)	19.6 (32.1)	13.2 (30.4)	44.9 (22.3)	0.50 [0.25, 0.78]
Semaglutide 2.4 mg (N = 35)	18.0 (35.4)	12.5 (38.3)	45.7 (29.2)	0.50 [0.25, 0.77]

Geometric mean (CV), Median [Range] for t_{max}
C_{max}, maximum plasma concentration of acetaminophen
$AUC_{0\text{-}1\ h}$, area under the plasma acetaminophen concentration-time curve from time 0 to 1 hour
$AUC_{0\text{-}5\ h}$, area under the plasma acetaminophen concentration-time curve from time 0 to 5 hours
t_{max}, time to maximum plasma concentration

The incidences of adverse events and adverse drug reactions were 91.7% (33 of 36) of subjects and 69.4% (25 of 36) of subjects, respectively, in the placebo group and 80.6% (29 of 36) of subjects and 75.0% (27 of 36) of subjects, respectively, in the semaglutide group. No deaths were reported. Serious adverse events occurred in 1 subject (colonic abscess) in the placebo group and 1 subject (road traffic accident) in the semaglutide group, but a causal relationship to trial drug was denied for the both events. An adverse event leading to treatment discontinuation occurred in 1 subject (colonic abscess) in the placebo group, but its causal relationship to trial drug was denied.

6.2.3 Population pharmacokinetic analysis (CTD5.3.3.5-2)

Using 13676 plasma semaglutide concentrations from 2366 subjects (889 men, 1477 women) in 3 global phase III trials in patients with overweight or obesity (Trials 4382, 4373, and 4374), a population pharmacokinetic (PPK) analysis was performed (software used: NONMEM [ver.7.3]).

As to the characteristics of subjects included in the PPK analysis, the mean age [range] was 49.8 [18, 86] years, the mean body weight was 101.2 [54.4, 245.6] kg, the mean BMI was 36.4 [26.5, 83] kg/m^2, and the mean hemoglobin A1c (HbA1c) at baseline was 6.6% [4.1%, 10.6%].

A 1-compartment model with first-order absorption and first-order elimination was developed as a base model. A full model was developed by incorporating sex, age (18-64 years, 65-74 years, ≥75 years), race (Caucasian, Black/African American, American Indian/Alaskan Native, Japanese, non-Japanese Asian), ethnicity (Hispanic/Latino, non-Hispanic/Latino), body weight, eGFR (mL/min/1.73 m^2) (≥90, 60-89, 30-59, 15-29), injection site (abdomen, thigh, upper arm), glycemic status (normoglycemia, prediabetes, diabetes), and clinical trial (Trial 4382, Trial 4373, Trial 4374) as covariates on apparent clearance (CL/F) and body weight as a covariate on apparent volume of distribution (V/F). The final model was developed by backward elimination to only retain sex, race, body weight, and glycemic status as covariates on CL/F and body weight as a covariate on V/F.

The results of covariate analysis with the full model approach indicated that body weight was the source of variability in the PK of semaglutide, and the average plasma semaglutide concentration in subjects with a body weight of 72 kg or 142 kg was estimated to be 1.33-fold or 0.74-fold that in subjects with a body weight of 100 kg, respectively.

6.R Outline of the review conducted by PMDA

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

The applicant's explanation:

With respect to pharmacokinetic evaluation in Japanese and non-Japanese populations during the development of semaglutide for type 2 diabetes, a clinical trial in healthy adult subjects (Trial 3634) showed no major differences in the pharmacokinetics of subcutaneous semaglutide between Japanese and non-Japanese subjects. In clinical trials in patients with type 2 diabetes, the steady-state plasma semaglutide concentrations following once weekly subcutaneous administration of semaglutide (0.5 and 1.0 mg) tended to be higher in Japanese patients than in non-Japanese patients, and one of its factors was considered differences in body weight. However, these differences had no major effects on the efficacy and safety evaluation of semaglutide in phase III trials (see "Review Report on Ozempic Subcutaneous Injection 2 mg as of November 16, 2017").

In global phase III trials in patients with overweight or obesity (Trials 4382, 4373, and 4374), the steady-state pharmacokinetic parameters following once weekly subcutaneous administration of semaglutide 2.4 mg estimated from the PPK analysis are shown in Table 8, and there was a trend towards higher values in Japanese patients than in non-Japanese patients in all trials. Given that the results of the PPK analysis indicated that body weight is the source of variability in the PK of semaglutide [see Section "6.2.3 Population pharmacokinetic analysis"], lower body weight in Japanese patients than in non-Japanese patients was considered one factor in the trend towards higher values in Japanese patients in all trials (mean body weight, 85 kg in Japanese patients and 97 kg in non-Japanese patients in Trial 4382, 84 kg in Japanese patients and 107 kg in non-Japanese patients in Trial 4373, 86 kg in Japanese patients and 102 kg in non-Japanese patients in Trial 4374).

Table 8. Estimated steady-state pharmacokinetic parameters following multiple subcutaneous administration of semaglutide 2.4 mg (Trials 4382, 4373, and 4374)

	Trial 4382		Trial 4373		Trial 4374	
	Japanese	Non-Japanese	Japanese	Non-Japanese	Japanese	Non-Japanese
C_{max} (nmol/L)	96 (18) (N = 176)	84 (22) (N = 18)	100 (19) (N = 66)	85 (23) (N = 1229)	88 (22) (N = 42)	77 (23) (N = 351)
$AUC_{0\text{-}168\ h}$ (nmol·h/L)	14222 (19) (N = 176)	12333 (23) (N = 18)	14959 (20) (N = 66)	12585 (24) (N = 1229)	13020 (23) (N = 42)	11276 (24) (N = 351)

Geometric mean (CV)
C_{max}, maximum plasma concentration
$AUC_{0\text{-}168\ h}$, area under the plasma concentration-time curve from time 0 to 168 hours

PMDA accepts the applicant's explanation about comparison of pharmacokinetics between Japanese and non-Japanese populations (semaglutide exposure tended to be higher in Japanese patients than in non-Japanese patients, and one of its factors is differences in body weight.), but will continue to evaluate the effect of body

weight on the efficacy and safety of semaglutide, taking also account of the efficacy and safety results [see Sections "7.R.2 Efficacy" and "7.R.3 Safety"].

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

The applicant submitted efficacy and safety evaluation data, in the form of the results from 3 trials presented in Table 9. The applicant also submitted the results from 2 foreign phase II trials and 3 foreign phase III trials as reference data.

Table 9. Listing of efficacy and safety clinical trials

Data category	Geographical location	Trial ID	Phase	Trial population	Number of subjects enrolled	Dosing regimen	Main endpoints
Evaluation	Global	4382	III	Patients with obesity and hypertension, dyslipidemia, or type 2 diabetes	401	Placebo, semaglutide 1.7 mg, or semaglutide 2.4 mg administered subcutaneously once weekly	Efficacy Safety
	Global	4373	III	Patients with overweight or obesity	1961	Placebo or semaglutide 2.4 mg administered subcutaneously once weekly	Efficacy Safety
	Global	4374	III	Patients with overweight or obesity and type 2 diabetes	1210	Placebo, semaglutide 1.0 mg, or semaglutide 2.4 mg administered subcutaneously once weekly	Efficacy Safety

The results from the main trials are described below. Unless otherwise specified, the safety data described are those during the period of treatment with trial drug and a follow-up.[10)]

7.1 Global phase III trial in patients with obesity and hypertension, dyslipidemia, or type 2 diabetes (CTD5.3.5.1-2, Trial 4382 [January 2019 to November 2020])

A placebo-controlled, randomized, double-blind, parallel-group trial was conducted to investigate the efficacy and safety of semaglutide as an adjunct to dietary and exercise therapy in Japanese or Korean patients with obesity and hypertension, dyslipidemia, or type 2 diabetes (target sample size, 400 subjects[11)] [100 in the placebo group, 100 in the semaglutide 1.7 mg group, 200 in the semaglutide 2.4 mg group]) [for pharmacokinetics, see Section "6.2.1.1 Global phase III trial in patients with obesity and hypertension, dyslipidemia, or type 2 diabetes"].

The key inclusion criteria were patients with obesity aged ≥18 years (≥20 years for Japanese patients) fulfilling the following criteria (1) and (2) [(1) BMI ≥27.0 kg/m^2 with ≥2 weight-related comorbidities[12)] or BMI ≥35.0

[10)] The end of this period (excluding temporary treatment interruption) was defined as 7 weeks after the last dose for adverse events, events assessed by EAC, and hypoglycemia and as 2 weeks after the last dose for ECG, clinical laboratory tests, physical examination, and pulse rate.

[11)] Comparisons between semaglutide 2.4 mg and placebo were made at the two-sided significance level of 5%. The co-primary endpoint of the percent change in body weight from baseline to Week 68 ± SD was assumed to be 11.9 ± 11% in the semaglutide 2.4 mg group and 2.7 ± 11% in the placebo group, and the other co-primary endpoint of the proportion of subjects achieving ≥5% weight loss at Week 68 was assumed to be 75% in the semaglutide 2.4 mg group and 41% in the placebo group. Given these assumptions, the target sample size of 400 subjects provided a power of >99% for each co-primary endpoint and an effective power of 84% for the 10 hypotheses in the hierarchical testing procedure. The target sample size was defined to support safety.

[12)] Patients with BMI ≥27.0 kg/m^2 were required to have hypertension or dyslipidemia (or type 2 diabetes for Japanese patients only) and at least 1 weight-related comorbidity (at least 1 obesity-related health disorder according to the Japanese guidelines for the management of obesity disease).
Obesity-related health disorders (1) to (11) specified by the guidelines:
(1) impaired glucose tolerance (type 2 diabetes, abnormal glucose tolerance, etc.), (2) dyslipidemia, (3) hypertension, (4) hyperuricemia/gout, (5) coronary artery disease, (6) cerebral infarction, (7) non-alcoholic fatty liver disease, (8) menstrual disorder/infertility, (9) obstructive sleep apnoea syndrome/obesity-hypoventilation syndrome, (10) locomotory disease, (11) obesity-related kidney disease

kg/m^2 with ≥1 weight-related comorbidity. At least one comorbidity should be hypertension, dyslipidemia, or type 2 diabetes[13)] and (2) history of at least one self-reported unsuccessful dietary effort to lose body weight]. Patients were excluded if the following criteria applied: previous or planned (during the trial period) obesity treatment with surgery or a weight loss device.

The trial consisted of a screening period (1 week), a treatment period (68 weeks), and a follow-up period (7 weeks).

Placebo, semaglutide 1.7 mg, or semaglutide 2.4 mg[14)] was to be injected subcutaneously in the thigh, abdomen, or upper arm once weekly (self-injection). The starting dose of semaglutide was 0.25 mg in both the semaglutide 1.7 mg and 2.4 mg groups, and the dose was to be escalated every 4 weeks to 0.5, 1.0, and 1.7 mg. In the semaglutide 2.4 mg group, the dose was to be further escalated to 2.4 mg after 4 weeks. If a subject did not tolerate the designated target dose (1.7 or 2.4 mg), the subject was allowed to stay at a lower dose level.

All of 401 randomized subjects[15)] (101 in the placebo group [including 89 Japanese subjects], 101 in the semaglutide 1.7 mg group [including 92 Japanese subjects], 199 in the semaglutide 2.4 mg group [including 179 Japanese subjects]) were included in the FAS, and the FAS was used for efficacy analyses. In the FAS, all of 400 subjects who received trial drug (101 in the placebo group [including 89 Japanese subjects], 100 in the semaglutide 1.7 mg group [including 91 Japanese subjects], 199 in the semaglutide 2.4 mg group [including 179 Japanese subjects]) were included in the safety analysis set. There were 6 trial withdrawals (2 subjects in the semaglutide 1.7 mg group [including 2 Japanese subjects], 4 subjects in the semaglutide 2.4 mg group [including 2 Japanese subjects]), and the reasons for trial withdrawals were all subject's request.

Table 10 shows the co-primary efficacy endpoints of the percent change in body weight from baseline to Week 68 and the proportion of subjects achieving ≥5% weight loss at Week 68, which demonstrated the superiority of semaglutide 2.4 mg to placebo.

[13)] The inclusion criteria as to type 2 diabetes applied to Japanese patients only: diagnosed with type 2 diabetes ≥180 days prior to the day of screening; and HbA1c of 7.0%-10.0%. Patients treated with either diet and exercise alone or stable treatment with up to 3 oral antidiabetic drugs (metformin, SU, SGLT2 inhibitors, or thiazolidinediones) for ≥90 days prior to screening were allowed to be enrolled in the trial.

[14)] Drug product A (semaglutide 1.0 or 3.0 mg/mL solution in a prefilled, multi-dose pen-injector that provides different injection volumes) was used. If a single dose of trial drug was missed, it was to be administered as soon as noticed, provided the time to the next scheduled dose was ≥2 days away. If a dose was missed and the next scheduled dose was <2 days away, the subject was not to administer a dose until the next scheduled dose.

[15)] Subjects were randomized in a 1:2:1:4 ratio to receive semaglutide 1.7 mg placebo, semaglutide 1.7 mg, semaglutide 2.4 mg placebo, or semaglutide 2.4 mg.

Table 10. Percent change in body weight from baseline to Week 68 and proportion of subjects achieving ≥5% weight loss at Week 68 (Trial 4382: FAS)

Endpoint	Entire trial population			Japanese subgroup		
	Placebo (N = 101)	Semaglutide 1.7 mg (N = 101)	Semaglutide 2.4 mg (N = 199)	Placebo (N = 89)	Semaglutide 1.7 mg (N = 92)	Semaglutide 2.4 mg (N = 179)
Body weight at baseline (kg)	90.2 ± 15.1 (N = 101)	86.1 ± 11.9 (N = 101)	86.9 ± 16.5 (N = 199)	90.1 ± 14.2 (N = 89)	85.1 ± 11.5 (N = 92)	85.8 ± 15.9 (N = 179)
Body weight at Week 68 (kg)	88.6 ± 15.5 (N = 100)	77.8 ± 13.9 (N = 98)	75.1 ± 17.0 (N = 193)	88.3 ± 14.8 (N = 88)	76.6 ± 13.5 (N = 89)	74.1 ± 16.2 (N = 175)
Percent change in body weight at Week 68 (%)	−1.9 ± 5.9 (N = 100)	−9.9 ± 7.8 (N = 98)	−13.4 ± 8.6 (N = 193)	−2.1 ± 5.9 (N = 88)	−10.3 ± 7.9 (N = 89)	−13.4 ± 8.4 (N = 175)
Difference from placebo[a)] [95% CI]	—	−7.52 [−9.62, −5.43]	−11.06 [d)] [−12.88, −9.24]	—	−7.51 [−9.72, −5.29]	−10.81 [−12.74, −8.89]
% of subjects losing ≥5% body weight[b)]	21.0 (21/100)	72.4 (71/98)	82.9 (160/193)	21.6 (19/88)	73.0 (65/89)	83.4 (146/175)
Odds ratio relative to placebo[c)] [95% CI]	—	11.08 [5.53, 22.22]	21.72 [d)] [11.27, 41.86]	—	11.06 [5.27, 23.24]	21.89 [10.87, 44.12]

Mean ± SD (Number of evaluable subjects), Proportion % (Number of responders/Number of evaluable subjects); —, Not applicable
a) Estimated using an analysis of covariance (ANCOVA) model with treatment and type 2 diabetes status at screening as fixed effects and baseline body weight as a covariate after missing values were imputed using a multiple imputation approach.
b) Proportion of subjects achieving ≥5% weight loss from baseline to Week 68 (%)
c) Estimated using a logistic regression with treatment and type 2 diabetes status at screening as fixed effects and baseline body weight as a covariate after missing values were imputed using a multiple imputation approach.
d) Multiplicity was controlled using a hierarchical testing procedure. $P < 0.0001$ with a two-sided significance level of 5%

Figure 1 shows the time course of the percent change in body weight from baseline through Week 68. The results of the key secondary endpoints are shown in Tables 11 and 12.

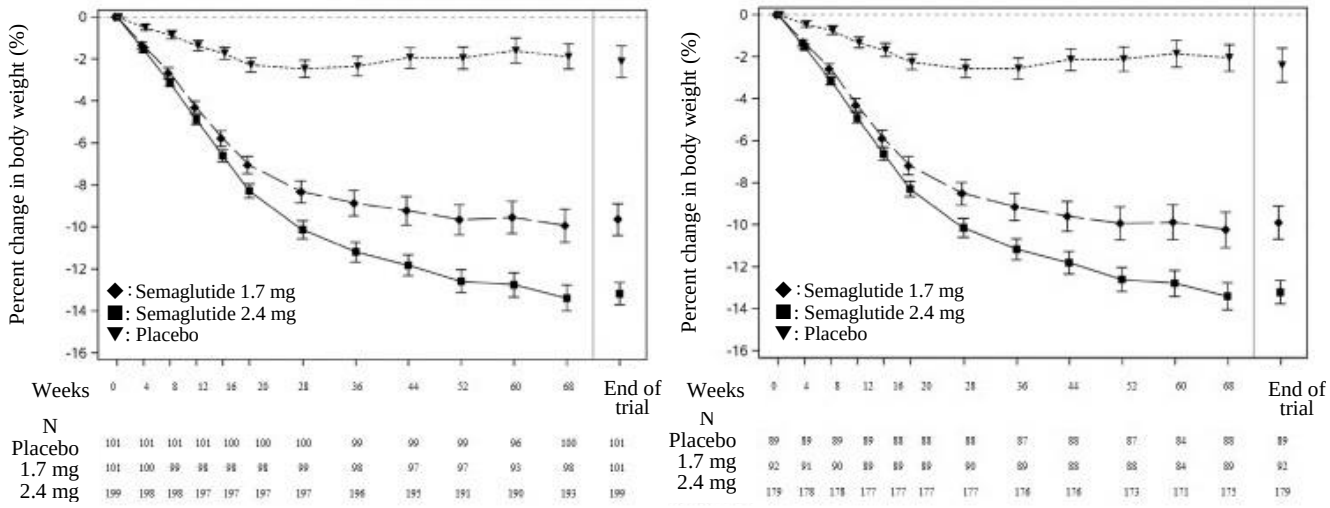

Figure 1. Time course of percent change in body weight from baseline through Week 68
(Left figure, Entire trial population; Right figure, Japanese subgroup) (Mean ± SE, Trial 4382: FAS)

Table 11. Results of body weight-related key secondary endpoints (Trial 4382: FAS)

Endpoint		Entire trial population			Japanese subgroup		
		Placebo (N = 101)	Semaglutide 1.7 mg (N = 101)	Semaglutide 2.4 mg (N = 199)	Placebo (N = 89)	Semaglutide 1.7 mg (N = 92)	Semaglutide 2.4 mg (N = 179)
% of subjects achieving weight loss[a)]	≥10%	5.0 (5/100)	41.8 (41/98)	60.6 (117/193)	5.7 (5/88)	43.8 (39/89)	62.3 (109/175)
	≥15%	3.0 (3/100)	24.5 (24/98)	40.9 (79/193)	3.4 (3/88)	27.0 (24/89)	41.1 (72/175)
Waist circumference[b)] (cm)	Baseline	103.8 ± 9.9 (N = 101)	101.4 ± 8.8 (N = 101)	103.8 ± 11.8 (N = 199)	103.6 ± 9.7 (N = 89)	100.8 ± 8.6 (N = 92)	103.3 ± 11.7 (N = 179)
	Change at Week 68	−1.8 ± 5.9 (N = 100)	−7.8 ± 6.9 (N = 98)	−11.2 ± 7.5 (N = 193)	−1.8 ± 6.0 (N = 88)	−7.9 ± 7.1 (N = 89)	−11.2 ± 7.3 (N = 175)
Waist circumference (JASSO)[b)] (cm)	Baseline	105.6 ± 10.7 (N = 101)	103.7 ± 9.3 (N = 101)	105.5 ± 11.3 (N = 199)	105.4 ± 10.7 (N = 89)	103.3 ± 9.2 (N = 92)	105.2 ± 11.3 (N = 179)
	Change at Week 68	−1.9 ± 5.3 (N = 100)	−7.6 ± 5.7 (N = 98)	−10.2 ± 6.8 (N = 193)	−1.8 ± 5.4 (N = 88)	−7.6 ± 5.9 (N = 89)	−10.0 ± 6.6 (N = 175)
BMI (kg/m^2)	Baseline	31.9 ± 4.2 (N = 101)	31.6 ± 3.7 (N = 101)	32.0 ± 4.6 (N = 199)	32.0 ± 4.3 (N = 89)	31.5 ± 3.8 (N = 92)	31.9 ± 4.7 (N = 179)
	Change at Week 68	−0.6 ± 2.0 (N = 100)	−3.1 ± 2.4 (N = 98)	−4.3 ± 2.8 (N = 193)	−0.7 ± 2.0 (N = 88)	−3.2 ± 2.4 (N = 89)	−4.3 ± 2.7 (N = 175)
Visceral fat area[c)] (CT scan) (cm^2)	Baseline	—	—	—	179.3 ± 62.8 (N = 43)	158.5 ± 67.1 (N = 45)	171.4 ± 68.9 (N = 86)
	Change at Week 68	—	—	—	−13.8 ± 38.6 (N = 43)	−41.7 ± 47.0 (N = 45)	−67.4 ± 43.0 (N = 86)

Mean ± SD (Number of evaluable subjects), Proportion % (Number of responders/Number of evaluable subjects); —, Not applicable
a) Proportion of subjects achieving a weight loss of ≥10% or ≥15% from baseline to Week 68 (%)
b) Waist circumference (cm) measured midway between the lower rib margin and the iliac crest
Waist circumference (JASSO) (cm) measured at the navel level
c) Measured in Japanese subjects only.

Table 12. Results of blood glucose, blood pressure, and lipid parameters-related key secondary endpoints (Trial 4382: FAS)

Endpoint		Entire trial population			Japanese subgroup		
		Placebo (N = 101)	Semaglutide 1.7 mg (N = 101)	Semaglutide 2.4 mg (N = 199)	Placebo (N = 89)	Semaglutide 1.7 mg (N = 92)	Semaglutide 2.4 mg (N = 179)
HbA1c (%)	Baseline	6.4 ± 1.1 (N = 101)	6.4 ± 1.1 (N = 101)	6.4 ± 1.2 (N = 199)	6.4 ± 1.1 (N = 89)	6.4 ± 1.2 (N = 92)	6.5 ± 1.3 (N = 179)
	Change at Week 68	0.0 ± 0.8 (N = 100)	−0.9 ± 0.8 (N = 98)	−1.0 ± 1.0 (N = 193)	0.0 ± 0.8 (N = 88)	−1.0 ± 0.8 (N = 89)	−1.0 ± 1.0 (N = 175)
Fasting plasma glucose (mg/dL)	Baseline	112.7 ± 29.5 (N = 100)	111.7 ± 26.2 (N = 101)	111.2 ± 27.2 (N = 199)	114.4 ± 30.8 (N = 88)	113.0 ± 27.1 (N = 92)	112.5 ± 28.2 (N = 179)
	Change at Week 68	1.7 ± 26.1 (N = 98)	−18.3 ± 21.9 (N = 97)	−19.3 ± 22.6 (N = 192)	2.5 ± 27.6 (N = 86)	−19.9 ± 22.1 (N = 88)	−20.5 ± 23.2 (N = 174)
Systolic blood pressure (mmHg)	Baseline	133 ± 14 (N = 101)	135 ± 13 (N = 101)	133 ± 14 (N = 199)	134 ± 14 (N = 89)	135 ± 13 (N = 92)	133 ± 14 (N = 179)
	Change at Week 68	−5 ± 15 (N = 100)	−12 ± 13 (N = 98)	−11 ± 15 (N = 193)	−5 ± 15 (N = 88)	−12 ± 13 (N = 89)	−10 ± 15 (N = 175)
Diastolic blood pressure (mmHg)	Baseline	86 ± 12 (N = 101)	85 ± 10 (N = 101)	83 ± 11 (N = 199)	86 ± 12 (N = 89)	85 ± 9 (N = 92)	83 ± 11 (N = 179)
	Change at Week 68	−3 ± 9 (N = 100)	−5 ± 10 (N = 98)	−5 ± 10 (N = 193)	−3 ± 10 (N = 88)	−5 ± 10 (N = 89)	−5 ± 10 (N = 175)
Total cholesterol (mg/dL)	Baseline	206.2 ± 36.4 (N = 101)	207.1 ± 39.9 (N = 101)	200.4 ± 35.6 (N = 199)	205.5 ± 37.0 (N = 89)	207.2 ± 38.2 (N = 92)	201.1 ± 34.2 (N = 179)
	Percent change at Week 68 (%)	1.2 ± 12.2 (N = 100)	−6.0 ± 16.1 (N = 98)	−7.8 ± 12.3 (N = 193)	2.0 ± 12.2 (N = 88)	−6.3 ± 13.9 (N = 89)	−8.6 ± 11.2 (N = 175)
LDL cholesterol (mg/dL)	Baseline	126.96 ± 31.50 (N = 101)	124.89 ± 33.53 (N = 101)	120.60 ± 31.77 (N = 199)	125.76 ± 30.98 (N = 89)	125.34 ± 32.42 (N = 92)	120.68 ± 30.81 (N = 179)
	Percent change at Week 68 (%)	−2.8 ± 18.5 (N = 99)	−7.1 ± 28.8 (N = 98)	−11.8 ± 20.3 (N = 193)	−2.2 ± 18.6 (N = 87)	−9.4 ± 19.5 (N = 89)	−13.1 ± 19.5 (N = 175)
HDL cholesterol (mg/dL)	Baseline	49.8 ± 10.9 (N = 101)	51.7 ± 12.3 (N = 101)	52.2 ± 12.3 (N = 199)	49.8 ± 10.9 (N = 89)	53.0 ± 11.9 (N = 92)	52.9 ± 12.1 (N = 179)
	Percent change at Week 68 (%)	7.1 ± 13.2 (N = 100)	8.0 ± 18.3 (N = 98)	9.5 ± 15.9 (N = 193)	7.5 ± 13.5 (N = 88)	8.1 ± 18.8 (N = 89)	9.1 ± 15.7 (N = 175)
Triglycerides (mg/dL)	Baseline	154.70 ± 108.98 (N = 101)	163.65 ± 120.06 (N = 101)	140.83 ± 68.20 (N = 199)	157.69 ± 114.14 (N = 89)	155.09 ± 116.36 (N = 92)	140.70 ± 68.38 (N = 179)
	Percent change at Week 68 (%)	13.3 ± 42.4 (N = 99)	−12.2 ± 54.7 (N = 98)	−13.6 ± 39.0 (N = 193)	15.1 ± 42.8 (N = 87)	−10.5 ± 56.4 (N = 89)	−13.9 ± 39.1 (N = 175)

Mean ± SD (Number of evaluable subjects)

Tables 13 and 14 show adverse events and/or adverse drug reactions occurring in ≥5% of subjects in any treatment group.

Table 13. Adverse events and/or adverse drug reactions occurring in ≥5% of subjects in any treatment group (Trial 4382 [Entire trial population]: Safety analysis set)

Event term	Placebo (N = 101)		Semaglutide 1.7 mg (N = 100)		Semaglutide 2.4 mg (N = 199)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	79.2 (80)	19.8 (20)	82.0 (82)	68.0 (68)	85.9 (171)	54.3 (108)
Nasopharyngitis	17.8 (18)	0 (0)	24.0 (24)	0 (0)	26.6 (53)	0 (0)
Constipation	3.0 (3)	2.0 (2)	19.0 (19)	18.0 (18)	26.1 (52)	24.1 (48)
Nausea	4.0 (4)	4.0 (4)	18.0 (18)	15.0 (15)	17.6 (35)	15.6 (31)
Diarrhoea	5.9 (6)	5.0 (5)	22.0 (22)	19.0 (19)	16.1 (32)	13.1 (26)
Back pain	8.9 (9)	0 (0)	8.0 (8)	0 (0)	9.5 (19)	0 (0)
Vomiting	2.0 (2)	1.0 (1)	10.0 (10)	8.0 (8)	8.5 (17)	7.5 (15)
Dizziness	0 (0)	0 (0)	3.0 (3)	1.0 (1)	7.0 (14)	2.5 (5)
Decreased appetite	0 (0)	0 (0)	5.0 (5)	5.0 (5)	6.5 (13)	6.5 (13)
Abdominal discomfort	1.0 (1)	1.0 (1)	11.0 (11)	9.0 (9)	6.0 (12)	6.0 (12)
Abdominal pain	0 (0)	0 (0)	3.0 (3)	2.0 (2)	6.0 (12)	3.5 (7)
Gastroenteritis	1.0 (1)	0 (0)	7.0 (7)	2.0 (2)	5.5 (11)	1.5 (3)
Upper respiratory tract inflammation	8.9 (9)	0 (0)	5.0 (5)	0 (0)	5.5 (11)	0 (0)
Dental caries	5.0 (5)	0 (0)	4.0 (4)	0 (0)	5.5 (11)	0 (0)
Upper abdominal pain	1.0 (1)	0 (0)	3.0 (3)	3.0 (3)	5.0 (10)	3.5 (7)
Headache	3.0 (3)	0 (0)	2.0 (2)	1.0 (1)	5.0 (10)	1.0 (2)
Dyspepsia	1.0 (1)	1.0 (1)	6.0 (6)	6.0 (6)	4.5 (9)	4.0 (8)
Abdominal distension	2.0 (2)	2.0 (2)	7.0 (7)	7.0 (7)	3.5 (7)	3.0 (6)
Arthralgia	5.9 (6)	0 (0)	9.0 (9)	0 (0)	2.5 (5)	0 (0)

Incidence % (n), MedDRA/J ver.23.1

Table 14. Adverse events and/or adverse drug reactions occurring in ≥5% of subjects in any treatment group (Trial 4382 [Japanese subgroup]: Safety analysis set)

Event term	Placebo (N = 89)		Semaglutide 1.7 mg (N = 91)		Semaglutide 2.4 mg (N = 179)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	78.7 (70)	20.2 (18)	81.3 (74)	67.0 (61)	85.5 (153)	53.1 (95)
Constipation	3.4 (3)	2.2 (2)	19.8 (18)	18.7 (17)	28.5 (51)	26.3 (47)
Nasopharyngitis	16.9 (15)	0 (0)	23.1 (21)	0 (0)	26.8 (48)	0 (0)
Nausea	4.5 (4)	4.5 (4)	17.6 (16)	14.3 (13)	16.2 (29)	14.0 (25)
Diarrhoea	6.7 (6)	5.6 (5)	20.9 (19)	17.6 (16)	14.5 (26)	11.2 (20)
Back pain	9.0 (8)	0 (0)	7.7 (7)	0 (0)	10.1 (18)	0 (0)
Vomiting	2.2 (2)	1.1 (1)	9.9 (9)	7.7 (7)	7.3 (13)	6.1 (11)
Decreased appetite	0 (0)	0 (0)	4.4 (4)	4.4 (4)	6.7 (12)	6.7 (12)
Abdominal discomfort	1.1 (1)	1.1 (1)	12.1 (11)	9.9 (9)	6.1 (11)	6.1 (11)
Gastroenteritis	1.1 (1)	0 (0)	7.7 (7)	2.2 (2)	6.1 (11)	1.7 (3)
Upper respiratory tract inflammation	10.1 (9)	0 (0)	5.5 (5)	0 (0)	6.1 (11)	0 (0)
Dental caries	4.5 (4)	0 (0)	4.4 (4)	0 (0)	6.1 (11)	0 (0)
Abdominal pain upper	1.1 (1)	0 (0)	2.2 (2)	2.2 (2)	5.0 (9)	3.4 (6)
Arthralgia	5.6 (5)	0 (0)	8.8 (8)	0 (0)	2.8 (5)	0 (0)
Abdominal distension	2.2 (2)	2.2 (2)	5.5 (5)	5.5 (5)	2.2 (4)	1.7 (3)

Incidence % (n), MedDRA/J ver.23.1

No deaths[16] were reported. Serious adverse events occurred in 7 subjects (intestinal obstruction; subdural haematoma; radius fracture; atrial fibrillation; ureterolithiasis; rhegmatogenous retinal detachment; and lung neoplasm malignant [all in Japanese subjects]) in the placebo group, 7 subjects (lymphadenitis; dizziness; infectious mononucleosis; and bile duct adenocarcinoma [all in Japanese subjects]; and endometrial hyperplasia; clear cell renal cell carcinoma; and road traffic accident, ligament sprain, and muscle strain) in the semaglutide 1.7 mg group, and 10 subjects (cholelithiasis [2 subjects]; ureterolithiasis and pyelonephritis; acute

16) Assessed based on the data during the period from the date of randomization to the end of trial (date of last contact with trial site).

myocardial infarction; carpal tunnel syndrome; large intestine polyp and acute pyelonephritis; ischaemic colitis; tendon rupture; and Meckel's diverticulitis [all in Japanese subjects]; and rhabdomyolysis) in the semaglutide 2.4 mg group. Those events reported by 2 subjects in the placebo group (intestinal obstruction; and atrial fibrillation) and those event reported by 5 subjects in the semaglutide 2.4 mg group (cholelithiasis [2 subjects]; ureterolithiasis; acute myocardial infarction; and ischaemic colitis) were classified as adverse drug reactions. Adverse events leading to treatment discontinuation occurred in 1 subject (sensory loss [Japanese subject]) in the placebo group, 3 subjects (nausea; and bile duct adenocarcinoma [both in Japanese subjects]; and eructation, dyspepsia, upper abdominal pain, and abdominal distension) in the semaglutide 1.7 mg group, and 5 subjects (nausea, weight decreased, and constipation; nausea and headache; ischaemic colitis; vomiting; and ureterolithiasis and pyelonephritis [all in Japanese subjects]) in the semaglutide 2.4 mg group. Those events reported by 2 subjects in the semaglutide 1.7 mg group (nausea; and eructation, dyspepsia, upper abdominal pain, and abdominal distension) and those events reported by 4 subjects in the semaglutide 2.4 mg group (nausea, weight decreased, and constipation; nausea and headache; ischaemic colitis; and ureterolithiasis) were classified as adverse drug reactions.

The proportions of subjects with positive anti-semaglutide antibodies at any time post-baseline were 1.0% (1 of 100) of subjects in the semaglutide 1.7 mg group and 3.0% (6 of 198) of subjects in the semaglutide 2.4 mg group, and none of them tested positive for neutralizing antibodies.

7.2 Global phase III trial in patients with overweight or obesity (CTD5.3.5.1-3, Trial 4373 [June 2018 to April 2020])

A placebo-controlled, randomized, double-blind, parallel-group trial was conducted to investigate the efficacy and safety of semaglutide as an adjunct to dietary and exercise therapy in patients with overweight or obesity including Japanese patients[17] (target sample size, 1950 subjects[18] [650 in the placebo group, 1300 in the semaglutide 2.4 mg group]) [for pharmacokinetics, see Section "6.2.1.2 Global phase III trial in patients with overweight or obesity"].

The key inclusion criteria were patients with overweight or obesity aged ≥18 years (≥20 years for Japanese patients) fulfilling the following criteria (1) and (2) [(1) BMI ≥27.0 kg/m^2 with hypertension, dyslipidemia, obstructive sleep apnoea, or cardiovascular disease or BMI ≥30.0 kg/m^2 and (2) history of at least one self-reported unsuccessful dietary effort to lose body weight]. Patients were excluded if any of the following criteria applied: history of type 1 or type 2 diabetes; HbA1c ≥6.5% at screening; and previous or planned (during the trial period) obesity treatment with surgery or a weight loss device.

[17] Japan, the US, the UK, Argentina, Canada, Germany, Russia, Belgium, Bulgaria, Denmark, Finland, France, India, Mexico, Poland, and Taiwan

[18] Comparisons between semaglutide 2.4 mg and placebo were made at the two-sided significance level of 5%. The co-primary endpoint of the percent change in body weight from baseline to Week 68 ± SD was assumed to be 12.5 ± 11% in the semaglutide 2.4 mg group and 3 ± 11% in the placebo group, and the other co-primary endpoint of the proportion of subjects achieving ≥5% weight loss at Week 68 was assumed to be 76% in the semaglutide 2.4 mg group and 42% in the placebo group. Given these assumptions, the target sample size of 1950 subjects provided a power of >99% for each co-primary endpoint and an effective power of >99% for the 8 hypotheses in the hierarchical testing procedure. The target sample size was defined to support safety.

The trial consisted of a screening period (1 week), a treatment period (68 weeks), and a follow-up period (7 weeks).

Placebo or semaglutide[14)] 2.4 mg was to be injected subcutaneously in the thigh, abdomen, or upper arm once weekly (self-injection). The starting dose of semaglutide was 0.25 mg, and the dose was to be escalated every 4 weeks to 0.5, 1.0, and 1.7 mg until the target dose of 2.4 mg was reached. If a subject did not tolerate the target dose of 2.4 mg, the subject was allowed to stay at the lower dose level of 1.7 mg.

All of 1961 randomized subjects[19)] (655 in the placebo group [including 33 Japanese subjects], 1306 in the semaglutide 2.4 mg group [including 67 Japanese subjects]) were included in the safety analysis set and in the FAS. The FAS was used for efficacy analyses. There were 112 trial withdrawals (46 in the placebo group, 66 in the semaglutide 2.4 mg group), and the reasons for trial withdrawals were lost to follow up (67 subjects) (28 in the placebo group, 39 in the semaglutide 2.4 mg group [including 1 Japanese subject]), subject's request (43 subjects) (17 in the placebo group, 26 in the semaglutide 2.4 mg group), and death (2 subjects) (1 in the placebo group, 1 in the semaglutide 2.4 mg group).

Table 15 shows the co-primary efficacy endpoints of the percent change in body weight from baseline to Week 68 and the proportion of subjects achieving ≥5% weight loss at Week 68, which demonstrated the superiority of semaglutide 2.4 mg to placebo.

Table 15. Percent change in body weight from baseline to Week 68 and proportion of subjects achieving ≥5% weight loss at Week 68 (Trial 4373: FAS)

Endpoint	Entire trial population		Japanese subgroup	
	Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)	Placebo (N = 33)	Semaglutide 2.4 mg (N = 67)
Body weight at baseline (kg)	105.2 ± 21.5 (N = 655)	105.4 ± 22.1 (N = 1306)	87.9 ± 12.6 (N = 33)	83.4 ± 13.4 (N = 67)
Body weight at Week 68 (kg)	101.9 ± 22.0 (N = 577)	89.0 ± 22.7 (N = 1212)	84.6 ± 13.6 (N = 33)	71.3 ± 16.6 (N = 66)
Percent change in body weight at Week 68 (%)	−2.8 ± 6.5 (N = 577)	−15.6 ± 10.1 (N = 1212)	−3.6 ± 6.4 (N = 33)	−15.2 ± 9.8 (N = 66)
Difference from placebo[a)] [95% CI]	—	−12.44 [d)] [−13.37, −11.51]	—	−10.78 [−14.42, −7.15]
% of subjects losing ≥5% body weight[b)]	31.5 (182/577)	86.4 (1047/1212)	39.4 (13/33)	84.8 (56/66)
Odds ratio relative to placebo[c)] [95% CI]	—	11.22 [d)] [8.88, 14.19]	—	8.36 [3.14, 22.21]

Mean ± SD (Number of evaluable subjects), Proportion % (Number of responders/Number of evaluable subjects);
—, Not applicable
a) Estimated using an ANCOVA model with treatment as a fixed effect and baseline body weight as a covariate after missing values were imputed using a multiple imputation approach.
b) Proportion of subjects achieving ≥5% weight loss from baseline to Week 68 (%)
c) Estimated using a logistic regression with treatment as a fixed effect and baseline body weight as a covariate after missing values were imputed using a multiple imputation approach.
d) Multiplicity was controlled using a hierarchical testing procedure. $P < 0.0001$ with a two-sided significance level of 5%

Figure 2 shows the time course of the percent change in body weight from baseline through Week 68. The results of the key secondary endpoints are shown in Tables 16 and 17.

[19)] Subjects were randomized in a 1:2 ratio to receive placebo or semaglutide 2.4 mg.

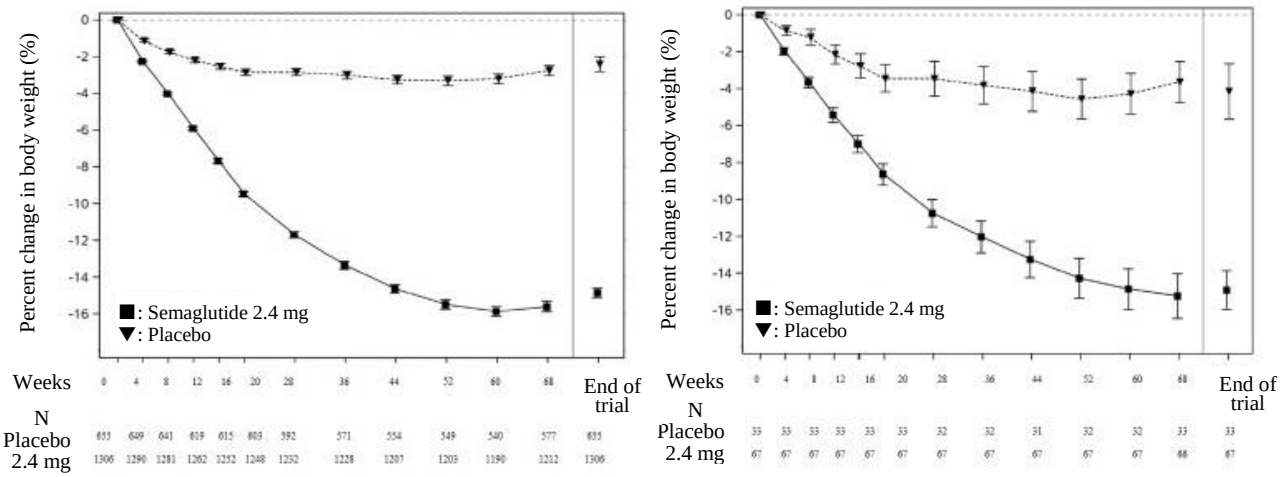

Figure 2. Time course of percent change in body weight from baseline through Week 68
(Left figure: Entire trial population, Right figure: Japanese subgroup) (Mean ± SE, Trial 4373: FAS)

Table 16. Results of body weight-related key secondary endpoints (Trial 4373: FAS)

Endpoint		Entire trial population		Japanese subgroup	
		Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)	Placebo (N = 33)	Semaglutide 2.4 mg (N = 67)
% of subjects achieving weight loss[a)]	≥10%	12.0 (69/577)	69.1 (838/1212)	18.2 (6/33)	69.7 (46/66)
	≥15%	4.9 (28/577)	50.5 (612/1212)	6.1 (2/33)	51.5 (34/66)
Waist circumference[b)] (cm)	Baseline	114.8 ± 14.4 (N = 655)	114.6 ± 14.8 (N = 1306)	103.7 ± 8.6 (N = 33)	102.6 ± 9.2 (N = 67)
	Change at Week 68	−4.4 ± 6.9 (N = 575)	−14.1 ± 9.6 (N = 1210)	−3.7 ± 5.0 (N = 33)	−12.4 ± 8.5 (N = 66)
BMI (kg/m^2)	Baseline	38.0 ± 6.5 (N = 655)	37.8 ± 6.7 (N = 1306)	32.1 ± 3.8 (N = 33)	31.1 ± 3.8 (N = 67)
	Change at Week 68	−1.0 ± 2.5 (N = 577)	−5.8 ± 3.8 (N = 1212)	−1.2 ± 2.2 (N = 33)	−4.7 ± 3.0 (N = 66)

Mean ± SD (Number of evaluable subjects), Proportion % (Number of responders/Number of evaluable subjects)
a) Proportion of subjects achieving a weight loss of ≥10% or ≥15% from baseline to Week 68 (%)
b) Waist circumference (cm) measured midway between the lower rib margin and the iliac crest

Table 17. Results of blood glucose, blood pressure, and lipid parameters-related key secondary endpoints (Trial 4373: FAS)

Endpoint		Entire trial population		Japanese subgroup	
		Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)	Placebo (N = 33)	Semaglutide 2.4 mg (N = 67)
HbA1c (%)	Baseline	5.7 ± 0.3 (N = 655)	5.7 ± 0.3 (N = 1306)	5.8 ± 0.3 (N = 33)	5.8 ± 0.3 (N = 67)
	Change at Week 68	−0.2 ± 0.3 (N = 563)	−0.5 ± 0.3 (N = 1197)	−0.2 ± 0.2 (N = 33)	−0.6 ± 0.2 (N = 66)
Fasting plasma glucose (mg/dL)	Baseline	94.7 ± 10.5 (N = 649)	95.4 ± 10.7 (N = 1291)	99.5 ± 7.7 (N = 33)	100.1 ± 9.3 (N = 67)
	Change at Week 68	−0.4 ± 12.7 (N = 557)	−9.2 ± 10.9 (N = 1175)	−2.2 ± 8.1 (N = 33)	−13.9 ± 8.5 (N = 65)
Systolic blood pressure (mmHg)	Baseline	127 ± 14 (N = 655)	126 ± 14 (N = 1306)	125 ± 14 (N = 33)	127 ± 13 (N = 67)
	Change at Week 68	−1 ± 13 (N = 574)	−7 ± 14 (N = 1210)	−1 ± 14 (N = 33)	−9 ± 13 (N = 66)
Diastolic blood pressure (mmHg)	Baseline	80 ± 10 (N = 655)	80 ± 10 (N = 1306)	77 ± 12 (N = 33)	81 ± 11 (N = 67)
	Change at Week 68	−1 ± 9 (N = 574)	−3 ± 9 (N = 1210)	1 ± 9 (N = 33)	−3 ± 11 (N = 66)
Total cholesterol (mg/dL)	Baseline	195.8 ± 39.0 (N = 649)	193.4 ± 38.7 (N = 1301)	209.7 ± 34.4 (N = 33)	207.6 ± 34.8 (N = 67)
	Percent change at Week 68 (%)	1.3 ± 15.0 (N = 561)	−2.6 ± 14.8 (N = 1196)	3.0 ± 12.4 (N = 33)	−8.7 ± 9.8 (N = 66)
LDL cholesterol (mg/dL)	Baseline	117.14 ± 33.33 (N = 648)	115.30 ± 33.23 (N = 1300)	123.36 ± 27.89 (N = 33)	123.40 ± 32.29 (N = 67)
	Percent change at Week 68 (%)	4.4 ± 25.9 (N = 558)	0.0 ± 28.1 (N = 1192)	8.2 ± 17.4 (N = 33)	−10.4 ± 16.5 (N = 66)
HDL cholesterol (mg/dL)	Baseline	51.0 ± 12.7 (N = 648)	51.0 ± 13.2 (N = 1300)	54.4 ± 12.4 (N = 33)	54.4 ± 12.8 (N = 67)
	Percent change at Week 68 (%)	3.0 ± 15.5 (N = 558)	6.6 ± 17.2 (N = 1192)	4.6 ± 17.6 (N = 33)	9.7 ± 17.5 (N = 66)
Triglycerides (mg/dL)	Baseline	146.36 ± 131.68 (N = 649)	140.99 ± 80.54 (N = 1300)	165.05 ± 87.94 (N = 33)	157.70 ± 92.21 (N = 67)
	Percent change at Week 68 (%)	−2.8 ± 33.9 (N = 561)	−17.5 ± 32.1 (N = 1194)	−9.4 ± 36.9 (N = 33)	−25.9 ± 28.9 (N = 66)

Mean ± SD (Number of evaluable subjects)

Tables 18 and 19 show adverse events and/or adverse drug reactions occurring in ≥5% of subjects in either treatment group.

Table 18. Adverse events and/or adverse drug reactions occurring in ≥5% of subjects in either treatment group (Trial 4373 [Entire trial population]: Safety analysis set)

Event term	Placebo (N = 655)		Semaglutide 2.4 mg (N = 1306)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	86.4 (566)	45.0 (295)	89.7 (1171)	70.9 (926)
Nausea	17.4 (114)	15.3 (100)	44.2 (577)	42.1 (550)
Diarrhoea	15.9 (104)	12.5 (82)	31.5 (412)	27.5 (359)
Vomiting	6.6 (43)	5.0 (33)	24.8 (324)	21.7 (283)
Constipation	9.5 (62)	7.5 (49)	23.4 (306)	19.8 (259)
Nasopharyngitis	20.3 (133)	0.2 (1)	21.5 (281)	0.3 (4)
Headache	12.2 (80)	4.1 (27)	15.2 (198)	6.6 (86)
Dyspepsia	3.5 (23)	2.7 (18)	10.3 (135)	9.4 (123)
Abdominal pain	5.5 (36)	3.2 (21)	10.0 (130)	8.0 (105)
Upper abdominal pain	5.3 (35)	3.8 (25)	9.6 (125)	7.9 (103)
Decreased appetite	3.4 (22)	3.2 (21)	9.5 (124)	9.2 (120)
Upper respiratory tract infection	12.2 (80)	0.3 (2)	8.7 (114)	0.2 (3)
Eructation	0.5 (3)	0.5 (3)	8.6 (112)	8.3 (108)
Back pain	8.2 (54)	0.3 (2)	8.2 (107)	0.2 (2)
Fatigue	4.3 (28)	2.0 (13)	8.0 (104)	4.3 (56)
Dizziness	3.5 (23)	1.5 (10)	7.5 (98)	4.1 (53)
Abdominal distension	4.7 (31)	4.1 (27)	7.4 (96)	6.6 (86)
Influenza	9.6 (63)	0.5 (3)	6.8 (89)	0.7 (9)
Gastroenteritis	4.6 (30)	2.1 (14)	6.5 (85)	2.4 (31)
Gastrooesophageal reflux disease	3.1 (20)	2.4 (16)	6.3 (82)	5.0 (65)
Arthralgia	6.6 (43)	0.3 (2)	6.2 (81)	0.2 (2)
Sinusitis	5.5 (36)	0.2 (1)	5.4 (71)	<0.1 (1)
Urinary tract infection	4.3 (28)	0 (0)	5.2 (68)	0 (0)
Flatulence	3.2 (21)	3.1 (20)	5.0 (65)	4.4 (58)
Cough	5.0 (33)	0 (0)	3.1 (40)	<0.1 (1)

Incidence % (n), MedDRA/J ver.22.1

Table 19. Adverse events and/or adverse drug reactions occurring in ≥5% of subjects in either treatment group (Trial 4373 [Japanese subgroup]: Safety analysis set)

Event term	Placebo (N = 33)		Semaglutide 2.4 mg (N = 67)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	90.9 (30)	27.3 (9)	88.1 (59)	52.2 (35)
Nasopharyngitis	33.3 (11)	0 (0)	35.8 (24)	0 (0)
Nausea	6.1 (2)	3.0 (1)	19.4 (13)	19.4 (13)
Constipation	9.1 (3)	6.1 (2)	16.4 (11)	11.9 (8)
Diarrhoea	12.1 (4)	3.0 (1)	13.4 (9)	7.5 (5)
Vomiting	3.0 (1)	0 (0)	10.4 (7)	6.0 (4)
Headache	9.1 (3)	3.0 (1)	10.4 (7)	1.5 (1)
Decreased appetite	0 (0)	0 (0)	9.0 (6)	7.5 (5)
Gastroenteritis	6.1 (2)	3.0 (1)	9.0 (6)	1.5 (1)
Abdominal discomfort	0 (0)	0 (0)	7.5 (5)	7.5 (5)
Influenza	6.1 (2)	0 (0)	7.5 (5)	0 (0)
Upper respiratory tract inflammation	12.1 (4)	0 (0)	7.5 (5)	0 (0)
Malaise	0 (0)	0 (0)	6.0 (4)	1.5 (1)
Pharyngitis	6.1 (2)	0 (0)	4.5 (3)	0 (0)
Back pain	15.2 (5)	0 (0)	3.0 (2)	0 (0)
Dental caries	18.2 (6)	0 (0)	1.5 (1)	0 (0)
Accidental overdose	6.1 (2)	0 (0)	1.5 (1)	0 (0)
Blood creatine phosphokinase increased	6.1 (2)	0 (0)	1.5 (1)	0 (0)
Osteoarthritis	6.1 (2)	0 (0)	0 (0)	0 (0)

Incidence % (n), MedDRA/J ver.22.1

One subject in the placebo group (glioblastoma, sepsis, and pneumonia aspiration) and 1 subject in the semaglutide 2.4 mg group (death) died,[16)] but a causal relationship to trial drug was denied for all those events. The incidences of serious adverse events were 6.4% (42 of 655) of subjects in the placebo group and 9.8% (128 of 1306) of subjects in the semaglutide 2.4 mg group. Those events reported by 4 subjects in the placebo group (weight increased; hypersensitivity; cholelithiasis; and toxoplasmosis) and those events reported by 27 subjects in the semaglutide 2.4 mg group (gastroenteritis [4 subjects]; acute cholecystitis [2 subjects]; atrial

tachycardia; cholecystitis; diarrhoea and vomiting; urinary calculus; bile duct stone; lipase increased; pyelonephritis; hypertransaminasaemia; lower abdominal pain, vomiting, and cholelithiasis; hiatus hernia; vomiting; gastrointestinal stromal tumour; vertigo; abdominal pain; ischaemic colitis [Japanese subject]; cholelithiasis; large intestine perforation and constipation; nausea, vomiting, colitis, and pancreatitis acute; non-cardiac chest pain; bacterial colitis; and enteritis) were classified as adverse drug reactions. The incidences of adverse events leading to treatment discontinuation were 3.1% (20 of 655) of subjects in the placebo group and 7.0% (92 of 1306) of subjects in the semaglutide 2.4 mg group. Those events reported by 8 subjects in the placebo group (upper abdominal pain; nausea; colitis; lymphadenopathy; urticaria [Japanese subject]; suicidal ideation; agitation; and abdominal discomfort) and those events reported by 77 subjects in the semaglutide 2.4 mg group (nausea [13 subjects]; vomiting [8 subjects]; diarrhoea [4 subjects]; constipation [3 subjects]; dyspepsia [3 subjects]; decreased appetite [3 subjects (including 1 Japanese subject)]; upper abdominal pain [3 subjects]; eructation [2 subjects]; impaired gastric emptying [2 subjects]; nausea and vomiting [2 subjects]; asthenia [2 subjects]; alopecia [2 subjects]; irritability; injection related reaction; lipase increased and cholelithiasis; nausea, diarrhoea, and vomiting; diarrhoea and abdominal pain; headache, diarrhoea, nausea, upper abdominal pain, depressed mood, and visual impairment; migraine and vomiting; hepatic enzyme increased; rash; hiatus hernia; diarrhoea and abdominal distension; gastroenteritis, gastritis, and nausea; gastroenteritis; essential hypertension; ischaemic colitis [Japanese subject]; muscle spasms and muscular weakness; vertigo; depression; anxiety; cholelithiasis; lethargy; gastrooesophageal reflux disease; large intestine perforation; nausea and gastritis; nausea, vomiting, upper abdominal pain, and diarrhoea; nausea, upper abdominal pain, and constipation; nausea, vomiting, colitis, and pancreatitis acute; fatigue; dysgeusia and vomiting; and abdominal discomfort) were classified as adverse drug reactions.

The proportion of subjects with positive anti-semaglutide antibodies at any time post-baseline was 2.9% (38 of 1304) of subjects in the semaglutide 2.4 mg group, and none of them tested positive for neutralizing antibodies.

7.3 Global phase III trial in patients with overweight or obesity and type 2 diabetes (CTD5.3.5.1-4, Trial 4374 [June 2018 to May 2020])

A placebo-controlled, randomized, double-blind, parallel-group trial was conducted to investigate the efficacy and safety of semaglutide as an adjunct to dietary and exercise therapy in patients with overweight or obesity and type 2 diabetes including Japanese patients[20] (target sample size, 1200 subjects[21] [400 each in the placebo, semaglutide 1.0 mg, and semaglutide 2.4 mg groups]) [for pharmacokinetics, see Section "6.2.1.3 Global phase III trial in patients with overweight or obesity and type 2 diabetes"].

[20] Japan, the US, the UK, Argentina, Canada, Germany, Greece, India, Russia, South Africa, Spain, and United Arab Emirates

[21] Comparisons between semaglutide 2.4 mg and placebo were made at the two-sided significance level of 5%. The co-primary endpoint of the percent change in body weight from baseline to Week 68 ± SD was assumed to be 10.2 ± 11% in the semaglutide 2.4 mg group and 1.7 ± 11% in the placebo group, and the other co-primary endpoint of the proportion of subjects achieving ≥5% weight loss at Week 68 was assumed to be 69% in the semaglutide 2.4 mg group and 37% in the placebo group. Given these assumptions, the target sample size of 1200 subjects provided a power of >99% for each co-primary endpoint and an effective power of 94% for the 10 hypotheses in the hierarchical testing procedure. The target sample size was defined to support safety.

The key inclusion criteria were patients with overweight or obesity aged ≥18 years (≥20 years for Japanese patients) fulfilling the following criteria (1) to (3) [(1) BMI ≥27.0 kg/m^2, (2) diagnosed with type 2 diabetes[22)] ≥180 days prior to the day of screening and HbA1c of 7.0% to 10.0%, and (3) history of at least one self-reported unsuccessful dietary effort to lose body weight]. Patients were excluded if the following criteria applied: previous or planned (during the trial period) obesity treatment with surgery or a weight loss device.

The trial consisted of a screening period (1 week), a treatment period (68 weeks), and a follow-up period (7 weeks).

Placebo, semaglutide 1.0 mg, or semaglutide 2.4 mg[14)] was to be injected subcutaneously in the thigh, abdomen, or upper arm once weekly (self-injection). The starting dose of semaglutide was 0.25 mg, and the dose was to be escalated every 4 weeks to 0.5 and 1.0 mg in the semaglutide 1.0 mg group or to 0.5, 1.0, 1.7, and 2.4 mg in the semaglutide 2.4 mg group. If a subject did not tolerate the target dose of 1.0 or 2.4 mg, the subject was allowed to stay at a lower dose level.

All of 1210 randomized subjects (403 in the placebo group [including 47 Japanese subjects], 403 in the semaglutide 1.0 mg group [including 36 Japanese subjects], 404 in the semaglutide 2.4 mg group [including 42 Japanese subjects]) were included in the FAS, and the FAS was used for efficacy analyses. In the FAS, all of 1207 subjects who received trial drug (402 in the placebo group [including 47 Japanese subjects], 402 in the semaglutide 1.0 mg group [including 36 Japanese subjects], 403 in the semaglutide 2.4 mg group [including 42 Japanese subjects]) were included in the safety analysis set. There were 46 trial withdrawals (20 in the placebo group, 13 in the semaglutide 1.0 mg group, 13 in the semaglutide 2.4 mg group), and the reasons for trial withdrawals were subject's request (27 subjects) (12 in the placebo group, 10 in the semaglutide 1.0 mg group, 5 in the semaglutide 2.4 mg group), lost to follow up (16 subjects) (7 in the placebo group, 2 in the semaglutide 1.0 mg group, 7 in the semaglutide 2.4 mg group), and death (3 subjects) (1 in the placebo group, 1 in the semaglutide 1.0 mg group, 1 in the semaglutide 2.4 mg group).

Table 20 shows the co-primary efficacy endpoints of the percent change in body weight from baseline to Week 68 and the proportion of subjects achieving ≥5% weight loss at Week 68, which demonstrated the superiority of semaglutide 2.4 mg to placebo.

[22)] Patients treated with either diet and exercise alone or stable treatment with up to 3 oral antidiabetic drugs (metformin, SU, SGLT2 inhibitors, or thiazolidinediones) for ≥90 days prior to screening were allowed to be enrolled in the trial.

Table 20. Percent change in body weight from baseline to Week 68 and proportion of subjects achieving ≥5% weight loss at Week 68 (Trial 4374: FAS)

Endpoint	Entire trial population			Japanese subgroup		
	Placebo (N = 403)	Semaglutide 1.0 mg (N = 403)	Semaglutide 2.4 mg (N = 404)	Placebo (N = 47)	Semaglutide 1.0 mg (N = 36)	Semaglutide 2.4 mg (N = 42)
Body weight at baseline (kg)	100.5 ± 20.9 (N = 403)	99.0 ± 21.1 (N = 403)	99.9 ± 22.5 (N = 404)	89.9 ± 16.2 (N = 47)	91.6 ± 19.4 (N = 36)	86.3 ± 16.8 (N = 42)
Body weight at Week 68 (kg)	96.8 ± 20.3 (N = 376)	92.3 ± 20.7 (N = 380)	89.6 ± 21.0 (N = 388)	87.2 ± 15.6 (N = 47)	85.7 ± 19.1 (N = 36)	77.6 ± 17.8 (N = 42)
Percent change in body weight at Week 68 (%)	−3.3 ± 5.5 (N = 376)	−7.2 ± 6.6 (N = 380)	−9.9 ± 8.0 (N = 388)	−2.9 ± 3.5 (N = 47)	−6.3 ± 6.4 (N = 36)	−10.4 ± 7.0 (N = 42)
Difference from placebo[a] [95% CI]	—	—	−6.21[d] [−7.28, −5.15]	—	—	−7.31 [−9.65, −4.96]
Difference from semaglutide 1.0 mg[a] [95% CI]	—	—	−2.65 [−3.66, −1.64]	—	—	−3.39 [−5.95, −0.82]
% of subjects losing ≥5% body weight[b]	28.5 (107/376)	57.1 (217/380)	68.8 (267/388)	23.4 (11/47)	55.6 (20/36)	71.4 (30/42)
Odds ratio relative to placebo[c] [95% CI]	—	—	4.88[d] [3.58, 6.64]	—	—	8.59 [3.20, 23.04]
Odds ratio relative to semaglutide 1.0 mg[c] [95% CI]	—	—	1.62 [1.21, 2.18]	—	—	1.70 [0.63, 4.59]

Mean ± SD (Number of evaluable subjects), Proportion % (Number of responders/Number of evaluable subjects); —, Not applicable

a) Estimated using an ANCOVA model with treatment, OAD treatment, HbA1c category at screening (<8.5%, ≥8.5%), and interaction between OAD treatment and HbA1c category at screening (<8.5%, ≥8.5%) as fixed effects and baseline body weight as a covariate after missing values were imputed using a multiple imputation approach.

b) Proportion of subjects achieving ≥5% weight loss from baseline to Week 68 (%)

c) Estimated using a logistic regression with treatment, ODA treatment, HbA1c category at screening (<8.5%, ≥8.5%), and interaction between OAD treatment and HbA1c category at screening (<8.5%, ≥8.5%) as fixed effects and baseline body weight as a covariate after missing values were imputed using a multiple imputation approach.

d) Multiplicity was controlled using a hierarchical testing procedure. $P < 0.0001$ with a two-sided significance level of 5%

Figure 3 shows the time course of the percent change in body weight from baseline through Week 68. The results of the key secondary endpoints are shown in Tables 21 and 22.

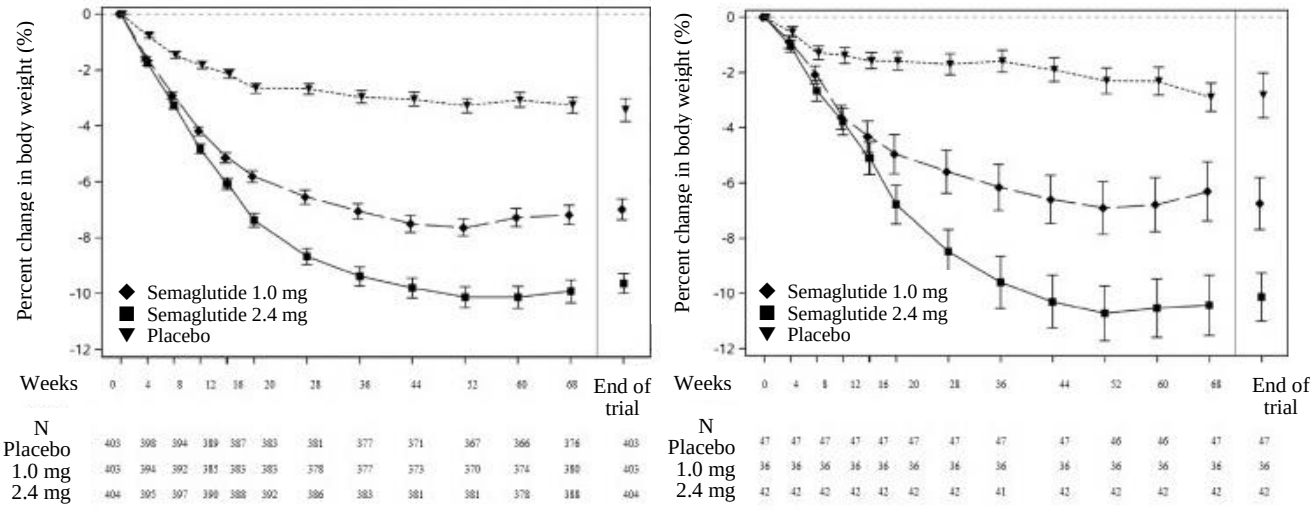

Figure 3. Time course of percent change in body weight from baseline through Week 68
(Left figure, Entire trial population; Right figure, Japanese subgroup) (Mean ± SE, Trial 4374: FAS)

Table 21. Results of body weight-related key secondary endpoints (Trial 4374: FAS)

Endpoint		Entire trial population			Japanese subgroup		
		Placebo (N = 403)	Semaglutide 1.0 mg (N = 403)	Semaglutide 2.4 mg (N = 404)	Placebo (N = 47)	Semaglutide 1.0 mg (N = 36)	Semaglutide 2.4 mg (N = 42)
% of subjects achieving weight loss[a)]	≥10%	8.2 (31/376)	28.7 (109/380)	45.6 (177/388)	4.3 (2/47)	16.7 (6/36)	42.9 (18/42)
	≥15%	3.2 (12/376)	13.7 (52/380)	25.8 (100/388)	0 (0/47)	11.1 (4/36)	26.2 (11/42)
Waist circumference[b)] (cm)	Baseline	115.5 ± 13.9 (N = 403)	113.9 ± 14.0 (N = 403)	114.5 ± 14.3 (N = 404)	107.8 ± 10.2 (N = 47)	107.1 ± 12.7 (N = 36)	104.0 ± 10.2 (N = 42)
	Change at Week 68	−4.3 ± 6.5 (N = 375)	−6.9 ± 6.8 (N = 380)	−9.7 ± 8.1 (N = 387)	−3.5 ± 3.9 (N = 47)	−6.0 ± 5.6 (N = 36)	−8.7 ± 6.1 (N = 42)
BMI (kg/m^2)	Baseline	35.9 ± 6.5 (N = 403)	35.3 ± 5.9 (N = 403)	35.9 ± 6.4 (N = 404)	32.2 ± 4.3 (N = 47)	32.7 ± 6.2 (N = 36)	31.7 ± 4.0 (N = 42)
	Change at Week 68	−1.2 ± 2.1 (N = 376)	−2.6 ± 2.4 (N = 380)	−3.6 ± 3.1 (N = 388)	−1.0 ± 1.2 (N = 47)	−2.1 ± 2.0 (N = 36)	−3.2 ± 2.1 (N = 42)

Mean ± SD (Number of evaluable subjects), Proportion % (Number of responders/Number of evaluable subjects)
a) Proportion of subjects achieving a weight loss of ≥10% or ≥15% from baseline to Week 68 (%)
b) Waist circumference (cm) measured midway between the lower rib margin and the iliac crest

Table 22. Results of blood glucose, blood pressure, and lipid parameters-related key secondary endpoints (Trial 4374: FAS)

Endpoint		Entire trial population			Japanese subgroup		
		Placebo (N = 403)	Semaglutide 1.0 mg (N = 403)	Semaglutide 2.4 mg (N = 404)	Placebo (N = 47)	Semaglutide 1.0 mg (N = 36)	Semaglutide 2.4 mg (N = 42)
HbA1c (%)	Baseline	8.1 ± 0.8 (N = 403)	8.1 ± 0.8 (N = 403)	8.1 ± 0.8 (N = 404)	7.9 ± 0.8 (N = 47)	8.2 ± 0.6 (N = 36)	8.0 ± 0.6 (N = 42)
	Change at Week 68	−0.3 ± 1.3 (N = 374)	−1.5 ± 1.1 (N = 376)	−1.7 ± 1.2 (N = 381)	−0.3 ± 1.0 (N = 47)	−1.9 ± 0.9 (N = 36)	−2.0 ± 0.7 (N = 42)
Fasting plasma glucose (mg/dL)	Baseline	157.9 ± 42.1 (N = 400)	155.7 ± 41.5 (N = 395)	152.7 ± 40.9 (N = 396)	140.5 ± 25.0 (N = 47)	148.5 ± 23.2 (N = 36)	144.1 ± 27.5 (N = 42)
	Change at Week 68	−2.3 ± 53.1 (N = 370)	−36.5 ± 45.1 (N = 367)	−37.9 ± 45.9 (N = 375)	−2.3 ± 32.7 (N = 47)	−40.6 ± 28.3 (N = 36)	−41.9 ± 24.8 (N = 42)
Systolic blood pressure (mmHg)	Baseline	130 ± 13 (N = 403)	130 ± 14 (N = 403)	130 ± 13 (N = 404)	131 ± 11 (N = 47)	129 ± 15 (N = 36)	132 ± 12 (N = 42)
	Change at Week 68	0 ± 15 (N = 376)	−3 ± 15 (N = 379)	−4 ± 14 (N = 387)	−3 ± 14 (N = 47)	−6 ± 16 (N = 36)	−5 ± 13 (N = 42)
Diastolic blood pressure (mmHg)	Baseline	80 ± 9 (N = 403)	80 ± 9 (N = 403)	80 ± 9 (N = 404)	82 ± 11 (N = 47)	81 ± 9 (N = 36)	81 ± 10 (N = 42)
	Change at Week 68	−1 ± 9 (N = 376)	−1 ± 9 (N = 379)	−2 ± 9 (N = 387)	−1 ± 8 (N = 47)	−2 ± 9 (N = 36)	−2 ± 8 (N = 42)
Total cholesterol (mg/dL)	Baseline	175.4 ± 40.8 (N = 402)	177.0 ± 42.5 (N = 399)	175.1 ± 38.8 (N = 402)	177.2 ± 27.9 (N = 47)	193.7 ± 37.7 (N = 36)	188.1 ± 32.3 (N = 42)
	Percent change at Week 68 (%)	1.8 ± 19.0 (N = 373)	−1.2 ± 19.6 (N = 372)	0.2 ± 18.4 (N = 380)	4.7 ± 13.5 (N = 47)	−4.3 ± 12.3 (N = 36)	−5.4 ± 13.6 (N = 42)
LDL cholesterol (mg/dL)	Baseline	95.87 ± 33.35 (N = 402)	96.60 ± 35.90 (N = 399)	95.87 ± 33.23 (N = 402)	98.14 ± 24.13 (N = 47)	111.03 ± 33.16 (N = 36)	102.22 ± 28.29 (N = 42)
	Percent change at Week 68 (%)	4.5 ± 28.5 (N = 369)	11.2 ± 170.1 (N = 372)	4.8 ± 32.5 (N = 376)	9.9 ± 21.2 (N = 47)	−0.6 ± 20.8 (N = 36)	−0.4 ± 27.4 (N = 42)
HDL cholesterol (mg/dL)	Baseline	45.1 ± 11.4 (N = 402)	44.2 ± 10.9 (N = 399)	46.0 ± 10.8 (N = 402)	51.0 ± 13.6 (N = 47)	51.1 ± 10.5 (N = 36)	53.9 ± 9.7 (N = 42)
	Percent change at Week 68 (%)	5.1 ± 16.3 (N = 369)	7.1 ± 18.2 (N = 372)	8.2 ± 17.0 (N = 375)	3.7 ± 11.2 (N = 47)	2.1 ± 13.7 (N = 36)	5.5 ± 16.4 (N = 42)
Triglycerides (mg/dL)	Baseline	181.70 ± 105.21 (N = 402)	196.74 ± 136.93 (N = 399)	177.67 ± 111.72 (N = 402)	150.56 ± 83.24 (N = 47)	161.71 ± 69.01 (N = 36)	163.08 ± 94.93 (N = 42)
	Percent change at Week 68 (%)	1.7 ± 57.3 (N = 373)	−12.3 ± 35.6 (N = 372)	−14.0 ± 40.5 (N = 380)	−6.5 ± 29.9 (N = 47)	−20.8 ± 26.9 (N = 36)	−25.7 ± 26.3 (N = 42)

Mean ± SD (Number of evaluable subjects)

Tables 23 and 24 show adverse events and/or adverse drug reactions occurring in ≥5% of subjects in any treatment group.

Table 23. Adverse events and/or adverse drug reactions occurring in ≥5% of subjects in any treatment group
(Trial 4374 [Entire trial population]: Safety analysis set)

Event term	Placebo (N = 402)		Semaglutide 1.0 mg (N = 402)		Semaglutide 2.4 mg (N = 403)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	76.9 (309)	32.1 (129)	81.8 (329)	55.2 (222)	87.6 (353)	63.8 (257)
Nausea	9.2 (37)	6.7 (27)	32.1 (129)	31.8 (128)	33.7 (136)	33.3 (134)
Vomiting	2.7 (11)	1.5 (6)	13.4 (54)	12.2 (49)	21.8 (88)	19.1 (77)
Diarrhoea	11.9 (48)	7.7 (31)	22.1 (89)	17.9 (72)	21.3 (86)	16.9 (68)
Constipation	5.5 (22)	4.5 (18)	12.7 (51)	10.0 (40)	17.4 (70)	13.9 (56)
Nasopharyngitis	14.7 (59)	0 (0)	11.7 (47)	0.2 (1)	16.9 (68)	0 (0)
Upper respiratory tract infection	9.5 (38)	0.2 (1)	9.2 (37)	0 (0)	10.4 (42)	0 (0)
Decreased appetite	3.7 (15)	3.2 (13)	7.2 (29)	7.0 (28)	9.4 (38)	9.4 (38)
Headache	5.0 (20)	1.0 (4)	8.2 (33)	2.7 (11)	7.7 (31)	3.0 (12)
Fatigue	1.0 (4)	0.5 (2)	4.7 (19)	4.0 (16)	6.9 (28)	4.0 (16)
Back pain	3.5 (14)	0 (0)	7.0 (28)	0.2 (1)	6.7 (27)	0.5 (2)
Dyspepsia	1.2 (5)	0.7 (3)	6.7 (27)	5.5 (22)	6.2 (25)	5.7 (23)
Abdominal distension	2.7 (11)	2.0 (8)	2.2 (9)	2.2 (9)	6.0 (24)	5.5 (22)
Arthralgia	5.0 (20)	0 (0)	6.0 (24)	0.2 (1)	5.7 (23)	0 (0)
Flatulence	1.7 (7)	1.2 (5)	5.2 (21)	4.7 (19)	4.0 (16)	3.0 (12)
Gastroenteritis	3.2 (13)	0.7 (3)	6.0 (24)	1.0 (4)	3.5 (14)	2.0 (8)

Incidence % (n), MedDRA/J ver.22.1

Table 24. Adverse events and/or adverse drug reactions occurring in ≥5% of subjects in any treatment group
(Trial 4374 [Japanese subgroup]: Safety analysis set)

Event term	Placebo (N = 47)		Semaglutide 1.0 mg (N = 36)		Semaglutide 2.4 mg (N = 42)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	80.9 (38)	36.2 (17)	91.7 (33)	55.6 (20)	83.3 (35)	52.4 (22)
Nasopharyngitis	42.6 (20)	0 (0)	41.7 (15)	0 (0)	52.4 (22)	0 (0)
Constipation	4.3 (2)	2.1 (1)	13.9 (5)	11.1 (4)	31.0 (13)	26.2 (11)
Diarrhoea	25.5 (12)	17.0 (8)	11.1 (4)	11.1 (4)	14.3 (6)	4.8 (2)
Diabetic retinopathy	6.4 (3)	0 (0)	5.6 (2)	0 (0)	14.3 (6)	2.4 (1)
Back pain	4.3 (2)	0 (0)	5.6 (2)	0 (0)	14.3 (6)	2.4 (1)
Nausea	4.3 (2)	4.3 (2)	22.2 (8)	22.2 (8)	11.9 (5)	11.9 (5)
Vomiting	6.4 (3)	0 (0)	5.6 (2)	5.6 (2)	11.9 (5)	9.5 (4)
Abdominal discomfort	4.3 (2)	4.3 (2)	13.9 (5)	13.9 (5)	9.5 (4)	9.5 (4)
Decreased appetite	0 (0)	0 (0)	11.1 (4)	8.3 (3)	9.5 (4)	9.5 (4)
Gastrooesophageal reflux disease	6.4 (3)	0 (0)	0 (0)	0 (0)	7.1 (3)	2.4 (1)
Gastroenteritis	4.3 (2)	0 (0)	13.9 (5)	0 (0)	4.8 (2)	4.8 (2)
Influenza	12.8 (6)	0 (0)	5.6 (2)	0 (0)	4.8 (2)	0 (0)
Dry eye	0 (0)	0 (0)	5.6 (2)	0 (0)	4.8 (2)	0 (0)
Gallbladder polyp	0 (0)	0 (0)	5.6 (2)	0 (0)	4.8 (2)	0 (0)
Dental caries	6.4 (3)	0 (0)	2.8 (1)	0 (0)	4.8 (2)	0 (0)
Arthralgia	6.4 (3)	0 (0)	0 (0)	0 (0)	4.8 (2)	0 (0)
Headache	6.4 (3)	0 (0)	2.8 (1)	0 (0)	2.4 (1)	2.4 (1)
Cystitis	0 (0)	0 (0)	5.6 (2)	0 (0)	2.4 (1)	0 (0)
Gastric polyps	4.3 (2)	0 (0)	5.6 (2)	0 (0)	2.4 (1)	0 (0)
Accidental overdose	2.1 (1)	0 (0)	5.6 (2)	2.8 (1)	2.4 (1)	0 (0)
Upper respiratory tract infection	2.1 (1)	0 (0)	5.6 (2)	0 (0)	0 (0)	0 (0)
Upper abdominal pain	2.1 (1)	2.1 (1)	5.6 (2)	2.8 (1)	0 (0)	0 (0)
Muscle spasms	0 (0)	0 (0)	5.6 (2)	0 (0)	0 (0)	0 (0)
Genital candidiasis	0 (0)	0 (0)	5.6 (2)	0 (0)	0 (0)	0 (0)
Pharyngitis	8.5 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Oral herpes	0 (0)	0 (0)	5.6 (2)	0 (0)	0 (0)	0 (0)

Incidence % (n), MedDRA/J ver.22.1

One subject in the placebo group (hepatocellular carcinoma, pulmonary embolism, and respiratory failure), 1 subject in the semaglutide 1.0 mg group (cardio-respiratory arrest), and 1 subject in the semaglutide 2.4 mg group (myocardial infarction) died,[16)] but a causal relationship to trial drug was denied for all those events. The incidences of serious adverse events were 9.2% (37 of 402) of subjects in the placebo group, 7.7% (31 of 402) of subjects in the semaglutide 1.0 mg group, and 9.9% (40 of 403) of subjects in the semaglutide 2.4 mg group. Those events reported by 3 subjects in the placebo group (gastroenteritis; diverticulitis, colonic abscess, and

diverticular perforation; and acute cholecystitis), those events reported by 3 subjects in the semaglutide 1.0 mg group (abdominal pain, nausea, decreased appetite, gastrointestinal stromal tumour, and gastric ulcer; cholelithiasis; and diarrhoea, gastroenteritis, nausea, and abdominal pain), and those events reported by 10 subjects in the semaglutide 2.4 mg group (gastroenteritis [2 subjects]; atrial fibrillation; supraventricular tachycardia; gastritis; small intestinal obstruction; ketoacidosis; chronic cholecystitis; post procedural haemorrhage; and viral infection, hyperaesthesia, and dehydration) were classified as adverse drug reactions. The incidences of adverse events leading to treatment discontinuation were 3.5% (14 of 402) of subjects in the placebo group, 5.0% (20 of 402) of subjects in the semaglutide 1.0 mg group, and 6.2% (25 of 403) of subjects in the semaglutide 2.4 mg group. Those events reported by 9 subjects in the placebo group (drug eruption [2 subjects]; pyrexia, dyspepsia, and diarrhoea; mood altered; abdominal distension; ageusia; nausea, diarrhoea, and dizziness; Barrett's oesophagus; and diverticulitis), those events reported by 17 subjects in the semaglutide 1.0 mg group (nausea [4 subjects]; vomiting [2 subjects]; gastrooesophageal reflux disease [2 subjects]; diabetic retinopathy; dyspepsia; fatigue; constipation; nausea and abdominal discomfort; pancreatic cyst; diarrhoea; vomiting and diarrhoea; and decreased appetite), and those events reported by 20 subjects in the semaglutide 2.4 mg group (nausea [6 subjects]; nausea, vomiting, and diarrhoea [3 subjects]; pruritic rash; gastritis; pancreatitis acute; fatigue; vomiting, headache, and abdominal distension; dizziness; diarrhoea; vomiting; abdominal discomfort; upper abdominal pain and muscle spasms; and lower abdominal pain) were classified as adverse drug reactions.

The proportions of subjects with positive anti-semaglutide antibodies at any time post-baseline were 1.0% (4 of 396) of subjects in the semaglutide 1.0 mg group and 3.0% (12 of 401) of subjects in the semaglutide 2.4 mg group, and none of them tested positive for neutralizing antibodies.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

The applicant's explanation:

Obesity is known to cause various health disorders. Obesity is a risk factor for the development of cardiovascular disease, certain types of cancer, type 2 diabetes, dyslipidemia, hypertension, etc., and impacts quality of life by imposing limitations on physical function and impairing mental well-being. Taking account of such situation, the major international organizations such as WHO define obesity as a disease (*Obesity*. 2019;27:7-9). Although the number of obese people with a BMI of >30 kg/m^2 is small in the Japanese population compared with the Western population, there are no major differences in the prevalences of many obesity-related diseases between the Japanese and Western populations, in spite of mild obesity in the Japanese population, and Japanese people are likely to experience health disorders even at a lower BMI, etc. Thus, the Japanese guidelines for the management of obesity disease define "obesity" as a BMI of ≥25 kg/m^2 and "obesity disease" as a medical condition that is accompanied by obesity-related health disorders and thus medically requires weight loss.

A weight loss of 5% to 10% has significant health benefits in patients with obesity by improving obesity-related comorbidities (*Arch Intern Med*. 2009;169:1619-26, *Ann Intern Med*. 1992;116:535-9, etc.). Lifestyle

intervention in the form of diet and exercise is first-line treatment for obesity, but most people with obesity struggle to achieve and maintain their weight loss. Thus, foreign clinical practice guidelines recommend that pharmacotherapy should be considered if weight reduction by lifestyle modifications is not adequate (*Obes Facts*. 2015;8:166-74, *J Clin Endocrinol Metab*. 2015;100:342-62). In foreign countries, a lipase inhibitor (Orlistat), centrally-acting appetite suppressants (naltrexone/bupropion, etc.), a GLP-1 receptor agonist (liragultide), etc., have been used. The Japanese guidelines for the management of obesity disease also recommend that pharmacotherapy should be considered if lifestyle intervention consisting of dietary, exercise, and behavioral therapy does not produce adequate weight loss. However, a mazindol formulation (Sanorex Tablets), which has been approved as an anti-obesity medication in Japan, is indicated only for patients with obesity disease with a BMI of ≥35 kg/m^2 and is limited to short-term use. Although bariatric surgery offers an alternative in Japan, it is indicated for patients with a BMI of ≥35 kg/m^2 and comorbidities such as diabetes, hypertension, and dyslipidemia who have not responded adequately to medical treatment, etc., and a limited number of health facilities perform bariatric surgery due to facility standards/the qualifications of physicians, etc. Thus, there is an unmet medical need for a new drug for obesity disease.

Clinical trials of semaglutide showed that patients treated with semaglutide achieved a clinically meaningful weight loss and improvements in blood glucose, blood pressure, and lipid parameters. The safety profile of the proposed product was similar to those of the commercially available semaglutide formulations for type 2 diabetes. On the basis of the above, the proposed product is considered to address the unmet medical need in the treatment of obesity disease and be useful as an anti-obesity medication for patients with obesity disease.

PMDA's view:
It is understandable that a new drug is needed as a treatment option for patients with obesity disease who are unable to achieve adequate weight loss with lifestyle intervention alone, in clinical practice in Japan. Three global phase III trials demonstrated the weight lowering effect of semaglutide and indicated that improvements in blood glucose, blood pressure, and lipid parameters are also expected [see Section "7.R.2 Efficacy"]. Semaglutide has acceptable safety, provided that appropriate precautionary statements are included in the package insert [see Section "7.R.3 Safety"]. Given the above findings, semaglutide can become an anti-obesity medication for patients with obesity with hypertension, dyslipidemia, or type 2 diabetes.

7.R.2 Efficacy

7.R.2.1 Weight reduction effect

The applicant's explanation:
Trial 4382 in patients with obesity and hypertension, dyslipidemia, or type 2 diabetes demonstrated the superiority of semaglutide 2.4 mg to placebo in the co-primary endpoints of the percent change in body weight from baseline to Week 68 and the proportion of subjects achieving ≥5% weight loss at Week 68, and the effect of semaglutide 1.7 mg also tended to be greater than that of placebo (Table 10). Both Trial 4373 in patients with overweight or obesity and Trial 4374 in patients with overweight or obesity and type 2 diabetes demonstrated the superiority of semaglutide 2.4 mg to placebo in the co-primary endpoints of the percent change in body weight from baseline to Week 68 and the proportion of subjects achieving ≥5% weight loss at

Week 68, and the effect of semaglutide 2.4 mg tended to be greater than that of semaglutide 1.0 mg in Trial 4374 (Tables 15 and 20).

With regard to body weight-related key secondary endpoints, all global phase III trials (Trials 4382, 4373, and 4374) showed a higher proportion of subjects achieving weight loss and greater reductions in waist circumference and BMI in the semaglutide 2.4 mg group than in the placebo group (Tables 11, 16, and 21). The proportion of subjects achieving weight loss was higher and the reductions in waist circumference and BMI were greater in the semaglutide 2.4 mg group as compared with the semaglutide 1.0 mg group (Trial 4374) or the semaglutide 1.7 mg group (Trial 4382). The effect of semaglutide on visceral fat area was assessed in the Japanese subgroup of Trial 4382, and reductions in visceral fat area were greater in the semaglutide groups than in the placebo group and in the semaglutide 2.4 mg group than in the semaglutide 1.7 mg group (Table 11).

The efficacy of semaglutide in the Japanese subgroup was evaluated as follows:
As to extrinsic ethnic factors, though there are differences in diet between Japanese and Western populations, and the carbohydrate ratio of the Japanese meal is higher, the Japanese diet has been getting closer to the Western diet in the last 10 years. Both in Japan and overseas, "obesity" is defined based on BMI, and the initiation of pharmacotherapy as an adjunct to lifestyle intervention should be considered if weight reduction by lifestyle intervention is not adequate. Both in Japan and overseas, the patient population intended for pharmacotherapy is patients who are unable to achieve weight loss with dietary and exercise therapy and is defined by BMI and obesity-related comorbidities. Thus, though there are differences in BMI cutoff values used for the diagnosis of obesity and the selection of intended patients for pharmacotherapy and pharmacotherapy options between Japan and overseas, the same concept of pharmacotherapy is used. As to intrinsic ethnic factors, the risk of obesity-related comorbidities etc. is known to increase with increasing BMI, and there should be no differences between Japan and overseas. As to the pharmacokinetics of semaglutide, semaglutide exposure tended to be higher in Japanese patients than in non-Japanese patients, and one of its factors was considered differences in body weight [see Section "6.R.1 Comparison of pharmacokinetics between Japanese and non-Japanese populations"].

Tables 25 to 27 show baseline subject characteristics in the global phase III trials. In Trial 4382, the majority was Japanese subjects, and there were no major differences between the entire trial population and the Japanese subgroup. In Trial 4373, the proportion of female subjects and the mean BMI and the mean body weight were lower and the proportion of subjects with hypertension and the proportion of subjects with dyslipidemia were higher in the Japanese subgroup than in the entire trial population. In Trial 4374, the proportion of female subjects and the mean BMI and the mean body weight were lower in the Japanese subgroup than in the entire trial population.

Table 25. Baseline subject characteristics (Trial 4382, Japanese subgroup and entire trial population: FAS)

Item		Japanese subgroup (N = 360)			Entire trial population (N = 401)		
		Placebo (N = 89)	Semaglutide 1.7 mg (N = 92)	Semaglutide 2.4 mg (N = 179)	Placebo (N = 101)	Semaglutide 1.7 mg (N = 101)	Semaglutide 2.4 mg (N = 199)
Age (years)		51 ± 8	52 ± 10	53 ± 11	50 ± 9	51 ± 10	52 ± 12
Sex[a)]	Male	77.5 (69)	63.0 (58)	55.9 (100)	74.3 (75)	63.4 (64)	57.3 (114)
	Female	22.5 (20)	37.0 (34)	44.1 (79)	25.7 (26)	36.6 (37)	42.7 (85)
Body weight (kg)		90.1 ± 14.2	85.1 ± 11.5	85.8 ± 15.9	90.2 ± 15.1	86.1 ± 11.9	86.9 ± 16.5
BMI (kg/m^2)	Mean ± SD	32.0 ± 4.3	31.5 ± 3.8	31.9 ± 4.7	31.9 ± 4.2	31.6 ± 3.7	32.0 ± 4.6
	<30[a)]	34.8 (31)	47.8 (44)	45.3 (81)	37.6 (38)	45.5 (46)	43.2 (86)
	≥30 and <35[a)]	47.2 (42)	33.7 (31)	36.3 (65)	43.6 (44)	35.6 (36)	37.7 (75)
	≥35 and <40[a)]	11.2 (10)	16.3 (15)	10.1 (18)	11.9 (12)	16.8 (17)	10.6 (21)
	≥40[a)]	6.7 (6)	2.2 (2)	8.4 (15)	6.9 (7)	2.0 (2)	8.5 (17)
HbA1c (%)		6.4 ± 1.1	6.4 ± 1.2	6.5 ± 1.3	6.4 ± 1.1	6.4 ± 1.1	6.4 ± 1.2
Diabetes[a)]	Yes	28.1 (25)	27.2 (25)	27.4 (49)	24.8 (25)	24.8 (25)	24.6 (49)
	No	71.9 (64)	72.8 (67)	72.6 (130)	75.2 (76)	75.2 (76)	75.4 (150)
Hypertension[a)]	Yes	75.3 (67)	73.9 (68)	79.3 (142)	72.3 (73)	73.3 (74)	76.4 (152)
	No	24.7 (22)	26.1 (24)	20.7 (37)	27.7 (28)	26.7 (27)	23.6 (47)
Dyslipidemia[a)]	Yes	80.9 (72)	87.0 (80)	90.5 (162)	79.2 (80)	87.1 (88)	89.4 (178)
	No	19.1 (17)	13.0 (12)	9.5 (17)	20.8 (21)	12.9 (13)	10.6 (21)

Mean ± SD, a) Proportion % (Number of subjects in category)

Table 26. Baseline subject characteristics (Trial 4373, Japanese subgroup and entire trial population: FAS)

Item		Japanese subgroup (N = 100)		Entire trial population (N = 1961)	
		Placebo (N = 33)	Semaglutide 2.4 mg (N = 67)	Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)
Age (years)		52 ± 8	51 ± 11	47 ± 12	46 ± 13
Sex[a)]	Male	57.6 (19)	52.2 (35)	24.0 (157)	26.9 (351)
	Female	42.4 (14)	47.8 (32)	76.0 (498)	73.1 (955)
Body weight (kg)		87.9 ± 12.6	83.4 ± 13.4	105.2 ± 21.5	105.4 ± 22.1
BMI (kg/m^2)	Mean ± SD	32.1 ± 3.8	31.1 ± 3.8	38.0 ± 6.5	37.8 ± 6.7
	<30[a)]	33.3 (11)	46.3 (31)	5.5 (36)	6.2 (81)
	≥30 and <35[a)]	48.5 (16)	41.8 (28)	31.6 (207)	33.4 (436)
	≥35 and <40[a)]	15.2 (5)	9.0 (6)	31.8 (208)	31.1 (406)
	≥40[a)]	3.0 (1)	3.0 (2)	31.1 (204)	29.3 (383)
Hypertension[a)]	Yes	51.5 (17)	53.7 (36)	35.7 (234)	36.1 (472)
	No	48.5 (16)	46.3 (31)	63.8 (418)	63.2 (825)
	Unknown	0 (0)	0 (0)	0.5 (3)	0.7 (9)
Dyslipidemia[a)]	Yes	75.8 (25)	74.6 (50)	34.5 (226)	38.2 (499)
	No	24.2 (8)	25.4 (17)	64.6 (423)	60.0 (784)
	Unknown	0 (0)	0 (0)	0.9 (6)	1.8 (23)

Mean ± SD, a) Proportion % (Number of subjects in category)

Table 27. Baseline subject characteristics (Trial 4374, Japanese subgroup and entire trial population: FAS)

Item		Japanese subgroup (N = 125)			Entire trial population (N = 1210)		
		Placebo (N = 47)	Semaglutide 1.0 mg (N = 36)	Semaglutide 2.4 mg (N = 42)	Placebo (N = 403)	Semaglutide 1.0 mg (N = 403)	Semaglutide 2.4 mg (N = 404)
Age (years)		51 ± 9	52 ± 10	55 ± 11	55 ± 11	56 ± 10	55 ± 11
Sex[a)]	Male	68.1 (32)	66.7 (24)	57.1 (24)	52.9 (213)	49.6 (200)	44.8 (181)
	Female	31.9 (15)	33.3 (12)	42.9 (18)	47.1 (190)	50.4 (203)	55.2 (223)
Body weight (kg)		89.9 ± 16.2	91.6 ± 19.4	86.3 ± 16.8	100.5 ± 20.9	99.0 ± 21.1	99.9 ± 22.5
BMI (kg/m^2)	Mean ± SD	32.2 ± 4.3	32.7 ± 6.2	31.7 ± 4.0	35.9 ± 6.5	35.3 ± 5.9	35.9 ± 6.4
	<30[a)]	42.6 (20)	36.1 (13)	40.5 (17)	19.1 (77)	16.4 (66)	16.8 (68)
	≥30 and <35[a)]	36.2 (17)	44.4 (16)	38.1 (16)	33.5 (135)	40.4 (163)	34.7 (140)
	≥35 and <40[a)]	12.8 (6)	8.3 (3)	16.7 (7)	24.1 (97)	24.8 (100)	25.5 (103)
	≥40[a)]	8.5 (4)	11.1 (4)	4.8 (2)	23.3 (94)	18.4 (74)	23.0 (93)
HbA1c (%)		7.9 ± 0.8	8.2 ± 0.6	8.0 ± 0.6	8.1 ± 0.8	8.1 ± 0.8	8.1 ± 0.8
Hypertension[a)]	Yes	63.8 (30)	69.4 (25)	76.2 (32)	71.2 (287)	70.7 (285)	68.3 (276)
	No	36.2 (17)	30.6 (11)	23.8 (10)	28.5 (115)	28.5 (115)	31.4 (127)
	Unknown	0 (0)	0 (0)	0 (0)	0.2 (1)	0.7 (3)	0.2 (1)
Dyslipidemia[a)]	Yes	83.0 (39)	77.8 (28)	85.7 (36)	70.5 (284)	68.7 (277)	65.6 (265)
	No	17.0 (8)	22.2 (8)	14.3 (6)	28.5 (115)	29.8 (120)	34.2 (138)
	Unknown	0 (0)	0 (0)	0 (0)	1.0 (4)	1.5 (6)	0.2 (1)

Mean ± SD, a) Proportion % (Number of subjects in category)

With regard to the co-primary endpoints of the percent change in body weight from baseline to Week 68 and the proportion of subjects achieving ≥5% weight loss at Week 68, a similar trend was observed in the Japanese subgroup and the entire trial population in all trials (Tables 10, 15, and 20).

Subgroup analyses of the percent change in body weight from baseline to Week 68 were performed according to the subject characteristics that differed between the Japanese subgroup and the entire trial population in Trial 4373 or 4374. Though there are limitations to the analyses due to the very limited number of subjects in some subgroups, there were no major differences across the subgroups (Tables 28 and 29)

Table 28. Percent change in body weight from baseline to Week 68 by subject characteristics
(Trial 4373, Japanese subgroup and entire trial population: FAS)

Item		Japanese subgroup		Entire trial population	
		Placebo (N = 33)	Semaglutide 2.4 mg (N = 67)	Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)
Sex	Male	−2.5 ± 5.1 (N = 19)	−10.8 ± 7.9 (N = 35)	−3.2 ± 6.5 (N = 146)	−11.7 ± 8.0 (N = 327)
	Female	−5.2 ± 7.7 (N = 14)	−20.3 ± 9.5 (N = 31)	−2.6 ± 6.5 (N = 431)	−17.0 ± 10.4 (N = 885)
Body weight (kg)	<90	−1.8 ± 4.6 (N = 19)	−16.4 ± 10.5 (N = 49)	−2.5 ± 5.7 (N = 148)	−16.7 ± 10.1 (N = 318)
	≥90 and <100	−7.8 ± 6.7 (N = 10)	−13.1 ± 6.8 (N = 13)	−3.4 ± 6.1 (N = 130)	−17.1 ± 11.2 (N = 260)
	≥100 and <115	−5.0 ± 8.4 (N = 3)	−10.3 ± 6.1 (N = 3)	−2.1 ± 6.6 (N = 148)	−15.9 ± 9.7 (N = 299)
	≥115	7.7 (N = 1)	−2.8 (N = 1)	−3.1 ± 7.3 (N = 151)	−13.1 ± 9.0 (N = 335)
BMI (kg/m^2)	<30	−3.7 ± 5.0 (N = 11)	−16.1 ± 9.1 (N = 30)	−3.2 ± 6.8 (N = 33)	−15.1 ± 10.3 (N = 78)
	≥30 and <35	−2.5 ± 5.5 (N = 16)	−15.9 ± 10.9 (N = 28)	−2.6 ± 6.0 (N = 192)	−16.8 ± 10.1 (N = 413)
	≥35 and <40	−4.9 ± 10.4 (N = 5)	−8.9 ± 5.9 (N = 6)	−3.2 ± 6.6 (N = 181)	−15.3 ± 10.5 (N = 375)
	≥40	−15.2 (N = 1)	−11.6 ± 12.4 (N = 2)	−2.4 ± 6.8 (N = 171)	−14.6 ± 9.4 (N = 346)
Hypertension	Yes	−5.4 ± 6.9 (N = 17)	−13.8 ± 10.1 (N = 35)	−2.8 ± 6.4 (N = 209)	−14.9 ± 9.2 (N = 445)
	No	−1.8 ± 5.5 (N = 16)	−16.9 ± 9.4 (N = 31)	−2.7 ± 6.6 (N = 368)	−16.0 ± 10.6 (N = 767)
Dyslipidemia	Yes	−4.8 ± 6.9 (N = 25)	−15.4 ± 9.1 (N = 49)	−2.5 ± 5.7 (N = 202)	−15.3 ± 9.7 (N = 477)
	No	−0.1 ± 2.2 (N = 8)	−14.8 ± 11.9 (N = 17)	−2.9 ± 6.9 (N = 375)	−15.8 ± 10.3 (N = 735)

Unit, %; Mean ± SD (Number of evaluable subjects)

Table 29. Percent change in body weight from baseline to Week 68 by subject characteristics
(Trial 4374, Japanese subgroup and entire trial population: FAS)

Item		Japanese subgroup			Entire trial population		
		Placebo (N = 47)	Semaglutide 1.0 mg (N = 36)	Semaglutide 2.4 mg (N = 42)	Placebo (N = 403)	Semaglutide 1.0 mg (N = 403)	Semaglutide 2.4 mg (N = 404)
Sex	Male	−2.8 ± 3.7 (N = 32)	−6.0 ± 6.2 (N = 24)	−9.6 ± 6.9 (N = 24)	−3.2 ± 5.8 (N = 200)	−5.5 ± 5.2 (N = 189)	−8.3 ± 7.1 (N = 172)
	Female	−3.1 ± 3.4 (N = 15)	−7.0 ± 7.0 (N = 12)	−11.6 ± 7.3 (N = 18)	−3.3 ± 5.3 (N = 176)	−8.8 ± 7.4 (N = 191)	−11.2 ± 8.4 (N = 216)
Body weight (kg)	<90	−3.0 ± 3.5 (N = 26)	−5.2 ± 7.1 (N = 19)	−11.8 ± 8.0 (N = 23)	−3.0 ± 4.0 (N = 133)	−6.6 ± 6.3 (N = 140)	−10.0 ± 7.9 (N = 142)
	≥90 and <100	−1.4 ± 1.3 (N = 7)	−9.2 ± 6.4 (N = 10)	−8.5 ± 4.5 (N = 13)	−2.0 ± 6.0 (N = 73)	−7.7 ± 6.7 (N = 80)	−8.9 ± 7.9 (N = 76)
	≥100 and <115	−3.2 ± 4.5 (N = 11)	−5.5 ± 3.2 (N = 5)	−12.5 ± 7.4 (N = 4)	−3.1 ± 4.7 (N = 89)	−9.1 ± 7.5 (N = 76)	−10.6 ± 8.7 (N = 87)
	≥115	−3.9 ± 4.6 (N = 3)	−3.9 ± 0.3 (N = 2)	−3.1 ± 1.6 (N = 2)	−4.9 ± 7.5 (N = 81)	−6.0 ± 5.8 (N = 84)	−10.1 ± 7.6 (N = 83)
BMI (kg/m^2)	<30	−2.2 ± 3.0 (N = 20)	−3.5 ± 5.8 (N = 13)	−12.2 ± 7.3 (N = 17)	−3.0 ± 4.1 (N = 71)	−5.0 ± 6.0 (N = 59)	−10.1 ± 7.6 (N = 68)
	≥30 and <35	−3.5 ± 4.1 (N = 17)	−9.3 ± 7.0 (N = 16)	−10.1 ± 7.9 (N = 16)	−2.5 ± 5.6 (N = 129)	−7.3 ± 6.2 (N = 153)	−8.7 ± 8.0 (N = 131)
	≥35 and <40	−1.5 ± 1.6 (N = 6)	−3.3 ± 2.6 (N = 3)	−7.0 ± 4.0 (N = 7)	−3.3 ± 5.9 (N = 89)	−8.2 ± 7.5 (N = 96)	−10.0 ± 7.9 (N = 100)
	≥40	−6.0 ± 4.3 (N = 4)	−5.7 ± 2.2 (N = 4)	−10.2 ± 3.6 (N = 2)	−4.5 ± 5.9 (N = 87)	−7.2 ± 6.5 (N = 72)	−11.4 ± 8.2 (N = 89)

Unit, %; Mean ± SD (Number of evaluable subjects)

Table 30 shows the percent change in body weight from baseline to Week 68 by sex, body weight, and BMI in Trial 4382. As in Trials 4373 and 4374 (Tables 28 and 29), there were no major differences across the subgroups.

Table 30. Percent change in body weight from baseline to Week 68 by sex, body weight, and BMI (Trial 4382: FAS)

Item		Placebo (N = 101)	Semaglutide 1.7 mg (N = 101)	Semaglutide 2.4 mg (N = 199)
Sex	Male	−2.3 ± 6.2 (N = 74)	−7.9 ± 6.3 (N = 61)	−11.0 ± 7.5 (N = 108)
	Female	−0.8 ± 5.1 (N = 26)	−13.2 ± 8.8 (N = 37)	−16.4 ± 8.9 (N = 85)
Body weight (kg)	<80	−2.6 ± 6.6 (N = 24)	−13.3 ± 9.8 (N = 32)	−15.0 ± 8.6 (N = 72)
	≥80 and <90	−0.3 ± 4.4 (N = 35)	−8.1 ± 6.5 (N = 34)	−12.4 ± 8.4 (N = 62)
	≥90 and <100	−3.0 ± 4.8 (N = 23)	−8.9 ± 5.8 (N = 17)	−13.3 ± 9.6 (N = 27)
	≥100	−2.5 ± 8.4 (N = 18)	−8.1 ± 5.4 (N = 15)	−11.9 ± 7.7 (N = 32)
BMI (kg/m^2)	<30	−1.0 ± 5.5 (N = 37)	−11.8 ± 9.4 (N = 44)	−13.1 ± 8.7 (N = 84)
	≥30 and <35	−2.5 ± 4.9 (N = 44)	−7.5 ± 5.9 (N = 35)	−13.9 ± 8.4 (N = 73)
	≥35 and <40	−2.0 ± 10.9 (N = 12)	−9.3 ± 4.6 (N = 17)	−14.3 ± 9.6 (N = 20)
	≥40	−2.1 ± 2.5 (N = 7)	−16.2 ± 8.3 (N = 2)	−11.4 ± 7.3 (N = 16)

Unit, %; Mean ± SD (Number of evaluable subjects)

Tables 31 and 32 show the percent change in body weight from baseline to Week 68 by comorbidity. When analyzed by glycemic status, the magnitude of body weight reduction was smaller in the subgroup with type 2 diabetes of Trial 4382 and Trial 4374 in patients with type 2 diabetes as compared with the subgroup without diabetes or the subgroup with prediabetes in Trials 4373 and 4382. These findings were considered attributable to a trend towards lower semaglutide exposure and a higher proportion of male subjects in the population with type 2 diabetes as compared with the population without type 2 diabetes. Other possible explanations are as follows: As typical features of type 2 diabetes, patients with type 2 diabetes are thought to lose less weight than people with normoglycemia because of decreased caloric loss and a lower energy expenditure due to normalization of metabolism following improved glycemic control (*Front Nutr*. 2016;3:56, *Diabetes.*

1986;35:1-5); and as a GLP-1 receptor agonist enhances glucose-dependent insulin secretion, it impairs weight loss in patients with type 2 diabetes due to the anabolic effect of increased insulin on fat and muscle (*Drug Saf*. 2007;30:1127-42). When analyzed by dyslipidemia status, while the percent change in body weight was smaller in the subgroup without dyslipidemia than in the subgroup with dyslipidemia in Trial 4382, a similar trend was not observed in Trials 4373 and 4374. When analyzed by hypertension status, no major differences were observed between the subgroups.

Table 31. Percent change in body weight from baseline to Week 68 by comorbidity (Trial 4382: FAS)

Item		Placebo (N = 101)	Semaglutide 1.7 mg (N = 101)	Semaglutide 2.4 mg (N = 199)
Glycemic status	Normoglycemia	−2.5 ± 7.5 (N = 50)	−11.4 ± 7.9 (N = 53)	−14.1 ± 8.1 (N = 102)
	Prediabetes	−1.8 ± 4.5 (N = 25)	−10.7 ± 7.7 (N = 20)	−16.1 ± 8.8 (N = 42)
	Diabetes mellitus	−0.8 ± 3.0 (N = 25)	−6.2 ± 6.5 (N = 25)	−9.6 ± 8.2 (N = 49)
Hypertension	Yes	−2.0 ± 5.1 (N = 72)	−9.4 ± 7.9 (N = 74)	−13.0 ± 8.4 (N = 148)
	No	−1.5 ± 7.9 (N = 28)	−11.5 ± 7.4 (N = 24)	−14.8 ± 9.1 (N = 45)
Dyslipidemia	Yes	−1.6 ± 6.1 (N = 79)	−10.3 ± 8.0 (N = 85)	−13.7 ± 8.7 (N = 173)
	No	−3.0 ± 5.4 (N = 21)	−7.7 ± 5.4 (N = 13)	−10.6 ± 6.7 (N = 20)

Unit, %; Mean ± SD (Number of evaluable subjects)
Glycemic status was categorized according to ADA definitions.

Table 32. Percent change in body weight from baseline to Week 68 by comorbidity (Trials 4373 and 4374: FAS)

Item		Trial 4373		Trial 4374		
		Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)	Placebo (N = 403)	Semaglutide 1.0 mg (N = 403)	Semaglutide 2.4 mg (N = 404)
Glycemic status	Normoglycemia	−2.8 ± 6.5 (N = 341)	−16.7 ± 10.5 (N = 661)	—	—	—
	Prediabetes	−2.7 ± 6.5 (N = 236)	−14.3 ± 9.4 (N = 551)	—	—	—
	Diabetes mellitus	—	—	−3.3 ± 5.5 (N = 376)	−7.2 ± 6.6 (N = 380)	−9.9 ± 8.0 (N = 388)
Hypertension	Yes	−2.8 ± 6.4 (N = 209)	−14.9 ± 9.2 (N = 445)	−3.5 ± 6.1 (N = 266)	−7.7 ± 6.9 (N = 271)	−10.5 ± 8.1 (N = 264)
	No	−2.7 ± 6.6 (N = 368)	−16.0 ± 10.6 (N = 767)	−2.8 ± 4.0 (N = 110)	−5.8 ± 5.7 (N = 109)	−8.6 ± 7.7 (N = 124)
Dyslipidemia	Yes	−2.5 ± 5.7 (N = 202)	−15.3 ± 9.7 (N = 477)	−3.2 ± 5.7 (N = 268)	−7.8 ± 6.6 (N = 264)	−10.2 ± 8.1 (N = 257)
	No	−2.9 ± 6.9 (N = 375)	−15.8 ± 10.3 (N = 735)	−3.5 ± 5.1 (N = 108)	−5.9 ± 6.6 (N = 116)	−9.5 ± 7.8 (N = 131)

Unit, %; Mean ± SD (Number of evaluable subjects)
Glycemic status was categorized according to ADA definitions.

PMDA's view:

All 3 global phase III trials demonstrated the superiority of semaglutide 2.4 mg to placebo in the co-primary endpoints of the percent change in body weight from baseline to Week 68 and the proportion of subjects achieving ≥5% weight loss at Week 68. Also, for body weight-related secondary endpoints, all trials showed a higher proportion of subjects achieving weight loss and greater reductions in waist circumference and BMI, etc., in the semaglutide 2.4 mg group than in the placebo group. There are no major differences between Japan and overseas, in terms of the diagnosis of obesity and patients appropriate for pharmacotherapy being defined by BMI and obesity-related comorbidities, etc. Semaglutide exposure was higher in Japanese patients than in non-Japanese patients, and one of its factors was considered differences in body weight. Differences in some baseline subject characteristics including body weight between the Japanese subgroup and the entire trial

population had no major effects on the efficacy evaluation of semaglutide, and a similar trend was seen for the primary endpoint of weight reduction in the Japanese subgroup and the entire trial population in all trials. Given the above points etc., it may be interpreted that the results of the clinical trials have demonstrated the weight reduction effect of semaglutide. The beneficial effect of improving comorbidities will be evaluated in the following section.

7.R.2.2 Beneficial effect of improving comorbidities

The applicant's explanation:

With respect to the beneficial effects of semaglutide on comorbidities, all global phase III trials (Trials 4382, 4373, and 4374) showed a trend towards improvements in all of blood glucose, blood pressure, and lipid parameters in the semaglutide 2.4 mg group compared with the placebo group, except for low density lipoprotein (LDL) cholesterol in Trial 4374 (Tables 12, 17, and 22). There were no major differences in blood glucose parameters between the semaglutide 2.4 mg and 1.0 mg (Trial 4374) or 1.7 mg (Trial 4382) groups. In Trial 4382, although there were no major differences in blood pressure parameters between the semaglutide 2.4 mg and 1.7 mg groups, the percent changes in lipid parameters were numerically higher in the semaglutide 2.4 mg group than in the semaglutide 1.7 mg group. These trends were similar between the Japanese subgroup and the entire trial population, except for LDL cholesterol in Trial 4374.

Changes in medications for hypertension, dyslipidemia, or type 2 diabetes are shown in Tables 33 and 34. In the subgroup with type 2 diabetes of Trial 4382 and Trial 4374, the proportion of subjects who decreased oral anti-diabetic drug (OAD) from baseline to Week 68 was higher in the semaglutide group than in the placebo group, and the proportion of subjects who increased OAD was lower in the semaglutide group than in the placebo group. The proportion of subjects who decreased antihypertensive medication was higher in the semaglutide group than in the placebo group in all trials. The proportion of subjects who decreased antihypertensive medication was higher in the semaglutide 2.4 mg group than in the semaglutide 1.0 mg group in Trial 4374 and in the semaglutide 2.4 mg group than in the semaglutide 1.7 mg group in Trial 4382. The proportion of subjects who increased antihypertensive medication was lower in the semaglutide group than in the placebo group, except for Trial 4374. There were no major differences in the proportion of subjects who decreased or increased lipid-lowering medication among the treatment groups in all trials.

Table 33. Use of medications for comorbidities at Week 68 (Trial 4382: FAS)

Comparison vs. baseline		Placebo (N = 101)	Semaglutide 1.7 mg (N = 101)	Semaglutide 2.4 mg (N = 199)
Oral anti-diabetic drug	Subjects on concomitant medication[a)]	100 (25/25)[b)]	84.0 (21/25)[b)]	79.6 (39/49)[b)]
	Decrease	0 (0/25)[b)]	8.0 (2/25)[b)]	18.4 (9/49)[b)]
	No change	72.0 (18/25)[b)]	76.0 (19/25)[b)]	55.1 (27/49)[b)]
	Increase	28.0 (7/25)[b)]	0 (0/25)[b)]	6.1 (3/49)[b)]
Antihypertensive medication	Subjects on concomitant medication[a)]	50.0 (50/100)	48.5 (48/99)	57.4 (112/195)
	Decrease	2.0 (2/100)	5.1 (5/99)	13.8 (27/195)
	No change	36.0 (36/100)	34.3 (34/99)	36.4 (71/195)
	Increase	10.0 (10/100)	4.0 (4/99)	3.6 (7/195)
	Stopped	2.0 (2/100)	5.1 (5/99)	3.6 (7/195)
Lipid-lowering medication	Subjects on concomitant medication[a)]	32.0 (32/100)	38.4 (38/99)	46.2 (90/195)
	Decrease	0 (0/100)	1.0 (1/99)	2.1 (4/195)
	No change	27.0 (27/100)	33.3 (33/99)	41.0 (80/195)
	Increase	5.0 (5/100)	2.0 (2/99)	1.5 (3/195)
	Stopped	0 (0/100)	2.0 (2/99)	1.5 (3/195)

Proportion % (Number of subjects in category/Number of evaluable subjects)
a) Subjects receiving medication between baseline and Week 68
b) Evaluated in subjects with type 2 diabetes (25 in the placebo group, 25 in the semaglutide 1.7 mg group, 49 in the semaglutide 2.4 mg group)

Table 34. Use of medications for comorbidities at Week 68 (Trials 4373 and 4374: FAS)

Comparison vs. baseline		Trial 4373		Trial 4374		
		Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)	Placebo (N = 403)	Semaglutide 1.0 mg (N = 403)	Semaglutide 2.4 mg (N = 404)
Oral anti-diabetic drug	Subjects on concomitant medication[a)]	—	—	95.3 (364/382)	95.9 (371/387)	94.9 (371/391)
	Decrease	—	—	6.8 (26/382)	24.0 (93/387)	27.1 (106/391)
	No change	—	—	65.2 (249/382)	66.7 (258/387)	63.2 (247/391)
	Increase	—	—	23.0 (88/382)	4.9 (19/387)	4.6 (18/391)
Antihypertensive medication	Subjects on concomitant medication[a)]	35.3 (205/580)	33.2 (405/1219)	68.6 (262/382)	69.8 (270/387)	64.7 (253/391)
	Decrease	1.7 (10/580)	4.6 (56/1219)	3.7 (14/382)	4.1 (16/387)	9.2 (36/391)
	No change	21.9 (127/580)	17.7 (216/1219)	50.5 (193/382)	49.4 (191/387)	40.9 (160/391)
	Increase	7.8 (45/580)	4.0 (49/1219)	8.9 (34/382)	9.0 (35/387)	7.2 (28/391)
	Stopped	3.8 (22/580)	6.8 (83/1219)	5.5 (21/382)	7.2 (28/387)	7.4 (29/391)
Lipid-lowering medication	Subjects on concomitant medication[a)]	20.2 (117/580)	18.5 (226/1219)	60.7 (232/382)	60.2 (233/387)	58.6 (229/391)
	Decrease	1.0 (6/580)	0.8 (10/1219)	0.8 (3/382)	1.8 (7/387)	2.0 (8/391)
	No change	12.8 (74/580)	12.7 (155/1219)	50.8 (194/382)	45.5 (176/387)	45.5 (178/391)
	Increase	4.0 (23/580)	1.8 (22/1219)	5.0 (19/382)	5.4 (21/387)	4.1 (16/391)
	Stopped	2.4 (14/580)	3.2 (39/1219)	4.2 (16/382)	7.5 (29/387)	6.9 (27/391)

Proportion % (Number of subjects in category/Number of evaluable subjects)
a) Subjects receiving medication between baseline and Week 68

Regarding the efficacy of semaglutide by comorbidity, Tables 35 and 36 show the degrees of improvements in blood glucose, blood pressure, and lipid parameters by baseline category. Except for LDL cholesterol in Trials 4382 and 4374, greater improvements in all parameters were observed in the semaglutide group of the other subgroup as compared with that of the subgroup with normal values (HbA1c <7.0%) at baseline.

Table 35. Changes in blood glucose and blood pressure parameters and percent changes in lipid parameters (%) from baseline to Week 68 by subject characteristics (Trial 4382: FAS)

Parameter	Baseline	Placebo (N = 101)	Semaglutide 1.7 mg (N = 101)	Semaglutide 2.4 mg (N = 199)
HbA1c	≥7.0%	0.3 ± 1.4 (N = 25)	−2.1 ± 0.7 (N = 25)	−2.2 ± 1.1 (N = 48)
	<7.0%	−0.1 ± 0.3 (N = 75)	−0.5 ± 0.3 (N = 73)	−0.5 ± 0.3 (N = 145)
Systolic blood pressure (mmHg)	High	−10.1 ± 14.2 (N = 47)	−13.0 ± 14.3 (N = 45)	−17.6 ± 13.1 (N = 83)
	Normal	−0.3 ± 14.2 (N = 53)	−10.6 ± 10.9 (N = 53)	−5.9 ± 13.6 (N = 110)
Diastolic blood pressure (mmHg)	High	−6.7 ± 8.8 (N = 47)	−5.0 ± 8.3 (N = 45)	−8.7 ± 8.9 (N = 83)
	Normal	0.8 ± 8.6 (N = 53)	−4.4 ± 10.6 (N = 53)	−2.3 ± 9.8 (N = 110)
Total cholesterol (mg/dL)	Outside normal range	−1.4 ± 13.5 (N = 60)	−7.0 ± 16.8 (N = 58)	−8.7 ± 13.4 (N = 105)
	Normal	4.9 ± 8.9 (N = 40)	−4.6 ± 15.0 (N = 40)	−6.7 ± 10.9 (N = 88)
LDL cholesterol (mg/dL)	Outside normal range	−5.9 ± 20.7 (N = 59)	−5.3 ± 33.3 (N = 58)	−9.9 ± 23.1 (N = 105)
	Normal	1.8 ± 13.8 (N = 40)	−9.6 ± 20.8 (N = 40)	−14.0 ± 16.4 (N = 88)
HDL cholesterol (mg/dL)	Outside normal range	6.2 ± 14.9 (N = 60)	10.5 ± 18.2 (N = 58)	10.4 ± 18.4 (N = 105)
	Normal	8.5 ± 10.3 (N = 40)	4.4 ± 18.0 (N = 40)	8.5 ± 12.4 (N = 88)
Triglycerides (mg/dL)	Outside normal range	12.2 ± 42.5 (N = 59)	−23.5 ± 34.4 (N = 58)	−21.2 ± 43.2 (N = 105)
	Normal	15.0 ± 42.6 (N = 40)	4.1 ± 72.4 (N = 40)	−4.5 ± 31.2 (N = 88)

Mean ± SD
High blood pressure parameter: Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg
Lipid parameter outside the normal range: LDL cholesterol ≥140 mg/dL, HDL cholesterol <40 mg/dL, or triglycerides ≥150 mg/dL

Table 36. Changes in blood pressure parameters and percent changes in lipid parameters (%) from baseline to Week 68 by subject characteristics (Trials 4373 and 4374: FAS)

Parameter	Baseline	Trial 4373		Trial 4374		
		Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)	Placebo (N = 403)	Semaglutide 1.0 mg (N = 403)	Semaglutide 2.4 mg (N = 404)
Systolic blood pressure (mmHg)	High	−8.5 ± 14.5 (N = 147)	−13.9 ± 16.0 (N = 299)	−7.1 ± 15.4 (N = 117)	−9.7 ± 16.5 (N = 123)	−10.1 ± 14.4 (N = 117)
	Normal	1.2 ± 11.2 (N = 427)	−4.1 ± 12.0 (N = 911)	3.2 ± 13.5 (N = 259)	−0.1 ± 12.7 (N = 256)	−1.3 ± 12.8 (N = 270)
Diastolic blood pressure (mmHg)	High	−5.1 ± 8.9 (N = 147)	−7.5 ± 9.7 (N = 299)	−4.7 ± 9.5 (N = 117)	−2.9 ± 10.0 (N = 123)	−4.8 ± 9.0 (N = 117)
	Normal	1.1 ± 8.4 (N = 427)	−1.6 ± 8.9 (N = 911)	0.9 ± 8.3 (N = 259)	0.4 ± 9.0 (N = 256)	−0.1 ± 7.9 (N = 270)
Total cholesterol (mg/dL)	Outside normal range	−0.7 ± 15.4 (N = 295)	−3.4 ± 16.4 (N = 648)	0.8 ± 19.9 (N = 250)	−1.7 ± 21.4 (N = 254)	−1.1 ± 18.7 (N = 238)
	Normal	3.4 ± 14.4 (N = 265)	−1.6 ± 12.7 (N = 547)	4.0 ± 16.9 (N = 123)	0.1 ± 15.0 (N = 118)	2.3 ± 17.9 (N = 142)
LDL cholesterol (mg/dL)	Outside normal range	3.5 ± 29.3 (N = 295)	−0.1 ± 33.0 (N = 646)	3.8 ± 29.8 (N = 248)	15.6 ± 205.1 (N = 254)	4.0 ± 33.5 (N = 235)
	Normal	5.3 ± 21.5 (N = 263)	0.2 ± 21.0 (N = 546)	5.9 ± 25.7 (N = 121)	1.7 ± 24.9 (N = 118)	6.1 ± 30.9 (N = 141)
HDL cholesterol (mg/dL)	Outside normal range	4.5 ± 16.2 (N = 295)	10.4 ± 18.1 (N = 646)	6.9 ± 17.2 (N = 248)	9.3 ± 19.6 (N = 254)	10.4 ± 17.6 (N = 234)
	Normal	1.2 ± 14.4 (N = 263)	2.2 ± 14.9 (N = 546)	1.5 ± 13.6 (N = 121)	2.3 ± 13.6 (N = 118)	4.6 ± 15.3 (N = 141)
Triglycerides (mg/dL)	Outside normal range	−7.1 ± 36.4 (N = 295)	−21.9 ± 34.5 (N = 648)	−0.9 ± 63.4 (N = 250)	−15.0 ± 36.1 (N = 254)	−17.7 ± 44.7 (N = 238)
	Normal	2.1 ± 30.1 (N = 265)	−12.3 ± 28.1 (N = 546)	7.1 ± 42.1 (N = 123)	−6.4 ± 33.9 (N = 118)	−7.9 ± 31.4 (N = 142)

Mean ± SD
High blood pressure parameter: Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg
Lipid parameter outside the normal range: LDL cholesterol ≥140 mg/dL, HDL cholesterol <40 mg/dL, or triglycerides ≥150 mg/dL

PMDA's view:

The 3 global phase III trials showed a trend towards improvements in blood glucose, blood pressure, and lipid parameters following administration of semaglutide. Likewise, a trend towards improvements was observed also in the Japanese subgroup. With respect to concomitant medications for hypertension, dyslipidemia, or type 2 diabetes, the proportion of subjects who increased these medications at baseline compared with Week 68 in the semaglutide group was similar to or lower than that in the placebo group. The proportion of subjects who decreased OAD or antihypertensive medication was higher in the semaglutide group than in the placebo group. Given the above points etc., semaglutide is expected to improve comorbidities (hypertension, dyslipidemia, and type 2 diabetes) in patients with obesity and hypertension, dyslipidemia, or type 2 diabetes.

7.R.3 Safety

The applicant's explanation:

The incidence and rate of adverse events in global phase III trials (Trials 4382, 4373, and 4374) are shown in Tables 37 to 39. No deaths[16)] were reported in Trial 4382. One subject in the placebo group (glioblastoma, sepsis, and pneumonia aspiration) and 1 subject in the semaglutide 2.4 mg group (death) in Trial 4373, and 1 subject in the placebo group (hepatocellular carcinoma, pulmonary embolism, and respiratory failure), 1 subject in the semaglutide 1.0 mg group (cardio-respiratory arrest), and 1 subject in the semaglutide 2.4 mg group (myocardial infarction) in Trial 4374 died, but a causal relationship to trial drug was denied for all those events. No deaths occurred in the Japanese subgroup. In all trials, the most commonly reported adverse events in the semaglutide group were gastrointestinal disorders (SOC). Events reported at a higher incidence in the semaglutide group than in the placebo group were gastrointestinal disorders (SOC), headache, dizziness, decreased appetite, etc. (Tables 13, 14, 18, 19, 23, and 24). The incidence and rate of adverse drug reactions were higher in the semaglutide group than in the placebo group, but many of the events were gastrointestinal disorders (SOC). Although the incidence of serious adverse events was higher in the semaglutide group than in the placebo group in Trial 4373, a causal relationship to trial drug was denied for most of the observed events, and the majority of the events had an outcome of "resolved" or "resolving." The incidence of adverse events leading to treatment discontinuation was higher in the semaglutide group than in the placebo group in all trials, and this difference was considered largely attributable to adverse events of gastrointestinal disorders. The commonly reported events in the SOC "gastrointestinal disorders" were nausea, constipation, and diarrhoea in Trial 4382, nausea, vomiting, diarrhoea, constipation, and upper abdominal pain in Trial 4373, and nausea, vomiting, and diarrhoea in Trial 4374. The majority of the observed events were non-serious and mild or moderate in severity.

As to comparison between the different doses of semaglutide, Trial 4382 showed no major differences in the incidence and rate of adverse events between the semaglutide 1.7 mg and 2.4 mg groups. In Trial 4374, the incidences and rates of adverse events, adverse drug reactions, and adverse events leading to treatment discontinuation were higher in the semaglutide 2.4 mg group than in the semaglutide 1.0 mg group. These differences were considered largely attributable to adverse events of gastrointestinal disorders, and adverse events of gastrointestinal disorders and gastrointestinal disorders leading to treatment discontinuation increased with increasing dose.

There was no trend towards differences in the incidence and rate of adverse events between the Japanese subgroup and the entire trial population in all trials.

Table 37. Incidence and rate of adverse events (Trial 4382, Japanese subgroup and entire trial population: Safety analysis set)

	Japanese subgroup			Entire trial population		
	Placebo (N = 89)	Semaglutide 1.7 mg (N = 91)	Semaglutide 2.4 mg (N = 179)	Placebo (N = 101)	Semaglutide 1.7 mg (N = 100)	Semaglutide 2.4 mg (N = 199)
All adverse events	78.7 (70) [152.3]	81.3 (74) [259.2]	85.5 (153) [290.9]	79.2 (80) [165.7]	82.0 (82) [354.6]	85.9 (171) [303.3]
All adverse drug reactions	20.2 (18) [21.6]	67.0 (61) [96.8]	53.1 (95) [119.4]	19.8 (20) [23.3]	68.0 (68) [184.3]	54.3 (108) [132.4]
Serious adverse events	7.9 (7) [5.6]	4.4 (4) [3.2]	5.0 (9) [4.5]	6.9 (7) [4.9]	7.0 (7) [7.3]	5.0 (10) [4.4]
Adverse events leading to treatment discontinuation	1.1 (1) [0.8]	2.2 (2) [1.6]	2.8 (5) [3.6]	1.0 (1) [0.7]	3.0 (3) [4.4]	2.5 (5) [3.3]
Gastrointestinal disorders (SOC)	28.1 (25)	63.7 (58)	58.7 (105)	29.7 (30)	64.0 (64)	59.3 (118)
Hypoglycaemia[a)]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gallbladder-related events[b)]	1.1 (1)	1.1 (1)	1.1 (2)	1.0 (1)	1.0 (1)	1.0 (2)
Pancreatitis acute[c)]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Injection site reactions[d)]	0 (0)	0 (0)	2.2 (4)	0 (0)	0 (0)	2.0 (4)
Allergic reactions[e)]	7.9 (7)	9.9 (9)	8.9 (16)	8.9 (9)	11.0 (11)	9.0 (18)
Cardiovascular disorders[f)]	5.6 (5)	8.8 (8)	7.3 (13)	6.9 (7)	9.0 (9)	8.0 (16)
Neoplasm-related events[g)]	3.4 (3)	6.6 (6)	5.0 (9)	4.0 (4)	8.0 (8)	5.0 (10)
Psychiatric disorders (SOC)	1.1 (1)	3.3 (3)	2.8 (5)	1.0 (1)	4.0 (4)	3.0 (6)

Incidence % (n) [Event rate (Number of events/100 person-years)]

a) Events in the SMQ "hypoglycaemia (narrow)" in subjects without type 2 diabetes

b) Events in the SMQs "functional, inflammatory and gallstone related biliary disorders (narrow)" and "infectious biliary disorders (narrow)"

c) Events in the SMQ "pancreatitis acute (narrow)" and events in the HLT "acute and chronic pancreatitis"

d) Events in the HLTs "administration site reactions NEC," "application and instillation site reactions," "infusion site reactions," and "injection site reactions"

e) Events in the SMQs "anaphylactic reaction (narrow)," "angioedema (narrow)," "severe cutaneous adverse reactions (narrow)," "anaphylactic/anaphylactoid shock conditions (narrow)," and "hypersensitivity (narrow)"

f) Events in the SMQs "central nervous system vascular disorders," "vasculitis," "ischaemic heart disease," "cardiac arrhythmias," "cardiac failure," "cardiomyopathy," "embolic and thrombotic events," "shock," and "torsade de pointes/QT prolongation"

g) Events in the SOC "neoplasms benign, malignant and unspecified (incl cysts and polyps)" and events in the SMQs "biliary neoplasms," "breast neoplasms, malignant and unspecified," "liver neoplasms, benign (incl cysts and polyps)," "liver neoplasms, malignant and unspecified," "malignancies," "malignant lymphomas," "oropharyngeal neoplasms," "ovarian neoplasms, malignant and unspecified," "premalignant disorders," "prostate neoplasms, malignant and unspecified," "skin neoplasms, malignant and unspecified," and "uterine and fallopian tube neoplasms, malignant and unspecified"

Table 38. Incidence and rate of adverse events (Trial 4373, Japanese subgroup and entire trial population: Safety analysis set)

	Japanese subgroup		Entire trial population	
	Placebo (N = 33)	Semaglutide 2.4 mg (N = 67)	Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)
All adverse events	90.9 (30) [211.8]	88.1 (59) [273.8]	86.4 (566) [398.0]	89.7 (1171) [566.1]
All adverse drug reactions	27.3 (9) [33.1]	52.2 (35) [90.9]	45.0 (295) [106.7]	70.9 (926) [284.2]
Serious adverse events	6.1 (2) [4.4]	3.0 (2) [2.1]	6.4 (42) [6.4]	9.8 (128) [9.6]
Adverse events leading to treatment discontinuation	3.0 (1) [2.2]	3.0 (2) [2.1]	3.1 (20) [2.8]	7.0 (92) [7.2]
Gastrointestinal disorders (SOC)	51.5 (17)	52.2 (35)	47.9 (314)	74.2 (969)
Hypoglycaemia[a)]	0 (0)	0 (0)	0.8 (5)	0.6 (8)
Gallbladder-related events[b)]	0 (0)	0 (0)	1.2 (8)	2.6 (34)
Pancreatitis acute[c)]	0 (0)	0 (0)	0 (0)	0.2 (2)
Injection site reactions[d)]	3.0 (1)	3.0 (2)	6.7 (44)	5.0 (65)
Allergic reactions[e)]	3.0 (1)	10.4 (7)	8.2 (54)	7.4 (96)
Cardiovascular disorders[f)]	18.2 (6)	6.0 (4)	11.5 (75)	8.2 (107)
Neoplasm-related events[g)]	0 (0)	4.5 (3)	7.5 (49)	7.1 (93)
Psychiatric disorders (SOC)	0 (0)	3.0 (2)	12.7 (83)	9.5 (124)

Incidence % (n) [Event rate (Number of events/100 person-years)]
a)-g) Footnote a)-g) in Table 37

Table 39. Incidence and rate of adverse events (Trial 4374, Japanese subgroup and entire trial population: Safety analysis set)

	Japanese subgroup			Entire trial population		
	Placebo (N = 47)	Semaglutide 1.0 mg (N = 36)	Semaglutide 2.4 mg (N = 42)	Placebo (N = 402)	Semaglutide 1.0 mg (N = 402)	Semaglutide 2.4 mg (N = 403)
All adverse events	80.9 (38) [267.5]	91.7 (33) [302.7]	83.3 (35) [349.9]	76.9 (309) [262.7]	81.8 (329) [350.9]	87.6 (353) [412.2]
All adverse drug reactions	36.2 (17) [33.1]	55.6 (20) [77.7]	52.4 (22) [99.0]	32.1 (129) [51.1]	55.2 (222) [141.8]	63.8 (257) [185.7]
Serious adverse events	10.6 (5) [10.5]	2.8 (1) [2.0]	7.1 (3) [6.8]	9.2 (37) [10.0]	7.7 (31) [10.0]	9.9 (40) [13.3]
Adverse events leading to treatment discontinuation	2.1 (1) [1.5]	0 (0) [0]	2.4 (1) [1.7]	3.5 (14) [3.4]	5.0 (20) [4.3]	6.2 (25) [6.4]
Gastrointestinal disorders (SOC)	46.8 (22)	61.1 (22)	54.8 (23)	34.3 (138)	57.5 (231)	63.5 (256)
Any hypoglycemic episode[a)]	0 (0)	5.6 (2)	21.4 (9)	8.5 (34)	18.7 (75)	21.6 (87)
Gallbladder-related events[b)]	2.1 (1)	2.8 (1)	0 (0)	0.7 (3)	1.0 (4)	0.2 (1)
Pancreatitis acute[c)]	0 (0)	0 (0)	0 (0)	0.2 (1)	0 (0)	0.2 (1)
Injection site reactions[d)]	0 (0)	0 (0)	0 (0)	2.5 (10)	1.5 (6)	3.0 (12)
Allergic reactions[e)]	8.5 (4)	8.3 (3)	9.5 (4)	4.5 (18)	5.5 (22)	6.5 (26)
Cardiovascular disorders[f)]	6.4 (3)	0 (0)	11.9 (5)	9.7 (39)	8.7 (35)	12.4 (50)
Neoplasm-related events[g)]	10.6 (5)	13.9 (5)	16.7 (7)	7.0 (28)	7.2 (29)	5.2 (21)
Psychiatric disorders (SOC)	4.3 (2)	2.8 (1)	0 (0)	3.7 (15)	5.7 (23)	6.0 (24)

Incidence % (n) [Event rate (Number of events/100 person-years)]
a) Levels 1-3 episodes of hypoglycaemia (ADA 2018 classification) (Level 1, plasma glucose <70 mg/dL and ≥54 mg/dL; Level 2, plasma glucose <54 mg/dL; Level 3, a hypoglycemic episode requiring assistance of another person)
b)-g) Footnote b)-g) in Table 37

Subgroup analyses of the incidence and rate of adverse events were performed according to the subject characteristics that differed between the Japanese subgroup and the entire trial population in Trial 4373 or 4374. There were no major differences across the subgroups in each treatment group (Tables 40 and 41).

Table 40. Incidence and rate of adverse events by subject characteristics
(Trial 4373, Japanese subgroup and entire trial population: Safety analysis set)

Item		Japanese subgroup		Entire trial population	
		Placebo (N = 33)	Semaglutide 2.4 mg (N = 67)	Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)
Sex	Male	89.5 (17) [131.9]	85.7 (30) [168.6]	86.0 (135) [282.6]	86.9 (305) [440.8]
	Female	92.9 (13) [317.2]	90.6 (29) [390.8]	86.5 (431) [435.9]	90.7 (866) [613.1]
Body weight (kg)	<90	84.2 (16) [228.6]	84.0 (42) [270.1]	79.6 (129) [375.9]	91.7 (311) [589.7]
	≥90 and <100	100 (10) [203.5]	100 (13) [301.5]	86.1 (130) [362.3]	86.9 (232) [530.4]
	≥100 and <115	100 (3) [163.5]	100 (3) [210.2]	91.4 (149) [430.3]	90.3 (299) [553.5]
	≥115	100 (1) [140.2]	100 (1) [281.0]	88.3 (158) [419.0]	89.2 (329) [581.8]
BMI (kg/m^2)	<30	81.8 (9) [89.5]	83.9 (26) [252.4]	83.3 (30) [259.3]	86.4 (70) [410.9]
	≥30 and <35	93.8 (15) [283.9]	89.3 (25) [249.1]	82.1 (170) [371.1]	89.9 (392) [533.7]
	≥35 and <40	100 (5) [267.2]	100 (6) [305.0]	89.9 (187) [417.5]	91.6 (372) [587.4]
	≥40	100 (1) [208.3]	100 (2) [843.7]	87.7 (179) [433.0]	88.0 (337) [614.4]
Hypertension	Yes	94.1 (16) [165.5]	80.6 (29) [213.7]	87.6 (205) [384.5]	90.5 (427) [510.2]
	No	87.5 (14) [259.2]	96.8 (30) [341.7]	85.7 (361) [405.9]	89.2 (744) [599.0]
Dyslipidemia	Yes	92.0 (23) [194.8]	88.0 (44) [260.2]	85.4 (193) [381.2]	90.2 (450) [525.0]
	No	87.5 (7) [264.9]	88.2 (15) [315.9]	86.9 (373) [407.3]	89.3 (721) [592.5]

Incidence % (n) [Event rate (Number of events/100 person-years)]

Table 41. Incidence and rate of adverse events by subject characteristics
(Trial 4374, Japanese subgroup and entire trial population: Safety analysis set)

Item		Japanese subgroup			Entire trial population		
		Placebo (N = 47)	Semaglutide 1.0 mg (N = 36)	Semaglutide 2.4 mg (N = 42)	Placebo (N = 402)	Semaglutide 1.0 mg (N = 402)	Semaglutide 2.4 mg (N = 403)
Sex	Male	81.3 (26) [268.1]	87.5 (21) [307.9]	83.3 (20) [276.0]	75.0 (159) [223.4]	81.0 (162) [310.5]	82.3 (149) [374.5]
	Female	80.0 (12) [266.2]	100 (12) [292.8]	83.3 (15) [445.0]	78.9 (150) [305.2]	82.7 (167) [390.3]	91.9 (204) [442.1]
Body weight (kg)	<90	73.1 (19) [212.9]	100 (19) [349.8]	87.0 (20) [383.6]	73.8 (104) [225.9]	84.7 (127) [331.1]	90.5 (133) [428.5]
	≥90 and <100	100 (7) [320.5]	70.0 (7) [245.7]	84.6 (11) [357.2]	76.9 (60) [248.7]	75.3 (64) [371.3]	83.1 (64) [381.5]
	≥100 and <115	90.9 (10) [357.3]	100 (5) [267.4]	75.0 (3) [210.4]	79.8 (75) [283.0]	81.5 (66) [351.0]	89.0 (81) [441.9]
	≥115	66.7 (2) [282.8]	100 (2) [246.3]	50.0 (1) [208.3]	78.7 (70) [312.7]	83.7 (72) [364.3]	85.2 (75) [381.5]
BMI (kg/m^2)	<30	70.0 (14) [170.9]	92.3 (12) [321.0]	88.2 (15) [378.4]	71.4 (55) [212.7]	87.9 (58) [307.9]	91.2 (62) [436.0]
	≥30 and <35	88.2 (15) [363.4]	87.5 (14) [319.9]	87.5 (14) [346.7]	79.3 (107) [257.9]	81.0 (132) [336.5]	84.9 (118) [429.6]
	≥35 and <40	83.3 (5) [316.0]	100 (3) [327.0]	57.1 (4) [230.3]	78.4 (76) [269.6]	77.8 (77) [378.0]	86.4 (89) [370.4]
	≥40	100 (4) [263.9]	100 (4) [158.9]	100 (2) [563.0]	76.3 (71) [302.6]	83.8 (62) [381.2]	90.3 (84) [417.1]

Incidence % (n) [Event rate (Number of events/100 person-years)]

Table 42 shows the incidence and rate of adverse events by sex, body weight, and BMI in Trial 4382. There was no trend towards major differences in the incidence and rate of adverse events across the subgroups in each treatment group.

Table 42. Incidence and rate of adverse events by sex, body weight, and BMI (Trial 4382: Safety analysis set)

Item		Placebo (N = 101)	Semaglutide 1.7 mg (N = 100)	Semaglutide 2.4 mg (N = 199)
Sex	Male	77.3 (58/75) [153.7]	79.7 (51/64) [356.0]	81.6 (93/114) [264.0]
	Female	84.6 (22/26) [199.7]	86.1 (31/36) [352.2]	91.8 (78/85) [353.9]
Body weight (kg)	<80	79.2 (19/24) [156.8]	80.6 (25/31) [281.7]	87.7 (64/73) [324.8]
	≥80 and <90	80.6 (29/36) [187.0]	81.1 (30/37) [241.1]	85.7 (54/63) [295.8]
	≥90 and <100	69.6 (16/23) [161.9]	70.6 (12/17) [287.1]	82.1 (23/28) [228.7]
	≥100	88.9 (16/18) [140.3]	100 (15/15) [863.8]	85.7 (30/35) [332.4]
BMI (kg/m^2)	<30	73.7 (28/38) [165.3]	78.3 (36/46) [227.1]	82.6 (71/86) [307.1]
	≥30 and <35	79.5 (35/44) [156.2]	82.9 (29/35) [515.5]	92.0 (69/75) [290.2]
	≥35 and <40	91.7 (11/12) [210.1]	88.2 (15/17) [345.9]	76.2 (16/21) [308.8]
	≥40	85.7 (6/7) [150.5]	100 (2/2) [527.8]	88.2 (15/17) [335.7]

Incidence % (Number of subjects with event/Number of subjects analyzed) [Event rate (Number of events/100 person-years)]

Regarding safety by comorbidity, the incidence and rate of adverse events by glycemic status and comorbidity status (hypertension or dyslipidemia) are shown in Tables 43 to 45. There was no consistent trend across the subgroups of comorbidity status.

Table 43. Incidence and rate of adverse events by glycemic status (Trials 4382 and 4373: Safety analysis set)

	Glycemic status	Trial 4382			Trial 4373	
		Placebo (N = 101)	Semaglutide 1.7 mg (N = 100)	Semaglutide 2.4 mg (N = 199)	Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)
All adverse events	Normo-glycemia	78.4 (40/51) [193.5]	81.8 (45/55) [274.0]	87.7 (93/106) [295.2]	84.2 (330/392) [375.6]	89.8 (640/713) [561.4]
	Prediabetes	80.0 (20/25) [129.0]	75.0 (15/20) [722.4]	90.9 (40/44) [255.4]	89.7 (236/263) [431.3]	89.5 (531/593) [571.8]
	Diabetes mellitus	80.0 (20/25) [146.0]	88.0 (22/25) [247.6]	77.6 (38/49) [363.3]	—	—
Serious adverse events	Normo-glycemia	7.8 (4/51) [5.6]	9.1 (5/55) [6.7]	6.6 (7/106) [6.2]	4.6 (18/392) [3.8]	8.7 (62/713) [8.7]
	Prediabetes	4.0 (1/25) [2.9]	10.0 (2/20) [18.8]	2.3 (1/44) [1.6]	9.1 (24/263) [10.2]	11.1 (66/593) [10.7]
	Diabetes mellitus	8.0 (2/25) [5.6]	0 (0/25) [0]	4.1 (2/49) [2.9]	—	—
Adverse events leading to treatment discontinuation	Normo-glycemia	0 (0/51) [0]	3.6 (2/55) [6.7]	3.8 (4/106) [4.1]	2.6 (10/392) [2.6]	6.7 (48/713) [6.5]
	Prediabetes	4.0 (1/25) [2.9]	5.0 (1/20) [3.8]	0 (0/44) [0]	3.8 (10/263) [3.0]	7.4 (44/593) [8.0]
	Diabetes mellitus	0 (0/25) [0]	0 (0/25) [0]	2.0 (1/49) [4.4]	—	—
Gastrointestinal disorders (SOC)	Normo-glycemia	35.3 (18/51) [40.7]	63.6 (35/55) [120.1]	57.5 (61/106) [127.0]	45.9 (180/392) [80.5]	74.9 (534/713) [253.6]
	Prediabetes	20.0 (5/25) [17.2]	70.0 (14/20) [519.3]	56.8 (25/44) [108.1]	51.0 (134/263) [101.8]	73.4 (435/593) [251.3]
	Diabetes mellitus	28.0 (7/25) [22.5]	60.0 (15/25) [81.6]	65.3 (32/49) [134.8]	—	—
Hypoglycaemia [a)]	Normo-glycemia	0 (0/51) [0]	0 (0/55) [0]	0 (0/106) [0]	1.0 (4/392) [1.0]	0.3 (2/713) [0.2]
	Prediabetes	0 (0/25) [0]	0 (0/20) [0]	0 (0/44) [0]	0.4 (1/263) [0.6]	1.0 (6/593) [1.7]

Incidence % (Number of subjects with event/Number of subjects analyzed) [Event rate (Number of events/100 person-years)];
—, No subjects in the subgroup
Glycemic status was categorized according to ADA definitions.
a) Events in the SMQ "hypoglycaemia (narrow)" in subjects without type 2 diabetes in Trials 4373 and 4382

Table 44. Incidence and rate of adverse events by comorbidity status (hypertension or dyslipidemia)
(Trial 4382: Safety analysis set)

	Comorbidity status	Placebo (N = 101)	Semaglutide 1.7 mg (N = 100)	Semaglutide 2.4 mg (N = 199)
All adverse events	With hypertension	76.7 (56/73) [153.0]	82.2 (60/73) [366.5]	85.5 (130/152) [293.4]
	Without hypertension	85.7 (24/28) [198.0]	81.5 (22/27) [318.0]	87.2 (41/47) [334.2]
	With dyslipidemia	77.5 (62/80) [157.9]	80.5 (70/87) [366.6]	85.4 (152/178) [304.3]
	Without dyslipidemia	85.7 (18/21) [195.7]	92.3 (12/13) [276.1]	90.5 (19/21) [294.9]
Serious adverse events	With hypertension	9.6 (7/73) [6.9]	5.5 (4/73) [6.8]	6.6 (10/152) [5.7]
	Without hypertension	0 (0/28) [0]	11.1 (3/27) [9.0]	0 (0/47) [0]
	With dyslipidemia	6.3 (5/80) [4.4]	8.0 (7/87) [8.5]	4.5 (8/178) [3.7]
	Without dyslipidemia	9.5 (2/21) [6.9]	0 (0/13) [0]	9.5 (2/21) [10.2]
Adverse events leading to treatment discontinuation	With hypertension	1.4 (1/73) [1.0]	1.4 (1/73) [1.0]	3.3 (5/152) [4.3]
	Without hypertension	0 (0/28) [0]	7.4 (2/27) [15.0]	0 (0/47) [0]
	With dyslipidemia	0 (0/80) [0]	3.4 (3/87) [5.1]	2.8 (5/178) [3.7]
	Without dyslipidemia	4.8 (1/21) [3.4]	0 (0/13) [0]	0 (0/21) [0]
Gastrointestinal disorders (SOC)	With hypertension	28.8 (21/73) [32.4]	65.8 (48/73) [209.0]	59.2 (90/152) [115.8]
	Without hypertension	32.1 (9/28) [25.1]	59.3 (16/27) [123.0]	59.6 (28/47) [152.7]
	With dyslipidemia	28.8 (23/80) [26.6]	60.9 (53/87) [199.8]	58.4 (104/178) [123.4]
	Without dyslipidemia	33.3 (7/21) [44.6]	84.6 (11/13) [110.4]	66.7 (14/21) [135.6]

Incidence % (Number of subjects with event/Number of subjects analyzed) [Event rate (Number of events/100 person-years)]

Table 45. Incidence and rate of adverse events by comorbidity status (hypertension or dyslipidemia)
(Trials 4373 and 4374: Safety analysis set)

	Comorbidity status	Trial 4373		Trial 4374		
		Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)	Placebo (N = 402)	Semaglutide 1.0 mg (N = 402)	Semaglutide 2.4 mg (N = 403)
All adverse events	With hypertension	87.6 (205/234) [384.5]	90.5 (427/472) [510.2]	76.6 (219/286) [271.3]	81.0 (230/284) [350.9]	90.9 (250/275) [418.5]
	Without hypertension	85.7 (361/421) [405.9]	89.2 (744/834) [599.0]	77.6 (90/116) [242.0]	83.9 (99/118) [351.0]	80.5 (103/128) [398.8]
	With dyslipidemia	85.4 (193/226) [381.2]	90.2 (450/499) [525.0]	79.2 (225/284) [275.7]	84.4 (233/276) [365.0]	89.8 (238/265) [439.9]
	Without dyslipidemia	86.9 (373/429) [407.3]	89.3 (721/807) [592.5]	71.2 (84/118) [230.9]	76.2 (96/126) [319.7]	83.3 (115/138) [360.0]
Serious adverse events	With hypertension	8.1 (19/234) [8.9]	12.5 (59/472) [12.2]	10.5 (30/286) [12.1]	8.8 (25/284) [11.4]	11.3 (31/275) [17.1]
	Without hypertension	5.5 (23/421) [5.0]	8.3 (69/834) [8.1]	6.0 (7/116) [5.2]	5.1 (6/118) [6.6]	7.0 (9/128) [5.3]
	With dyslipidemia	7.5 (17/226) [7.1]	11.8 (59/499) [10.6]	11.6 (33/284) [12.8]	8.3 (23/276) [11.0]	10.6 (28/265) [16.7]
	Without dyslipidemia	5.8 (25/429) [6.0]	8.6 (69/807) [9.0]	3.4 (4/118) [3.3]	6.3 (8/126) [7.9]	8.7 (12/138) [7.0]
Adverse events leading to treatment discontinuation	With hypertension	1.7 (4/234) [1.3]	5.9 (28/472) [6.0]	4.2 (12/286) [4.3]	4.2 (12/284) [4.0]	7.3 (20/275) [7.5]
	Without hypertension	3.8 (16/421) [3.6]	7.7 (64/834) [7.9]	1.7 (2/116) [1.3]	6.8 (8/118) [5.2]	3.9 (5/128) [4.1]
	With dyslipidemia	2.7 (6/226) [2.0]	6.8 (34/499) [6.3]	3.5 (10/284) [3.2]	5.4 (15/276) [4.9]	8.7 (23/265) [9.2]
	Without dyslipidemia	3.3 (14/429) [3.2]	7.2 (58/807) [7.8]	3.4 (4/118) [3.9]	4.0 (5/126) [3.0]	1.4 (2/138) [1.1]
Gastrointestinal disorders (SOC)	With hypertension	44.4 (104/234) [70.7]	69.3 (327/472) [218.6]	31.1 (89/286) [44.5]	54.2 (154/284) [131.2]	64.0 (176/275) [165.3]
	Without hypertension	49.9 (210/421) [99.8]	77.0 (642/834) [272.5]	42.2 (49/116) [62.0]	65.3 (77/118) [150.2]	62.5 (80/128) [190.3]
	With dyslipidemia	45.1 (102/226) [78.7]	69.9 (349/499) [219.4]	34.5 (98/284) [49.9]	59.8 (165/276) [137.7]	66.0 (175/265) [173.0]
	Without dyslipidemia	49.4 (212/429) [94.8]	76.8 (620/807) [274.0]	33.9 (40/118) [48.9]	52.4 (66/126) [134.4]	58.7 (81/138) [174.1]

Incidence % (Number of subjects with event/Number of subjects analyzed) [Event rate (Number of events/100 person-years)]

PMDA's view:

PMDA conducted its safety review, focusing on the incidence and rate of adverse events in the global phase III trials. The main events reported were known events with the commercially available semaglutide formulations. Also, when analyzed by glycemic status and comorbidity status (hypertension or dyslipidemia), there was no trend towards increases in specific adverse events. As to comparison between the different doses of semaglutide, although the incidences and rates of adverse events and adverse events leading to treatment discontinuation tended to be higher in the semaglutide 2.4 mg group than in the semaglutide 1.0 mg group in Trial 4374, there were no major differences in the incidence and rate of serious adverse events among the treatment groups including the placebo group. Trial 4382 showed no major differences in the incidence and rate of adverse events between the semaglutide 1.7 mg and 2.4 mg groups. In Trials 4382, 4373, and 4374, which were conducted as global studies, there was no trend towards differences in the incidence and rate of adverse events between the Japanese subgroup and the entire trial population.

In addition to the above analyses etc., taking account of the mechanism of action of semaglutide, clinical trial results, etc., PMDA assessed adverse events of special interest individually as shown below, and concluded that semaglutide at doses up to 2.4 mg has acceptable safety, provided that as with the commercially available semaglutide formulations, appropriate precautionary statements are included in the package insert.

7.R.3.1 Gastrointestinal disorders

The applicant's explanation:

Table 46 shows the incidence and rate of gastrointestinal disorders (SOC) in the global phase III trials (Trials 4382, 4373, and 4374). In all trials, the incidence and rate of gastrointestinal disorders were higher in the semaglutide group than in the placebo group. The commonly reported events of gastrointestinal disorders in the semaglutide group were nausea, diarrhoea, vomiting, and constipation. The majority of the events of gastrointestinal disorders reported with semaglutide were non-serious and mild or moderate in severity, with an outcome of "resolved." With regard to serious gastrointestinal disorders, there were no major differences among the treatment groups, and all those events resolved, except that hiatus hernia reported by 1 subject in the semaglutide 2.4 mg group in Trial 4373 and gastric ulcer reported by 1 subject in the semaglutide 1.0 mg group in Trial 4374 remained unresolved. Although the incidence of gastrointestinal disorders leading to treatment discontinuation was higher in the semaglutide group than in the placebo group, most of the events were non-serious and mild or moderate in severity, with an outcome of "resolved" or "resolving." When analyzed by dose of semaglutide, while the incidences and rates of all gastrointestinal disorders and gastrointestinal disorders leading to treatment discontinuation tended to be higher in the semaglutide 2.4 mg group than in the semaglutide 1.0 mg group in Trial 4374, there was no trend towards higher incidences and rates in the semaglutide 2.4 mg group than in the semaglutide 1.7 mg group in Trial 4382.

Table 46. Incidence and rate of gastrointestinal disorders (SOC) (Safety analysis set)

	Trial 4382		
	Placebo (N = 101)	Semaglutide 1.7 mg (N = 100)	Semaglutide 2.4 mg (N = 199)
All gastrointestinal disorders	29.7 (30) 43 [30.3]	64.0 (64) 256 [187.9]	59.3 (118) 343 [124.7]
Serious gastrointestinal disorders	1.0 (1) 1 [0.7]	0 (0) 0 [0]	1.0 (2) 2 [0.7]
Gastrointestinal disorders leading to treatment discontinuation	0 (0) 0 [0]	2.0 (2) 5 [3.7]	2.0 (4) 5 [1.8]

	Trial 4373		Trial 4374		
	Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)	Placebo (N = 402)	Semaglutide 1.0 mg (N = 402)	Semaglutide 2.4 mg (N = 403)
All gastrointestinal disorders	47.9 (314) 739 [89.1]	74.2 (969) 4309 [252.6]	34.3 (138) 262 [49.6]	57.5 (231) 724 [136.7]	63.5 (256) 924 [173.3]
Serious gastrointestinal disorders	0 (0) 0 [0]	1.4 (18) 25 [1.5]	0.7 (3) 3 [0.6]	0.7 (3) 7 [1.3]	1.5 (6) 7 [1.3]
Gastrointestinal disorders leading to treatment discontinuation	0.8 (5) 5 [0.6]	4.5 (59) 78 [4.6]	1.0 (4) 6 [1.1]	3.5 (14) 16 [3.0]	4.2 (17) 24 [4.5]

Incidence % (n) No. of events [Event rate (Number of events/100 person-years)]

With regard to the time to the onset of gastrointestinal disorders, the first event had mostly been reported during the first 20 weeks of treatment, regardless of treatment group, in the global phase III trials (Trials 4382, 4373, and 4374). The proportion of subjects reporting their first event during the first 20 weeks of treatment was higher in the semaglutide group than in the placebo group. In all treatment groups, fewer subjects reported a new event beyond 20 weeks of treatment compared with during the first 20 weeks. The median durations of nausea, vomiting, and diarrhoea were short and similar among the treatment groups (nausea, 5-10 days; vomiting, 1-2 days; diarrhoea, 2-5 days).

The above clinical trial results showed that although the incidence of gastrointestinal disorders was higher in the semaglutide group than in the placebo group, most events were non-serious and mild or moderate in severity, with an outcome of "resolved." While the incidences and rates of gastrointestinal disorders and gastrointestinal disorders leading to treatment discontinuation tended to be higher in the semaglutide 2.4 mg group than in the semaglutide 1.0 mg group in Trial 4374, there was no trend towards higher incidences and rates in the semaglutide 2.4 mg group than in the semaglutide 1.7 mg group in Trial 4382. Thus, the safety profile of the proposed product as to gastrointestinal disorders is similar to those of the commercially available semaglutide formulations for type 2 diabetes, and no new clinically relevant concerns have been identified.

PMDA's view:

There is no particular problem with the applicant's view. Although the incidence and rate of gastrointestinal disorders were higher in the semaglutide group than in the placebo group in the clinical trials, the safety profile of the proposed product as to gastrointestinal disorders, including their severity and outcome, is similar to those of the commercially available semaglutide formulations for type 2 diabetes, and no new clinically relevant concerns have been identified. Taking also into account that gastrointestinal disorders leading to treatment discontinuation and serious gastrointestinal disorders occurred following administration of semaglutide also in the clinical trials in patients with obesity disease, as with the commercially available semaglutide formulations, appropriate precautionary statements should be included in the package insert.

7.R.3.2 Hypoglycaemia

The applicant's explanation:

In clinical trials in patients without type 2 diabetes (Trial 4373, etc.), episodes of hypoglycaemia reported as adverse events[23)] were evaluated. In Trial 4373, the incidence and rate of hypoglycaemia were 0.8% (5 of 655) of subjects and 0.8, respectively, in the placebo group and 0.6% (8 of 1306) of subjects and 0.9, respectively, in the semaglutide 2.4 mg group, i.e., the incidence and rate of hypoglycaemia were low in the both treatment groups and similar between the treatment groups. In the both treatment groups, no severe events, serious adverse events, or adverse events leading to treatment discontinuation were reported, and most events were mild in severity with an outcome of "resolved." In Trial 4382, hypoglycaemia was not reported in subjects without type 2 diabetes.

According to a pooled analysis of phase III trials (a pooled analysis of Trials 4373, 4375,[24)] and 4376[25)]), there were no major differences in the incidence and rate of hypoglycaemia according to glycemic status (Table 47).

[23)] Events in the SMQ "hypoglycemia (narrow)"

[24)] A 68-week, randomized, double-blind, parallel-group trial to investigate the efficacy and safety of placebo or semaglutide 2.4 mg administered subcutaneously once weekly as an adjunct to intensive behavioral therapy including low-calorie diet and exercise in patients with overweight or obesity (target sample size, 600 subjects [200 in the placebo group, 400 in the semaglutide 2.4 mg group]). Key inclusion criteria were patients with BMI ≥30.0 kg/m^2 or BMI ≥27.0 kg/m^2 in the presence of hypertension, dyslipidemia, obstructive sleep apnoea, or cardiovascular disease, ≥18 years of age. Patients with HbA1c ≥6.5% were excluded. The starting dose of semaglutide was 0.25 mg, and the dose was to be escalated every 4 weeks to 0.5, 1.0, 1.7, and 2.4 mg.

[25)] A 68-week, randomized, double-blind trial to investigate the efficacy and safety of placebo or semaglutide 2.4 mg administered subcutaneously once weekly as an adjunct to dietary and exercise therapy in patients with overweight or obesity (target sample size, 750 subjects [250 in the switch to placebo group, 500 in the continued semaglutide 2.4 mg group]). Key inclusion criteria were patients with BMI ≥30.0 kg/m^2 or BMI ≥27.0 kg/m^2 in

Table 47. Incidence and rate of hypoglycaemia by glycemic status according to pooled analysis of phase III trials[a)] (Safety analysis set)

	Glycemic status	Placebo	Semaglutide 2.4 mg
Hypoglycaemia[b)]	Normoglycemia	0.9 (6/642) 7 [0.9]	0.6 (7/1196) 7 [0.5]
	Prediabetes	0.4 (2/485) 3 [0.5]	0.6 (6/1051) 13 [0.9]

Incidence % (Number of subjects with episode/Number of evaluable subjects)
No. of episodes [Rate of episodes (Number of episodes/100 person-years)]
Glycemic status was categorized according to ADA definitions.
a) Pooled analysis of Trials 4373, 4375, and 4376
b) Events in the SMQ "hypoglycaemia (narrow)"

In clinical trials in obese patients with type 2 diabetes (Trials 4382 and 4374), episodes of hypoglycaemia reported on hypoglycemic episode forms were evaluated according to the American Diabetes Association (ADA) classification (2013 [*Diabetes Care*. 2013;36:1384-95] and 2018 [*Diabetes Care*. 2018;41(Suppl 1):S55-S64]) and the classification pre-defined by the applicant. Table 48 shows the incidence and rate of hypoglycaemia in the subgroup with type 2 diabetes of Trial 4382 and Trial 4374. The incidence and rate of hypoglycaemia according to the ADA 2018 classification were higher in the semaglutide group than in the placebo group in the both trials. While the rate of hypoglycaemia tended to be higher in the semaglutide 2.4 mg group than in the semaglutide 1.0 mg group, the incidence was similar, and there were no clear differences between the 2 doses of semaglutide. Only 1 subject in the semaglutide 2.4 mg group of Trial 4374 experienced 1 episode of severe hypoglycaemia (level 3 [ADA 2018 classification]). This event occurred in the subject taking metformin at baseline, and the subject was hospitalized due to a serious adverse event (chronic cholecystitis) during dose escalation, and a plasma glucose of 56 mg/dL was reported at admission. The subject recovered following hydration and intravenous administration of glucose. Although the incidence and rate of hypoglycaemia according to the ADA 2013 classification were similar to the trend of occurrence according to the ADA 2018 classification in the both trials, the incidence and rate of any hypoglycemic episode were higher in the semaglutide 2.4 mg group than in the semaglutide 1.7 mg group in Trial 4382. The incidence and rate of blood glucose (BG) confirmed hypoglycaemia[26)] were higher in the semaglutide 2.4 mg and 1.0 mg groups than in the placebo group in Trial 4374, and the rate tended to be higher in the semaglutide 2.4 mg group than in the semaglutide 1.0 mg group, whereas the incidence was similar between the doses. In the both trials, no hypoglycemic episodes were reported as serious adverse events.

the presence of hypertension, dyslipidemia, obstructive sleep apnoea, or cardiovascular disease, ≥18 years of age. Patients with HbA1c ≥6.5% were excluded. All subjects were to receive semaglutide during the run-in period (20 weeks). The starting dose of semaglutide was 0.25 mg, and the dose was to be escalated every 4 weeks to 0.5, 1.0, 1.7, and 2.4 mg. After 20 weeks, subjects were to be randomized to receive placebo or semaglutide 2.4 mg for 48 weeks (a total of 68 weeks).

[26)] Severe hypoglycemia (an episode requiring assistance of another person) or plasma glucose <56 mg/dL with or without symptoms consistent with hypoglycemia

Table 48. Incidence and rate of hypoglycaemia in patients with overweight or obesity and type 2 diabetes (Safety analysis set)

		Trial 4382 (Subgroup with type 2 diabetes)			Trial 4374		
		Placebo (N = 25)	Semaglutide 1.7 mg (N = 25)	Semaglutide 2.4 mg (N = 49)	Placebo (N = 402)	Semaglutide 1.0 mg (N = 402)	Semaglutide 2.4 mg (N = 403)
ADA 2013 classification	Any hypoglycemic episode[a)]	0 (0)	8.0 (2)	16.3 (8)	11.9 (48)	21.9 (88)	25.1 (101)
		0 [0]	5 [14.1]	19 [27.8]	117 [22.1]	292 [55.1]	378 [70.9]
	Severe hypoglycaemia[b)]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.2 (1)
		0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 [0.2]
	Documented symptomatic hypoglycaemia[c)]	0 (0)	0 (0)	4.1 (2)	7.2 (29)	12.7 (51)	15.1 (61)
		0 [0]	0 [0]	3 [4.4]	70 [13.2]	99 [18.7]	178 [33.4]
	Asymptomatic hypoglycaemia[d)]	0 (0)	8.0 (2)	6.1 (3)	3.5 (14)	10.9 (44)	14.4 (58)
		0 [0]	5 [14.1]	4 [5.9]	21 [4.0]	173 [32.7]	168 [31.5]
	Pseudo-hypoglycaemia[e)]	0 (0)	0 (0)	8.2 (4)	3.0 (12)	2.7 (11)	2.0 (8)
		0 [0]	0 [0]	4 [5.9]	15 [2.8]	12 [2.3]	15 [2.8]
	Probable symptomatic hypoglycaemia[f)]	0 (0)	0 (0)	8.2 (4)	2.2 (9)	1.7 (7)	2.7 (11)
		0 [0]	0 [0]	8 [11.7]	11 [2.1]	8 [1.5]	16 [3.0]
ADA 2018 classification	Any hypoglycemic episode[g)]	0 (0)	8.0 (2)	10.2 (5)	8.5 (34)	18.7 (75)	21.6 (87)
		0 [0]	5 [14.1]	7 [10.3]	87 [16.5]	243 [45.9]	316 [59.3]
	Level 3[b)]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.2 (1)
		0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	1 [0.2]
	Level 2[h)]	0 (0)	0 (0)	0 (0)	2.5 (10)	6.7 (27)	6.2 (25)
		0 [0]	0 [0]	0 [0]	17 [3.2]	38 [7.2]	57 [10.7]
	Level 1[i)]	0 (0)	8.0 (2)	10.2 (5)	7.7 (31)	15.7 (63)	20.3 (82)
		0 [0]	5 [14.1]	7 [10.3]	70 [13.2]	205 [38.7]	258 [48.4]
BG confirmed hypoglycaemia[j)]		0 (0)	0 (0)	0 (0)	4.0 (16)	7.7 (31)	7.2 (29)
		0 [0]	0 [0]	0 [0]	23 [4.4]	47 [8.9]	77 [14.4]

Upper row, Incidence % (n); Lower row, Number of episodes [Number of episodes/100 person-years]

a) Severe hypoglycaemia, documented symptomatic hypoglycaemia, asymptomatic hypoglycaemia, pseudo-hypoglycaemia, or probable symptomatic hypoglycaemia

b) An episode requiring assistance of another person

c) An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤70 mg/dL

d) An episode not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration ≤70 mg/dL

e) An episode during which the subject reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration >70 mg/dL but approaching that level

f) An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤70 mg/dL

g) Levels 1-3

h) Plasma glucose <54 mg/dL

i) Plasma glucose <70 mg/dL and ≥54 mg/dL

j) Severe hypoglycaemia or plasma glucose <56 mg/dL with or without symptoms consistent with hypoglycaemia

With regard to the influence of concomitant OAD use, patients treated with up to 3 OADs (metformin, sulfonylurea [SU], sodium glucose co-transporter 2 [SGLT2] inhibitors, or thiazolidinediones) were eligible for enrollment in Trials 4382 and 4374. The risk of hypoglycaemia is known to be increased when the commercially available semaglutide formulations for type 2 diabetes are used in combination with insulin or an SU than when used alone. The influence of concomitant SUs on the occurrence of hypoglycaemia was assessed based on the data from Trial 4374. Among subjects with level 2 or 3 episodes of hypoglycaemia (ADA 2018 classification), the proportion of subjects taking SUs at the onset of the event was 70.0% (7 of 10) of subjects in the placebo group, 55.6% (15 of 27) of subjects in the semaglutide 1.0 mg group, and 61.5% (16 of 26) of subjects in the semaglutide 2.4 mg group, which were higher than the proportion of subjects taking SUs at baseline in the entire trial population (22.7%). This trend was similar to the results obtained with the commercially available semaglutide formulations for type 2 diabetes.

The above clinical trial results showed no trend towards an increased risk of hypoglycaemia following administration of the proposed product in patients with obesity disease, compared with the commercially available semaglutide formulations indicated for type 2 diabetes.

PMDA's view:
There was no trend towards a higher incidence or rate of hypoglycaemia in the semaglutide group than in the placebo group among patients without type 2 diabetes. With regard to the occurrence of hypoglycaemia in patients with type 2 diabetes, although there was a trend towards a dose-dependent increase in the rate of hypoglycaemia, very few severe hypoglycemic episodes occurred. The proposed product has acceptable safety, provided that as with the commercially available semaglutide formulations, an appropriate precautionary statement about hypoglycaemia is included in the package insert. It should be noted that there was a trend towards increases in hypoglycemic episodes when semaglutide was used with SUs, and that concomitant use of semaglutide with insulin was not evaluated in clinical trials in patients with obesity disease. As with the commercially available semaglutide formulations, an appropriate precautionary statement about concomitant use with insulin or SUs should be included in the package insert.

7.R.3.3 Pancreatitis- and gallbladder-related events

The applicant's explanation:
During the period from the date of randomization to the end of trial in the global phase III trials (Trials 4382, 4373, and 4374), the event adjudication committee (EAC) (composed of medical specialists)-confirmed event of pancreatitis acute was not reported in Trial 4382, and 5 EAC-confirmed events of pancreatitis acute occurred in 3 subjects in the semaglutide 2.4 mg group (mild pancreatitis acute [3 subjects, 4 events], moderate to severe pancreatitis acute [1 subject, 1 event]) in Trial 4373. In Trial 4374, 1 EAC-confirmed event of pancreatitis acute occurred in 1 subject in the placebo group (mild pancreatitis acute) and 2 EAC-confirmed events of pancreatitis acute occurred in 1 subject in the semaglutide 2.4 mg group (moderate to severe pancreatitis acute).

No pancreatitis-related events[27)] were reported in Trial 4382. Two pancreatitis-related events occurred in 2 subjects in the semaglutide 2.4 mg group (pancreatitis acute [2 subjects]) in Trial 4373. In Trial 4374, 1 pancreatitis-related event occurred in 1 subject in the placebo group (obstructive pancreatitis) and 1 pancreatitis-related event occurred in 1 subject in the semaglutide 2.4 mg group (pancreatitis acute). Among which, 1 event occurring in 1 subject in the semaglutide 2.4 mg group (pancreatitis acute) in Trial 4373 and 1 event occurring in 1 subject in the semaglutide 2.4 mg group (pancreatitis acute) in Trial 4374 were classified as adverse drug reactions. In Trial 4373, 2 events occurring in 2 subjects in the semaglutide 2.4 mg group (pancreatitis acute [2 subjects]) were classified as serious adverse events, of which 1 event occurring in 1 subject led to treatment discontinuation. The both events had an outcome of "resolved." In Trial 4374, 1 event occurring in 1 subject in the placebo group (obstructive pancreatitis) was classified as a serious adverse event with an outcome of "resolved," and 1 event occurring in 1 subject in the semaglutide 2.4 mg group (pancreatitis acute) led to treatment discontinuation, but was non-serious with an outcome of "resolved with sequelae."

27) Events in the SMQ "pancreatitis acute (narrow)" and events in the HLT "acute and chronic pancreatitis"

Table 49 shows the incidence and rate of gallbladder-related events.[28)] The number of gallbladder-related events was limited in Trials 4382 and 4374, there were no clear differences between the placebo and semaglutide groups, and no dose-response relationship between the doses of semaglutide was observed. In Trial 4373, gallbladder-related events occurred more frequently in the semaglutide 2.4 mg group than in the placebo group, but the majority of the events were mild or moderate in severity. The events reported by 2 subjects in the semaglutide 2.4 mg group (cholelithiasis [2 subjects]) led to treatment discontinuation, but the both events had an outcome of "resolved." In all trials, the most commonly reported event was cholelithiasis.

Table 49. Incidence and rate of gallbladder-related events (Safety analysis set)

	Trial 4382		
	Placebo (N = 101)	Semaglutide 1.7 mg (N = 100)	Semaglutide 2.4 mg (N = 199)
Gallbladder-related events	1.0 (1) [0.7]	1.0 (1) [0.7]	1.0 (2) [0.7]
Serious gallbladder-related events	0 (0) [0]	0 (0) [0]	1.0 (2) [0.7]

	Trial 4373		Trial 4374		
	Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)	Placebo (N = 402)	Semaglutide 1.0 mg (N = 402)	Semaglutide 2.4 mg (N = 403)
Gallbladder-related events	1.2 (8) [1.0]	2.6 (34) [2.5]	0.7 (3) [0.8]	1.0 (4) [0.8]	0.2 (1) [0.4]
Serious gallbladder-related events	0.3 (2) [0.2]	1.3 (17) [1.2]	0.2 (1) [0.2]	0.2 (1) [0.2]	0.2 (1) [0.4]

Incidence % (n) [Event rate (Number of events/100 person-years)]

Table 50 shows the incidences and rates of EAC-confirmed pancreatitis, pancreatitis-related events, and gallbladder-related events according to a pooled analysis of phase III trials.[29)] All those events occurred infrequently.

Table 50. Incidences and rates of EAC-confirmed pancreatitis and pancreatitis- or gallbladder-related events according to pooled analysis of phase III trials[a)] (Safety analysis set)

	Placebo (N = 1529)	Semaglutide 2.4 mg (N = 2650)
EAC-confirmed pancreatitis	<0.1 (1) [<0.1]	0.2 (4) [0.2]
Pancreatitis-related events	<0.1 (1) [<0.1]	0.1 (3) [<0.1]
Gallbladder-related events	1.6 (24) [1.5]	2.5 (70) [2.4]

Incidence % (n) [Event rate (Number of events/100 person-years)]
a) Pooled analysis of Trials 4373, 4374, 4375, and 4376

Concerning the levels of pancreatic enzymes, Table 51 shows the proportion of subjects with elevated lipase 2-5 times the upper limit of normal (ULN) or >5 times the ULN at Week 68 among subjects with baseline lipase or amylase <2 times the ULN. There were no subjects with elevated amylase 2-5 times or >5 times the ULN at Week 68 in Trials 4382 and 4373. In Trial 4374, amylase increased to 2-5 times the ULN in only 2 subjects in the semaglutide 1.0 mg group.

28) Events in the SMQs "functional, inflammatory and gallstone related biliary disorders (narrow)" and "infectious biliary disorders (narrow)"
29) Pooled analysis of Trials 4373, 4374, 4375, and 4376

Table 51. Proportion of subjects with elevated lipase at Week 68 (Safety analysis set)

	Trial 4382		
	Placebo (N = 100)	Semaglutide 1.7 mg (N = 99)	Semaglutide 2.4 mg (N = 199)
2-5 × ULN	0 (0/97)	0 (0/93)	1.1 (2/186)
>5 × ULN	0 (0/97)	0 (0/93)	0.5 (1/186)

	Trial 4373		Trial 4374		
	Placebo (N = 652)	Semaglutide 2.4 mg (N = 1304)	Placebo (N = 389)	Semaglutide 1.0 mg (N = 400)	Semaglutide 2.4 mg (N = 399)
2-5 × ULN	0.4 (2/494)	1.3 (14/1051)	1.2 (4/330)	2.3 (8/348)	4.6 (16/347)
>5 × ULN	0 (0/494)	0.2 (2/1051)	0 (0/330)	0.6 (2/348)	0 (0/347)

Incidence % (Number of subjects with elevated lipase/Number of subjects with baseline lipase <2 times the ULN)

The above clinical trial results indicated no evidence of an increased risk of pancreatitis following administration of semaglutide. Though cholelithiasis tended to occur more frequently in the semaglutide group than in the placebo group, clinically relevant gallbladder-related events were uncommon. These results were similar to the findings with the commercially available semaglutide formulations indicated for type 2 diabetes, and no new clinically relevant concerns have been identified.

PMDA's view:

There is no particular problem with the applicant's view (The trend of occurrence of pancreatitis- or gallbladder-related events in the clinical trials was similar to that with the commercially available semaglutide formulations indicated for type 2 diabetes, and no new clinically relevant concerns have been identified.). Taking also into account that pancreatitis acute, gallbladder-related events, and elevated pancreatic enzymes occurred following administration of semaglutide also in the clinical trials in patients with obesity disease, as with the commercially available semaglutide formulations, a precautionary statement about pancreatitis etc. should be included in the package insert.

7.R.3.4 Diabetic retinopathy

The applicant's explanation:

The incidences of events of retinal disorders[30)] during the period from the date of randomization to the end of trial in the subgroup with type 2 diabetes of Trial 4382 and Trial 4374 in patients with type 2 diabetes were determined. In Trial 4382, the incidences of retinal disorders were 8.0% (2 of 25) of subjects in the placebo group, 8.0% (2 of 25) of subjects in the semaglutide 1.7 mg group, and 14.3% (7 of 49) of subjects in the semaglutide 2.4 mg group, showing a higher incidence in the semaglutide 2.4 mg group than in the placebo or semaglutide 1.7 mg group. In Trial 4374, the incidences were 4.2% (17 of 402) of subjects in the placebo group, 6.2% (25 of 402) of subjects in the semaglutide 1.0 mg group, and 6.9% (28 of 403) of subjects in the semaglutide 2.4 mg group, showing a higher incidence in the semaglutide 1.0 mg or 2.4 mg group than in the placebo group. The majority of the observed events were diabetic retinopathy. In the both trials, no serious adverse events were reported, and most of the events were mild in severity. An event leading to treatment discontinuation occurred in 1 subject in the semaglutide 1.0 mg group in Trial 4374.

30) Events in the SMQ "retinal disorders (narrow)" and events in the HLT "visual impairment and blindness (excl colour blindness)"

The incidences of adverse events classified by the investigator as new onset or worsening of diabetic retinopathy were 8.0% (2 of 25) of subjects in the placebo group, 4.0% (1 of 25) of subjects in the semaglutide 1.7 mg group, and 6.1% (3 of 49) of subjects in the semaglutide 2.4 mg group in Trial 4382 and 3.0% (12 of 402) of subjects in the placebo group, 3.0% (12 of 402) of subjects in the semaglutide 1.0 mg group, and 4.7% (19 of 403) of subjects in the semaglutide 2.4 mg group in Trial 4374, showing no major differences among the treatment groups. The findings from a dilated fundoscopy/fundus photography shifted from "normal" or "abnormal, clinically not problematic" at baseline to "abnormal, clinically problematic" at Week 68 in a limited number of subjects, and there were no major differences in the proportion among the treatment groups (0% [0 of 20] of subjects in the placebo group, 0% [0 of 19] of subjects in the semaglutide 1.7 mg group, and 5.4% [2 of 37] of subjects in the semaglutide 2.4 mg group in Trial 4382; 1.4% [5 of 345] of subjects in the placebo group, 1.2% [4 of 342] of subjects in the semaglutide 1.0 mg group, and 1.7% [6 of 352] of subjects in the semaglutide 2.4 mg group in Trial 4374).

The above indicated that, although the incidence of retinal disorders was higher in the semaglutide group than in the placebo group, no serious adverse events were reported, and most of the events were mild in severity. There were no major differences in the incidence of adverse events classified by the investigator as new onset or worsening of diabetic retinopathy between the placebo and semaglutide groups. These results were similar to the findings with the commercially available semaglutide formulations indicated for type 2 diabetes, and no new clinically relevant concerns have been identified.

PMDA's view:
In the clinical trials in obese patients with type 2 diabetes, although the incidence of retinal disorders was higher in the semaglutide group than in the placebo group, there was no trend towards a clear dose-dependent increase, and most of the events were mild in severity. There is no particular problem with the applicant's view (Given that there were no major differences in the incidence of adverse events classified by the investigator as new onset or worsening of diabetic retinopathy between the placebo and semaglutide groups, etc., the risk of diabetic retinopathy is similar to that with the commercially available semaglutide formulations indicated for type 2 diabetes, and no new clinically relevant concerns have been identified.).

7.R.3.5 Cardiovascular risk

The applicant's explanation:
During the period from the date of randomization to the end of trial in the global phase III trials (Trials 4382, 4373, and 4374), the incidences of EAC-confirmed cardiovascular events were 0.5% (1 of 199 subjects [2 events: acute myocardial infarction and coronary revascularisation]) in the semaglutide 2.4 mg group in Trial 4382, 0.6% (4 of 655 subjects [4 events: acute myocardial infarction (3), stroke (1)]) in the placebo group and 0.5% (6 of 1306 subjects [8 events: acute myocardial infarction (3), coronary revascularisation (3), angina unstable (1), stroke (1)]) in the semaglutide 2.4 mg group in Trial 4373, and 1.2% (5 of 402 subjects [7 events: stroke (2), cardiac failure (2), acute myocardial infarction (1), transient ischaemic attack (1), coronary revascularisation (1)]) in the placebo group, 1.5% (6 of 402 subjects [7 events: acute myocardial infarction (3), coronary revascularisation (3), stroke (1)]) in the semaglutide 1.0 mg group, and 1.5% (6 of 403 subjects: 6

events: stroke (3), acute myocardial infarction (1), angina unstable (1), cardiac failure (1)]) in the semaglutide 2.4 mg group in Trial 4374. EAC-confirmed cardiovascular events occurred infrequently in all trials, and the incidence was similar between the placebo and semaglutide groups.

Table 52 shows the incidence and rate of cardiovascular events,[31] and there were no major differences among the treatment groups.

Table 52. Incidence and rate of cardiovascular events (Safety analysis set)

	Trial 4382		
	Placebo (N = 101)	Semaglutide 1.7 mg (N = 100)	Semaglutide 2.4 mg (N = 199)
Cardiovascular events	6.9 (7) [4.8]	9.0 (9) [7.0]	8.0 (16) [5.9]
Serious cardiovascular events	2.0 (2) [1.4]	0 (0) [0]	0.5 (1) [0.3]

	Trial 4373		Trial 4374		
	Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)	Placebo (N = 402)	Semaglutide 1.0 mg (N = 402)	Semaglutide 2.4 mg (N = 403)
Cardiovascular events	11.5 (75) [10.5]	8.2 (107) [7.2]	9.7 (39) [9.7]	8.7 (35) [7.7]	12.4 (50) [12.6]
Serious cardiovascular events	1.8 (12) [1.4]	1.2 (16) [1.2]	3.0 (12) [2.5]	3.0 (12) [2.8]	3.2 (13) [3.1]

Incidence % (n) [Event rate (Number of events/100 person-years)]

According to a pooled analysis of the phase III trials,[29] the incidences of EAC-confirmed cardiovascular events were 0.7% (11 of 1529) of subjects in the placebo group and 0.6% (15 of 2650) of subjects in the semaglutide 2.4 mg group, showing no major differences between the treatment groups.

The estimated mean changes in pulse rate from baseline to Week 68 were 2.43 beats/min in the placebo group, 6.29 beats/min in the semaglutide 1.7 mg group, and 4.38 beats/min in the semaglutide 2.4 mg group in Trial 4382, −0.74 beats/min in the placebo group and 3.52 beats/min in the semaglutide 2.4 mg group in Trial 4373, and −0.23 beats/min in the placebo group, 1.77 beats/min in the semaglutide 1.0 mg group, and 2.49 beats/min in the semaglutide 2.4 mg group in Trial 4374. Although pulse rate tended to increase in the semaglutide group compared with the placebo group, no clear dose-response relationship between the doses of semaglutide was observed, and the findings were similar to those reported with the commercially available semaglutide formulations for type 2 diabetes.

There were no clear differences in ECG findings among the treatment groups in any of Trials 4382, 4373, and 4374, and most subjects had normal ECG findings at baseline and throughout the trial period. In Trial 4382, no exposure-response relationship was observed for QT interval corrected for heart rate according to Fridericia's formula (QTcF) changes in the semaglutide 2.4 mg group. The proportions of subjects with a QTcF >450 ms, >480 ms, or >500 ms, or a >30 ms increase from baseline in QTcF were low at baseline and Weeks 20 and 68, and there were no clear differences among the treatment groups. Although QT prolongation-related events (electrocardiogram QT prolonged, electrocardiogram QRS complex prolonged) occurred in 2 subjects

[31] Events in the SMQs "central nervous system vascular disorders," "vasculitis," "ischaemic heart disease," "cardiac arrhythmias," "cardiac failure," "cardiomyopathy," "embolic and thrombotic events," "shock," and "torsade de pointes/QT prolongation"

in the semaglutide 1.7 mg group, the both events were non-serious and mild in severity, and their causal relationship to trial drug was denied.

The above clinical trial results indicated no trend towards increases in cardiovascular events following administration of semaglutide, and clinical laboratory findings also did not suggest an increased cardiovascular risk. Increases in the mean pulse rate were observed in the semaglutide group, which were similar to the findings reported with the commercially available semaglutide formulations for type 2 diabetes. Thus, this risk is similar to that associated with the commercially available semaglutide formulations indicated for type 2 diabetes, and no new clinically relevant concerns have been identified.

PMDA's view:
In the clinical trials, increases in pulse rate were observed with semaglutide, but there was no clear dose-response relationship. There were no clinically relevant changes in blood pressure and lipid parameters, etc. [see Section "7.R.2.2 Beneficial effect of improving comorbidities"]. Given these findings etc., there is no particular problem with the applicant's view (The currently available information has not suggested an increased cardiovascular risk.).

7.R.3.6 Relationship to tumor development

The applicant's explanation:
Table 53 shows the incidences and rates of neoplasm-related events[32)] and malignant neoplasm-related events[33)] during the period from the date of randomization to the end of trial in the global phase III trials (Trials 4382, 4373, and 4374), and these incidences were similar among the treatment groups. There was no particular trend in the organs and tissues in which the observed neoplasms developed, and adverse events of specific types of malignant neoplasms did not occur more frequently. No events of medullary thyroid cancer or pancreatic carcinoma were reported.

[32)] Events in the SOC "neoplasms benign, malignant and unspecified (incl cysts and polyps)" and events in the SMQs "biliary neoplasms," "breast neoplasms, malignant and unspecified," "liver neoplasms, benign (incl cysts and polyps)," "liver neoplasms, malignant and unspecified," "malignancies," "malignant lymphomas," "oropharyngeal neoplasms," "ovarian neoplasms, malignant and unspecified," "premalignant disorders," "prostate neoplasms, malignant and unspecified," "skin neoplasms, malignant and unspecified," and "uterine and fallopian tube neoplasms, malignant and unspecified"
[33)] Events in the SMQ "malignant tumours"

Table 53. Incidence and rate of neoplasm-related events (Safety analysis set)

	Trial 4382		
	Placebo (N = 101)	Semaglutide 1.7 mg (N = 100)	Semaglutide 2.4 mg (N = 199)
Neoplasm-related events	4.0 (4) [3.4]	8.0 (8) [5.6]	5.0 (10) [4.9]
Serious neoplasm-related events	1.0 (1) [0.7]	3.0 (3) [2.1]	0.5 (1) [0.3]
Malignant neoplasm-related events	1.0 (1) [0.7]	2.0 (2) [1.4]	0 (0) [0]

	Trial 4373		Trial 4374		
	Placebo (N = 655)	Semaglutide 2.4 mg (N = 1306)	Placebo (N = 402)	Semaglutide 1.0 mg (N = 402)	Semaglutide 2.4 mg (N = 403)
Neoplasm-related events	7.5 (49) [6.1]	7.1 (93) [6.0]	7.0 (28) [6.0]	7.2 (29) [6.3]	5.2 (21) [4.7]
Serious neoplasm-related events	0.8 (5) [0.5]	0.9 (12) [0.6]	1.2 (5) [1.1]	2.0 (8) [1.4]	1.0 (4) [0.7]
Malignant neoplasm-related events	1.1 (7) [0.8]	1.1 (14) [0.8]	2.0 (8) [1.6]	1.7 (7) [1.4]	1.2 (5) [1.0]

Incidence % (n) [Event rate (Number of events/100 person-years)]

According to a pooled analysis of the phase III trials,[29] the incidences of neoplasm-related events[32] were 7.1% (108 of 1529) of subjects in the placebo group and 6.9% (187 of 2650) of subjects in the semaglutide 2.4 mg group, and the incidences of serious neoplasm-related events were 0.8% (13 of 1529) of subjects in the placebo group and 1.0% (27 of 2650) of subjects in the semaglutide 2.4 mg group, showing no major differences between the treatment groups.

The mean serum calcitonin was slightly reduced in all groups of Trials 4382, 4373, and 4374, but the changes were small. There were no major differences in the proportion of subjects with a serum calcitonin level greater than the ULN between baseline and Week 68. In Trial 4374, a calcitonin level ≥50 ng/L was detected in 1 subject in the semaglutide 2.4 mg group during treatment with semaglutide. This subject had a calcitonin level ≥50 ng/L at screening and was diagnosed with papillary thyroid carcinoma. In all trials, no subjects had a calcitonin level ≥100 ng/L at any time point post-baseline.

The above clinical trial results showed no relationship between semaglutide and tumor development, as with the commercially available semaglutide formulations indicated for type 2 diabetes.

PMDA's view:
There is no particular problem with the applicant's explanation (The clinical trial results have suggested no increased risk of events related to tumor development at present.).

7.R.4 Indication

The applicant's explanation:
In foreign countries, lifestyle intervention in the form of diet and exercise is first-line treatment for obesity, and pharmacotherapy should be considered if weight reduction by lifestyle modifications is not adequate (*Obes Facts*. 2015;8:166-74, *J Clin Endocrinol Metab*. 2015;100:342-62). The concept of the treatment of obesity in Japan is also similar, and lifestyle intervention consisting of dietary, exercise, and behavioral therapy for 3 to 6 months is recommended for patients with obesity disease, a medical condition that requires weight loss, and

pharmacotherapy should be considered if lifestyle intervention does not produce effective weight loss or improvement of comorbidities.

According to the Japanese guidelines for the management of obesity disease, the diagnostic criteria for obesity disease are BMI ≥25 kg/m^2 and (1) a medical condition that is accompanied by health disorders caused by or related to obesity and thus requires weight loss (that will be improved or slowed by weight loss) or (2) visceral fat accumulation suspected at screening by measuring waist circumference and a definitive diagnosis of visceral fat obesity made by abdominal computed tomography (CT) scan. Higher BMI is associated with increases in the number of obesity-related comorbidities and the mortality, and the number of obesity-related comorbidities and the mortality tended to increase with a BMI of >27 kg/m^2 (*BMJ*. 2016;353:i2156, *N Engl J Med*. 2011;364:719-29, *J Epidemiol*. 2011;21:417-30). High frequency of cardiovascular risk factors in Japanese obese adults with a BMI of ≥27 kg/m^2 has also been suggested (*Arch Med Res*. 2007;38:337-44, *Stroke*. 2005;36:1377-82). In addition, people with visceral fat obesity, which is commonly observed in the Japanese population, have risk factors for impaired glucose tolerance, hypertension, and dyslipidemia and are considered at an increased risk of developing cardiovascular disease and death, and Japanese subjects with ≥2 risk factors have been reported to have a 2.2-times greater risk of developing cardiovascular disease (*Hypertens Res*. 2005;28:203-8). On the basis of the above reports etc., pharmacotherapy intervention should be more important for patients with obesity who have comorbidities and a BMI of ≥27 kg/m^2.

Taking account of the real situation in Japan as described above, Trial 4382 in patients with obesity and hypertension, dyslipidemia, or type 2 diabetes was planned and conducted. The percent change in body weight from baseline to Week 68 (mean ± SD) was −13.4 ± 8.6% and the proportion of subjects achieving ≥5% weight loss at Week 68 was 82.9% (160 of 193) of subjects in the semaglutide 2.4 mg group, showing a clinically meaningful weight loss. Moreover, a trend towards improvements in blood glucose, blood pressure, and lipid parameters was also observed. Its safety profile was similar to that of the commercially available semaglutide formulations for type 2 diabetes. Trials 4373 and 4374 were planned based on the real situation of the treatment of obesity overseas and enrolled broader patient populations as compared with Trial 4382. Trial 4373 included patients with (1) BMI ≥27.0 kg/m^2 with hypertension, dyslipidemia, obstructive sleep apnoea, or cardiovascular disease or (2) BMI ≥30.0 kg/m^2. Trial 4374 included patients with BMI ≥27.0 kg/m^2 and type 2 diabetes. Efficacy and safety trends were similar between Trial 4382 and Trials 4373 and 4374. The results in a patient subgroup from Trial 4373 or 4374 meeting the inclusion criteria for Trial 4382[34)] showed a similar trend to the results in the entire trial population.

The proposed indication reflecting the trial population of Trial 4382, which is the real situation in Japan, is appropriate: Patients with obesity and hypertension, dyslipidemia, or type 2 diabetes mellitus who have (1) a BMI of ≥27 kg/m^2 and ≥2 obesity-related health disorders, or (2) a BMI of ≥35 kg/m^2 and ≥1 obesity-related

[34)] Subjects who had (1) BMI ≥27.0 kg/m^2 with ≥2 weight-related comorbidities or (2) BMI ≥35.0 kg/m^2 with ≥1 weight-related comorbidity (At least one comorbidity should be hypertension, dyslipidemia, or type 2 diabetes). The percent changes in body weight from baseline to Week 68 in this patient subgroup (mean ± SD) are shown below.
Trial 4373: −3.0 ± 6.2% (N = 265) in the placebo group, −15.1 ± 9.4% (N = 605) in the semaglutide 2.4 mg group
Trial 4374: −3.2 ± 5.6% (N = 357) in the placebo group, −7.4 ± 6.6% (N = 354) in the semaglutide 1.0 mg group, −10.1 ± 8.0% (N = 361) in the semaglutide 2.4 mg group

health disorder. Given the positioning of pharmacotherapy in the treatment of obesity disease, the following statement should be included in the PRECAUTIONS CONCERNING INDICATION section: "Semaglutide should be used in patients with obesity disease who have not responded adequately to dietary and exercise therapy beforehand."

PMDA asked the applicant to present the comorbidities of subjects enrolled in the clinical trials of semaglutide and then explain the definition of "obesity-related health disorders."

The applicant's response:
In Trial 4382, "obesity-related health disorders (weight-related comorbidities)" were defined as 11 health disorders specified by the Japanese guidelines for the management of obesity disease, which are essential for the diagnostic criteria for obesity disease. In Trial 4382, the frequencies of some health disorders may have been lower than seen in clinical practice due to the inclusion/exclusion criteria established to ensure the safety of subjects, but all of the 11 health disorders were enrolled (Table 54). Thus, these 11 health disorders should be considered as "obesity-related health disorders."

Table 54. Types and number of obesity-related health disorders by BMI (Trial 4382: FAS)

Obesity-related health disorders		BMI <30	BMI ≥30 and <35	BMI ≥35	Total
Impaired glucose tolerance (type 2 diabetes)		26.3 (44/167)	21.7 (34/157)	27.3 (21/77)	24.7 (99/401)
Impaired glucose tolerance (except for type 2 diabetes)		46.1 (77/167)	42.7 (67/157)	29.9 (23/77)	41.6 (167/401)
Dyslipidemia		88.6 (148/167)	89.8 (141/157)	74.0 (57/77)	86.3 (346/401)
Hypertension		74.9 (125/167)	70.7 (111/157)	81.8 (63/77)	74.6 (299/401)
Hyperuricemia/Gout		32.9 (55/167)	38.9 (61/157)	32.5 (25/77)	35.2 (141/401)
Coronary artery disease		4.2 (7/167)	1.3 (2/157)	1.3 (1/77)	2.5 (10/401)
Cerebral infarction		2.4 (4/167)	0 (0/157)	2.6 (2/77)	1.5 (6/401)
Non-alcoholic fatty liver disease		44.9 (75/167)	48.4 (76/157)	36.4 (28/77)	44.6 (179/401)
Menstrual disorder/Infertility		1.8 (3/167)	2.5 (4/157)	3.9 (3/77)	2.5 (10/401)
Obstructive sleep apnoea syndrome/Obesity-hypoventilation syndrome		6.0 (10/167)	12.1 (19/157)	14.3 (11/77)	10.0 (40/401)
Locomotory disease		8.4 (14/167)	12.7 (20/157)	9.1 (7/77)	10.2 (41/401)
Obesity-related kidney disease		0.6 (1/167)	0 (0/157)	0 (0/77)	0.2 (1/401)
Number of health disorders	1	0 (0/167)	0 (0/157)	9.1 (7/77)	1.7 (7/401)
	2	19.8 (33/167)	18.5 (29/157)	19.5 (15/77)	19.2 (77/401)
	3	38.3 (64/167)	38.2 (60/157)	36.4 (28/77)	37.9 (152/401)
	4	29.3 (49/167)	29.3 (46/157)	22.1 (17/77)	27.9 (112/401)
	≥5	12.6 (21/167)	14.0 (22/157)	13.0 (10/77)	13.2 (53/401)

Proportion % (Number of subjects in category/Number of evaluable subjects)

PMDA's view:
In the 3 global phase III trials including Trial 4382, semaglutide induced weight loss, and a percent weight loss that has been reported to be useful for the treatment of obesity [see Section "7.R.1 Clinical positioning" etc.] was observed. The global phase III trials of semaglutide showed a trend towards improvements in blood glucose, blood pressure, and lipid parameters. Given these findings etc., it may be interpreted that treatment with semaglutide is clinically meaningful to a certain extent. Taking also into account that semaglutide has acceptable safety, provided that as with the commercially available semaglutide formulations, appropriate precautionary statements are included in the package insert, there is no problem with the target disease of obesity with hypertension, dyslipidemia, or type 2 diabetes or the proposed indication statement reflecting the

inclusion criteria as to BMI and obesity-related health disorders (weight-related comorbidities) in Trial 4382, which was planned based on the real situation in Japan. Given the positioning of pharmacotherapy in the treatment of obesity disease, semaglutide should be used in patients who have not responded adequately to dietary and exercise therapy beforehand. The specific statements in the INDICATION and PRECAUTIONS CONCERNING INDICATION sections will be finalized, taking account of comments from the Expert Discussion.

7.R.5 Dosage and administration

7.R.5.1 Dosing regimen

The applicant's explanation:

In the development of the semaglutide subcutaneous formulation for type 2 diabetes, the possibility that large fluctuations in semaglutide plasma concentrations increase gastrointestinal side effects was suggested. Thus, a foreign phase II, dose-finding trial in patients with obesity (Trial 4153[35)]) investigated once-daily doses of semaglutide (0.05, 0.1, 0.2, 0.3, or 0.4 mg) with dose escalation every 4 weeks and once-daily doses of semaglutide (0.3 or 0.4 mg) with dose escalation every 2 weeks so as to reach a high total exposure level while minimizing fluctuations in semaglutide plasma concentrations. The results from this trial showed that semaglutide 0.4 mg once daily with dose escalation every 4 weeks was most effective in terms of weight loss.[36)] Semaglutide displayed an acceptable safety profile in all semaglutide groups.[37)]

The results from foreign phase II (Trial 4191, a once-daily dose) and phase III trials (Trial 3623, Trial 3626, etc., a once-weekly dose) in patients with type 2 diabetes, and Trial 4153 in patients with obesity showed no marked differences between once-daily and once-weekly semaglutide with respect to weight loss and the incidences of gastrointestinal disorders and adverse events leading to treatment discontinuation during the treatment period including the dose escalation period, when the mean plasma semaglutide concentration was similar between once-daily and once-weekly doses, etc. Thus, the once-weekly dosing regimen, which was anticipated to ease the burden of drug administration, was chosen for the phase III trials. A maintenance dose of 2.4 mg was selected for the phase III trials because the results of an exposure-response analysis including the data from Trial 4153 showed that the incidence of gastrointestinal disorders increased with increasing

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35) A 52-week, randomized, double-blind, parallel-group trial to investigate the safety and efficacy of placebo, semaglutide (0.05, 0.1, 0.2, 0.3, or 0.4 mg), or liraglutide 3.0 mg administered subcutaneously once daily in non-Japanese obese patients without diabetes (BMI ≥30.0 kg/m^2)

36) Percent change in body weight from baseline to Week 52 (mean ± SD): −2.28 ± 5.67% (N = 103) in the placebo group, −6.79 ± 5.76% (N = 77) in the semaglutide 0.05 mg group (dose escalation every 4 weeks), −9.76 ± 7.97% (N = 88) in the semaglutide 0.1 mg group (dose escalation every 4 weeks), −13.68 ± 8.94% (N = 87) in the semaglutide 0.2 mg group (dose escalation every 4 weeks), −12.97 ± 8.22% (N = 88) in the semaglutide 0.3 mg group (dose escalation every 4 weeks), −14.95 ± 8.06% (N = 74) in the semaglutide 0.3 mg group (dose escalation every 2 weeks), −16.17 ± 8.37% (N = 82) in the semaglutide 0.4 mg group (dose escalation every 4 weeks), −17.95 ± 9.18% (N = 91) in the semaglutide 0.4 mg group (dose escalation every 2 weeks), −9.20 ± 6.66% (N = 86) in the liraglutide 3.0 mg group

37) Incidence of adverse events % (Number of subjects with event/Number of evaluable subjects): 78.7% (107 of 136) of subjects in the placebo group, 90.3% (93 of 103) of subjects in the semaglutide 0.05 mg group (dose escalation every 4 weeks), 92.2% (94 of 102) of subjects in the semaglutide 0.1 mg group (dose escalation every 4 weeks), 93.2% (96 of 103) of subjects in the semaglutide 0.2 mg group (dose escalation every 4 weeks), 90.3% (93 of 103) of subjects in the semaglutide 0.3 mg group (dose escalation every 4 weeks), 96.1% (98 of 102) of subjects in the semaglutide 0.4 mg group (dose escalation every 4 weeks), 96.1% (98 of 102) of subjects in the semaglutide 0.3 mg group (dose escalation every 2 weeks), 93.2% (96 of 103) of subjects in the semaglutide 0.4 mg group (dose escalation every 2 weeks), 85.4% (88 of 103) of subjects in the liraglutide 3.0 mg group
Incidence of events leading to treatment discontinuation % (Number of subjects with event/Number of evaluable subjects): 2.9% (4 of 136) of subjects in the placebo group, 6.8% (7 of 103) of subjects in the semaglutide 0.05 mg group (dose escalation every 4 weeks), 7.8% (8 of 102) of subjects in the semaglutide 0.1 mg group (dose escalation every 4 weeks), 4.9% (5 of 103) of subjects in the semaglutide 0.2 mg group (dose escalation every 4 weeks), 3.9% (4 of 103) of subjects in the semaglutide 0.3 mg group (dose escalation every 4 weeks), 14.7% (15 of 102) of subjects in the semaglutide 0.4 mg group (dose escalation every 4 weeks), 16.7% (17 of 102) of subjects in the semaglutide 0.3 mg group (dose escalation every 2 weeks), 7.8% (8 of 103) of subjects in the semaglutide 0.4 mg group (dose escalation every 2 weeks), 8.7% (9 of 103) of subjects in the liraglutide 3.0 mg group

semaglutide exposure, and the PPK modelling estimated that a once-weekly maintenance dose of 2.4 mg semaglutide would result in similar C_{max} at steady-state as that obtained by the once-daily 0.4 mg semaglutide dose. In order to determine the recommended clinical dose of semaglutide for Japanese patients with obesity disease, the 1.7 mg group was also included in Trial 4382. In all phase III trials, the starting dose was 0.25 mg once weekly, and the dose was to be escalated every 4 weeks to 0.5, 1.0, and 1.7 mg until the target dose of 2.4 mg was reached.

Trials 4382, 4373, and 4374 demonstrated the superiority of semaglutide 2.4 mg to placebo for weight reduction and showed a trend towards improvements in blood glucose, blood pressure, and lipid parameters. When analyzed by dose level, there was a trend towards a dose-dependent decease in body weight in Trials 4382 and 4374, which included a dose group other than the semaglutide 2.4 mg group, and the percent change in body weight from baseline to Week 68 and the proportion of subjects achieving ≥5% weight loss at Week 68 in the semaglutide 2.4 mg group tended to be higher than those in the semaglutide 1.0 mg group (Trial 4374) or the semaglutide 1.7 mg group (Trial 4382) (Tables 10 and 20). A larger proportion of subjects achieved ≥10% or ≥15% weight loss and the reductions in waist circumference and BMI were greater with semaglutide 2.4 mg compared to semaglutide 1.0 mg or 1.7 mg in these trials (Tables 11 and 21). Visceral fat area was measured in the Japanese subgroup of Trial 4382, and the change in visceral fat area was greater in the semaglutide 2.4 mg group than in the semaglutide 1.7 mg group (Table 11).

As to the clinical significance of weight loss in patients with obesity, a weight loss of 5% to 10% has significant health benefits by improving obesity-related comorbidities (*Arch Intern Med*. 2009;169:1619-26, *Ann Intern Med*. 1992;116:535-9, etc.). A weight loss of 10% to 15% has been reported to improve cardiovascular disease and lower its risk (*Endocr Pract.* 2016;22(Suppl. 3):1-203). It has also been suggested that a weight loss of >15% can lead to remission of type 2 diabetes especially in people with short-duration type 2 diabetes, improvement of heart failure with preserved left ventricular ejection fraction, and a reduction in cardiovascular mortality (*Lancet.* 2018;391:541-51, *Curr Opin Cardiol*. 2011;26:555-61). In a retrospective study in Japan, the remission rate of diabetes was higher in patients with >20% total weight loss after laparoscopic sleeve gastrectomy, and the remission rate of dyslipidemia tended to be slightly higher in patients with >15% total weight loss (*Ann gastroenterol surg*. 2019;3:638-47). Thus, since a greater weight reduction, a trend towards improvements in lipid parameters, reduced use of OADs or antihypertensive medication, etc., were observed in the semaglutide 2.4 mg group as compared with the semaglutide 1.0 mg group (Trial 4374) or the semaglutide 1.7 mg group (Trial 4382) in Trials 4382 and 4374, semaglutide 2.4 mg should have more favorable effects than semaglutide 1.7 mg in terms of weight loss and improvement of comorbidities in patients with obesity disease.

Regarding the safety of the proposed product, no new adverse events etc. were reported as compared with the commercially available semaglutide formulations for type 2 diabetes. The most commonly reported adverse events were gastrointestinal disorders including nausea, diarrhoea, constipation, and vomiting, and a higher incidence of adverse events leading to treatment discontinuation in the semaglutide 2.4 mg group than in the placebo group was largely attributable to adverse events of gastrointestinal disorders. The incidence and rate

of gastrointestinal disorders (SOC) were largely similar between the semaglutide 2.4 mg and 1.7 mg groups in Trial 4382, and the incidence of adverse events leading to treatment discontinuation was also similar. There was no trend towards differences in the incidence and rate of adverse events between the Japanese subgroup and the entire trial population in Trials 4382, 4373, and 4374.

As described in the above, semaglutide 2.4 mg showed more favorable effects than semaglutide 1.7 mg in terms of weight loss and improvement of comorbidities in Trial 4382. No new clinically relevant concerns were identified as to the safety of semaglutide 2.4 mg as compared with the safety profiles of the commercially available semaglutide formulations indicated for type 2 diabetes, and there were no major differences in the incidence and rate of adverse events between the semaglutide 1.7 mg and 2.4 mg groups. Thus, the recommended clinical dose of semaglutide for Japanese patients with obesity disease is 2.4 mg, and if patients do not tolerate the 2.4 mg dose, a temporary dose decrease etc. should be considered.

PMDA's view:
On the basis of the clinical trial results, higher efficacy is expected with semaglutide 2.4 mg as compared with semaglutide 1.7 mg, and semaglutide 2.4 mg has acceptable safety, provided that appropriate precautionary statements are included in the package insert. Thus, there is no problem with the recommended clinical dose of 2.4 mg for Japanese patients with obesity disease. As in the clinical trials, patients should be initiated at a once-weekly dose of 0.25 mg and follow a fixed-dose escalation regimen, with dose increases every 4 weeks to doses of 0.5, 1.0, and 1.7 mg until 2.4 mg is reached. The specific dosage and administration statement, including a precautionary statement regarding patients who do not well tolerate the 2.4 mg dose, will be finalized, taking account of comments from the Expert Discussion.

7.R.5.2 Decision to continue treatment

The applicant's explanation:
Changes in body weight and comorbidity-related parameters following treatment withdrawal were explored in the extension phase of Trial 4373. During the extension period of Trial 4373 (Weeks 68-120), changes in body weight and blood glucose, blood pressure, and lipid parameters were explored from Week 68 to Week 120 without trial drug and structured lifestyle intervention. A subset of subjects who completed 68 weeks of treatment with placebo or semaglutide 2.4 mg in the main phase were eligible for the extension. The percent changes from baseline in body weight (mean ± SD) were −2.0 ± 6.1% at Week 68 (N = 99) and −0.1 ± 5.8% at Week 120 (N = 93) in the placebo group and −17.3 ± 9.3% at Week 68 (N = 228) and −5.6 ± 8.9% at Week 120 (N = 197) in the semaglutide 2.4 mg group. During the non-intervention period from Week 68 to Week 120, the mean body weight increased in both treatment groups, but body weight remained below baseline in the semaglutide group. With respect to blood glucose, blood pressure, and lipid parameters, while many parameters including blood pressure, total cholesterol, and LDL cholesterol reverted towards baseline, the semaglutide 2.4 mg group maintained a small relative improvement versus the placebo group in HbA1c, high density lipoprotein (HDL) cholesterol, and triglycerides.

Obesity is recognized as a chronic disease, and continuous treatment is needed to maintain weight loss and treatment effects on comorbidities (*Obes Rev*. 2017;18:715-23, *Endocr Pract.* 2017;23:372-8, etc.), which was supported by the results of the extension phase of Trial 4373. A foreign phase III trial (Trial 4378[38)]) investigated the 2-year effect of placebo or semaglutide 2.4 mg as an adjunct to dietary and exercise therapy in patents with overweight or obesity. There were no major changes in the mean body weight in the placebo group. In the semaglutide 2.4 mg group, the mean body weight decreased from baseline to Week 68 and then reached a plateau, and weight loss was maintained through Week 104 (the percent change from baseline in body weight [mean ± SD]: −2.7 ± 7.4% at Week 68 [N = 89] and −1.9 ± 8.9% at Week 104 [N = 128] in the placebo group, −17.4 ± 10.4% at Week 68 [N = 101] and −15.9 ± 12.3% at Week 104 [N = 144] in the semaglutide 2.4 mg group). Likewise, a trend towards improvements in blood glucose, blood pressure, and lipid parameters was also maintained through Week 104.

The above indicated that continuous treatment with semaglutide sustains weight loss and improvements in blood glucose, blood pressure, and lipid parameters, and weight regain or worsening of obesity-related comorbidities can be avoided. On the other hand, since treatment with semaglutide should not be continued aimlessly without a clear treatment goal, if weight loss and improvement of comorbidities by semaglutide are not adequate, changes to instructions regarding diet and exercise or semaglutide discontinuation should be considered.

PMDA's view:
Continuous treatment with semaglutide has sustained weight loss and improvements in blood glucose, blood pressure, and lipid parameters. However, the patient's condition, including improvement of comorbidities, should be monitored periodically to decide whether to continue treatment with semaglutide, so as not to aimlessly continue treatment. If patients do not respond adequately to semaglutide, appropriate measures should be taken, including discontinuation of therapy. The package insert should advise these points. The specific precautionary statements will be finalized, taking account of comments from the Expert Discussion.

7.R.6 Proper use

PMDA asked the applicant to explain the measures for the proper use of semaglutide so that appropriate patients are selected to receive semaglutide for the indication of obesity.

The applicant's response:
Patients are required to have hypertension, dyslipidemia, or type 2 diabetes to receive semaglutide for the indication of obesity, and these diseases are diagnosed according to the respective relevant academic society's diagnostic criteria.[39)] Patients with a BMI of ≥27 kg/m^2 and <35 kg/m^2 who have ≥2 obesity-related health

[38)] A 104-week, randomized, double-blind, parallel-group trial to investigate the efficacy and safety of placebo or semaglutide 2.4 mg administered subcutaneously once weekly as an adjunct to dietary and exercise therapy in patients with overweight or obesity (target sample size, 300 subjects [150 each in the placebo and semaglutide 2.4 mg groups]). Key inclusion criteria were patients with BMI ≥30.0 kg/m^2 or BMI ≥27.0 kg/m^2 with hypertension, dyslipidemia, obstructive sleep apnoea, or cardiovascular disease, ≥18 years of age. Patients with HbA1c ≥6.5% were excluded. The starting dose of semaglutide was 0.25 mg, and the dose was to be escalated every 4 weeks to 0.5, 1.0, 1.7, and 2.4 mg.

[39)] Guidelines for the Management of Hypertension 2019 (Japanese Society of Hypertension), Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017 (Japan Atherosclerosis Society), and Treatment Guide for Diabetes 2022-2023 (Japan Diabetes Society)

disorders (at least 1 health disorder should be hypertension, dyslipidemia, or type 2 diabetes) are appropriate for semaglutide. Written information explaining "obesity-related health disorders," i.e., 11 health disorders specified by the Japanese guidelines for the management of obesity disease, which are essential for the diagnostic criteria for obesity disease, and a video in which an obesity specialist explains health disorders, will be prepared and distributed widely to healthcare professionals. According to the Japanese guidelines for the management of obesity disease, patients should try dietary and exercise therapy prior to pharmacotherapy, and the treatment effect in achieving a set weight loss goal should be assessed after 3 to 6 months. Thus, patients will be treated and assessed accordingly, also when semaglutide is indicated.

PMDA's view:
It is necessary to appropriately provide information on the criteria for appropriate patients for semaglutide, etc., using information materials for healthcare professionals etc., so that the use of semaglutide will be considered only for patients with obesity disease that medically requires weight loss who are considered to need pharmacotherapy.

7.R.7 Special populations

7.R.7.1 Patients with renal impairment

The applicant's explanation:
According to Trial 4382 and a pooled analysis of the phase III trials,[29)] the incidence and rate of adverse events by renal function (normal [baseline eGFR[40)] (mL/min/1.73 m^2) ≥90], mild impairment [≥60 and <90], moderate impairment [≥30 and <60], severe impairment [≥15 and <30]) are shown in Tables 55 and 56. There were no patients with severe renal impairment in Trial 4382. In the pooled phase III trials, only 2 patients had severe renal impairment in the semaglutide 2.4 mg group. The number of patients with moderate renal impairment was also limited, and only 1 patient each in the semaglutide 1.7 mg and 2.4 mg groups had moderate renal impairment in Trial 4382. Although rigorous comparison is difficult due to particularly very few patients with severe renal impairment, there was no trend towards substantial increases in adverse events according to the degree of renal impairment.

[40)] Calculated with the CKD-EPI equation as defined by KDIGO 2021.

Table 55. Incidence and rate of adverse events by renal function in Trial 4382 (Safety analysis set)

	Renal function	Placebo (N = 101)	Semaglutide 1.7 mg (N = 100)	Semaglutide 2.4 mg (N = 199)
All adverse events	Normal	83.3 (65/78) [177.2]	87.7 (64/73) [382.3]	86.4 (121/140) [318.3]
	Mild impairment	65.2 (15/23) [125.9]	65.4 (17/26) [260.0]	84.5 (49/58) [269.4]
	Moderate impairment	—	100 (1/1) [703.8]	100 (1/1) [140.8]
All adverse drug reactions	Normal	19.2 (15/78) [22.7]	71.2 (52/73) [212.6]	53.6 (75/140) [137.5]
	Mild impairment	21.7 (5/23) [25.2]	57.7 (15/26) [89.6]	55.2 (32/58) [120.9]
	Moderate impairment	—	100 (1/1) [492.6]	100 (1/1) [70.4]
Serious adverse events	Normal	6.4 (5/78) [4.5]	8.2 (6/73) [9.0]	3.6 (5/140) [2.6]
	Mild impairment	8.7 (2/23) [6.3]	3.8 (1/26) [2.9]	8.6 (5/58) [8.8]
	Moderate impairment	—	0 (0/1) [0]	0 (0/1) [0]
Adverse events leading to treatment discontinuation	Normal	1.3 (1/78) [0.9]	1.4 (1/73) [4.0]	0.7 (1/140) [1.0]
	Mild impairment	0 (0/23) [0]	7.7 (2/26) [5.8]	6.9 (4/58) [8.8]
	Moderate impairment	—	0 (0/1) [0]	0 (0/1) [0]
Gastrointestinal disorders (SOC)	Normal	29.5 (23/78) [30.0]	67.1 (49/73) [214.6]	57.9 (81/140) [130.8]
	Mild impairment	30.4 (7/23) [31.5]	53.8 (14/26) [98.2]	62.1 (36/58) [110.8]
	Moderate impairment	—	100 (1/1) [492.6]	100 (1/1) [70.4]

Incidence % (Number of subjects with event/Number of subjects analyzed) [Event rate (Number of events/100 person-years)]
—, Not applicable

Table 56. Incidence and rate of adverse events by renal function according to pooled analysis of phase III trials[a)] (Safety analysis set)

	Renal function	Placebo	Semaglutide 2.4 mg
All adverse events	Normal	83.0 (832/1009) [358.7]	87.6 (1539/1752) [506.8]
	Mild impairment	84.8 (405/479) [376.6]	90.6 (753/833) [542.7]
	Moderate impairment	88.2 (35/41) [399.8]	87.6 (54/63) [739.9]
	Severe impairment	—	100 (2/2) [214.9]
All adverse drug reactions	Normal	40.0 (397/1009) [88.2]	65.0 (1147/1752) [240.8]
	Mild impairment	40.7 (193/479) [84.2]	67.4 (558/833) [254.8]
	Moderate impairment	41.7 (17/41) [82.9]	64.8 (39/63) [313.7]
	Severe impairment	—	0 (0/2) [0]
Serious adverse events	Normal	5.9 (61/1009) [5.5]	8.3 (146/1752) [8.8]
	Mild impairment	7.0 (34/479) [9.1]	10.1 (83/833) [10.9]
	Moderate impairment	9.8 (5/41) [9.6]	28.9 (17/63) [69.8]
	Severe impairment	—	0 (0/2) [0]
Adverse events leading to treatment discontinuation	Normal	3.1 (31/1009) [3.0]	4.9 (88/1752) [5.2]
	Mild impairment	3.1 (15/479) [3.1]	6.5 (52/833) [6.8]
	Moderate impairment	2.9 (1/41) [3.3]	18.0 (9/63) [16.8]
	Severe impairment	—	0 (0/2) [0]
Hypoglycaemia[b)]	Normal	0.9 (7/750) [0.9]	0.6 (9/1482) [0.9]
	Mild impairment	0.3 (1/359) [0.4]	0.6 (4/719) [0.5]
	Moderate impairment	0 (0/18) [0]	0 (0/45) [0]
	Severe impairment	—	0 (0/1) [0]
Gastrointestinal disorders (SOC)	Normal	44.2 (439/1009) [81.1]	66.2 (1172/1752) [217.1]
	Mild impairment	41.2 (195/479) [73.7]	69.3 (573/833) [229.9]
	Moderate impairment	42.6 (17/41) [63.3]	70.8 (41/63) [259.5]
	Severe impairment	—	0 (0/2) [0]

Incidence % (Number of subjects with event/Number of subjects analyzed) [Event rate (Number of events/100 person-years)]
—, Not applicable
a) Pooled analysis of Trials 4373, 4374, 4375, and 4376
b) Adverse events of hypoglycaemia according to pooled analysis of Trials 4373, 4375, and 4376

Table 57 shows the incidence and rate of any hypoglycemic episode (levels 1-3) according to the ADA 2018 classification in the subgroup with type 2 diabetes of Trial 4382 and Trial 4374. There was no obvious trend according to differences in renal function.

Table 57. Incidence and rate of any hypoglycemic episode[a)] by renal function (Safety analysis set)

Renal function[b)]	Trial 4382 (Subgroup with type 2 diabetes)			Trial 4374		
	Placebo (N = 25)	Semaglutide 1.7 mg (N = 25)	Semaglutide 2.4 mg (N = 49)	Placebo (N = 402)	Semaglutide 1.0 mg (N = 402)	Semaglutide 2.4 mg (N = 403)
Normal	0 (0/22) 0 [0]	10.0 (2/20) 5 [17.6]	11.9 (5/42) 7 [12.0]	6.2 (16/259) 51 [14.7]	19.6 (52/265) 103 [29.4]	18.9 (51/270) 179 [49.2]
Mild impairment	0 (0/3) 0 [0]	0 (0/5) 0 [0]	0 (0/7) 0 [0]	10.0 (12/120) 16 [10.4]	15.0 (18/120) 116 [73.8]	27.2 (31/114) 125 [83.7]
Moderate impairment	—	—	—	26.1 (6/23) 20 [70.4]	29.4 (5/17) 24 [109.9]	27.8 (5/18) 12 [66.1]

Upper row, Incidence % (Number of subjects with episode/Number of evaluable subjects)
Lower row, Number of episodes [Rate of episodes (Number of episodes/100 person-years)]
—, Not applicable
a) Levels 1-3 episodes of hypoglycaemia (ADA 2018 classification)
b) In Trials 4382 and 4374, there was 1 patient with severe renal impairment in the semaglutide 2.4 mg group of Trial 4374, and the patient did not experience hypoglycaemia.

Although the number of subjects with moderate or severe renal impairment evaluated was limited, the above clinical trial results showed no major safety problem with the use of semaglutide in patients with renal impairment.

PMDA's view:

Although it should be taken into account that the limited number of patients with moderate or severe renal impairment were evaluated in the clinical trials, there was no trend towards a particularly increased safety risk in the subgroups according to the degree of renal impairment.

7.R.7.2 Elderly

The applicant's explanation:

According to Trial 4382 and a pooled analysis of the phase III trials,[29)] the incidence and rate of adverse events by age group are shown in Tables 58 and 59. Although rigorous comparison is difficult due to the limited number of subjects aged ≥65 years in Trial 4382 and the limited number of subjects aged ≥75 years also in the pooled phase III trials, there was no trend towards substantial increases in adverse events with increasing age.

Table 58. Incidence and rate of adverse events by age group in Trial 4382 (Safety analysis set)

	Age group	Placebo (N = 101)	Semaglutide 1.7 mg (N = 100)	Semaglutide 2.4 mg (N = 199)
All adverse events	<65 years	78.9 (75/95) [168.1]	81.1 (73/90) [344.8]	85.5 (142/166) [302.2]
	≥65 and <75 years	83.3 (5/6) [128.2]	88.9 (8/9) [436.4]	90.0 (27/30) [310.9]
	≥75 years	—	100 (1/1) [510.1]	66.7 (2/3) [285.4]
All adverse drug reactions	<65 years	20.0 (19/95) [23.3]	66.7 (60/90) [183.8]	51.2 (85/166) [126.6]
	≥65 and <75 years	16.7 (1/6) [23.3]	77.8 (7/9) [187.0]	70.0 (21/30) [160.2]
	≥75 years	—	100 (1/1) [204.1]	66.7 (2/3) [166.5]
Serious adverse events	<65 years	5.3 (5/95) [3.8]	6.7 (6/90) [7.4]	4.8 (8/166) [4.4]
	≥65 and <75 years	33.3 (2/6) [23.3]	0 (0/9) [0]	6.7 (2/30) [4.8]
	≥75 years	—	100 (1/1) [102.0]	0 (0/3) [0]
Adverse events leading to treatment discontinuation	<65 years	1.1 (1/95) [0.8]	2.2 (2/90) [4.1]	1.8 (3/166) [2.2]
	≥65 and <75 years	0 (0/6) [0]	0 (0/9) [0]	3.3 (1/30) [2.4]
	≥75 years	—	100 (1/1) [102.0]	33.3 (1/3) [71.3]
Gastrointestinal disorders (SOC)	<65 years	30.5 (29/95) [30.8]	62.2 (56/90) [187.9]	57.2 (95/166) [124.0]
	≥65 and <75 years	16.7 (1/6) [23.3]	77.8 (7/9) [194.8]	70.0 (21/30) [129.1]
	≥75 years	—	100 (1/1) [102.0]	66.7 (2/3) [118.9]

Incidence % (Number of subjects with event/Number of subjects analyzed) [Event rate (Number of events/100 person-years)]
—, Not applicable

Table 59. Incidence and rate of adverse events by age group according to pooled analysis of phase III trials[a)] (Safety analysis set)

	Age group	Placebo	Semaglutide 2.4 mg
All adverse events	<65 years	83.5 (1132/1362) [368.0]	88.1 (2113/2394) [519.3]
	≥65 and <75 years	84.5 (129/154) [348.0]	92.0 (213/233) [544.4]
	≥75 years	85.2 (11/13) [312.3]	94.1 (22/23) [489.8]
All adverse drug reactions	<65 years	40.6 (547/1362) [89.1]	65.7 (1577/2394) [247.7]
	≥65 and <75 years	35.9 (54/154) [68.2]	64.3 (149/233) [232.1]
	≥75 years	41.1 (6/13) [47.9]	76.5 (18/23) [223.6]
Serious adverse events	<65 years	5.6 (78/1362) [6.1]	8.8 (207/2394) [9.2]
	≥65 and <75 years	11.4 (18/154) [11.2]	13.9 (35/233) [21.1]
	≥75 years	33.1 (4/13) [30.0]	17.6 (4/23) [32.1]
Adverse events leading to treatment discontinuation	<65 years	3.0 (40/1362) [3.0]	5.1 (123/2394) [5.5]
	≥65 and <75 years	4.1 (7/154) [4.2]	10.1 (23/233) [8.9]
	≥75 years	0 (0/13) [0]	10.8 (3/23) [9.8]
Hypoglycaemia[b)]	<65 years	0.8 (8/1045) [0.8]	0.6 (12/2079) [0.7]
	≥65 and <75 years	0 (0/77) [0]	0.6 (1/155) [0.5]
	≥75 years	0 (0/5) [0]	0 (0/13) [0]
Gastrointestinal disorders (SOC)	<65 years	43.3 (582/1362) [79.4]	66.7 (1605/2394) [222.5]
	≥65 and <75 years	41.9 (63/154) [71.7]	70.3 (164/233) [210.7]
	≥75 years	38.5 (6/13) [34.2]	70.5 (17/23) [209.6]

Incidence % (Number of subjects with event/Number of subjects analyzed) [Event rate (Number of events/100 person-years)]
a) Pooled analysis of Trials 4373, 4374, 4375, and 4376
b) Adverse events of hypoglycaemia according to pooled analysis of Trials 4373, 4375, and 4376

Table 60 shows the incidence and rate of any hypoglycemic episode (levels 1-3) according to the ADA 2018 classification in the subgroup with type 2 diabetes of Trial 4382 and Trial 4374 in patients with type 2 diabetes. The incidence and rate were higher in the semaglutide group than in the placebo group in all subgroups. In Trial 4374, the rate tended to be higher in the subgroup of subjects aged ≥65 years than in the subgroup of subjects aged <65 years in all treatment groups.

Table 60. Incidence and rate of any hypoglycemic episode[a)] by age group (Safety analysis set)

Age group	Trial 4382 (Subgroup with type 2 diabetes)			Trial 4374		
	Placebo (N = 25)	Semaglutide 1.7 mg (N = 25)	Semaglutide 2.4 mg (N = 49)	Placebo (N = 402)	Semaglutide 1.0 mg (N = 402)	Semaglutide 2.4 mg (N = 403)
<65 years	0 (0/24) 0 [0]	8.3 (2/24) 5 [14.7]	12.2 (5/41) 7 [12.3]	7.6 (24/317) 53 [12.5]	18.2 (58/319) 135 [32.1]	20.0 (63/315) 201 [47.6]
≥65 and <75 years	0 (0/1) 0 [0]	0 (0/1) 0 [0]	0 (0/7) 0 [0]	13.0 (10/77) 34 [35.7]	20.5 (16/78) 107 [103.6]	29.5 (23/78) 110 [109.5]
≥75 years	—	—	0 (0/1) 0 [0]	0 (0/8) 0 [0]	20.0 (1/5) 1 [16.8]	10.0 (1/10) 5 [47.8]

Upper row, Incidence % (Number of subjects with episode/Number of evaluable subjects)
Lower row, Number of episodes [Rate of episodes (Number of episodes/100 person-years)]
—, Not applicable
a) Levels 1-3 episodes of hypoglycaemia (ADA 2018 classification)

The above clinical trial results showed no trend towards a consistently higher incidence or rate of adverse events in the subgroup of subjects aged ≥65 years, and no clear differences were observed in the safety profile according to age group.

PMDA's view:

Although it cannot be concluded that the clinical trials conducted showed a trend towards a consistently higher safety risk in the elderly, the elderly often has reduced physiological function, and there is limited clinical experience with semaglutide in patients aged ≥75 years in the clinical trials, etc. Thus, as with the commercially

available semaglutide formulations, the package insert should advise that semaglutide should be administered to the elderly with caution.

7.R.8 Post-marketing investigations

The applicant's explanation:

In clinical trials in patients with overweight or obesity, the events reported with semaglutide 2.4 mg were known events with the commercially available semaglutide formulations, and there was no particular trend in the incidence/rate or severity of adverse events with increasing dose of semaglutide. Gastrointestinal disorders were the most commonly reported events in clinical trials, and the incidence and rate of gastrointestinal disorders tended to be higher with semaglutide 2.4 mg than with semaglutide 1.0 mg. Taking account of these findings, a specified use-results survey (an observation period of 1 year, a survey period of 2.5 years, 630 enrolled patients) will be conducted to evaluate the safety of semaglutide 2.4 mg in clinical practice, focusing on the occurrence of gastrointestinal disorders.

PMDA's view:

In clinical trials in patients with overweight or obesity, the main events reported were known events with the commercially available semaglutide formulations. On the other hand, as the proposed product is likely to be used in even more patients as compared with the current indication of the semaglutide formulations (type 2 diabetes), and safety information from Japanese patients with obesity disease treated with semaglutide 2.4 mg in clinical trials is limited etc., long-term information on the safety etc. of semaglutide 2.4 mg in clinical practice should be collected extensively. Given that commercially available anti-obesity medications are limited in Japan at present, etc., information on the proper use of the proposed product should also be collected. The details of post-marketing surveillance will be finalized, taking account of comments from 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 (CTD5.3.5.1-2) 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 semaglutide has efficacy in patients with obesity disease, and that semaglutide has acceptable safety in view of its benefits. Semaglutide is clinically meaningful because it offers a new treatment option for patients with obesity disease.

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

Review Report (2)

December 21, 2022

Product Submitted for Approval

Brand Name	(a)	Wegovy Subcutaneous Injection 0.25 mg SD
		Wegovy Subcutaneous Injection 0.5 mg SD
		Wegovy Subcutaneous Injection 1.0 mg SD
	(b)	Wegovy Subcutaneous Injection 1.7 mg SD
		Wegovy Subcutaneous Injection 2.4 mg SD
Non-proprietary Name	Semaglutide (Genetical Recombination)	
Applicant	Novo Nordisk Pharma Ltd.	
Date of Application	August 25, 2021	

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).

1.1 Clinical positioning

PMDA's view:

It is understandable that a new drug is needed in clinical practice in Japan as a treatment option for patients with obesity disease who are unable to achieve adequate weight loss with lifestyle intervention alone. Three global phase III trials (Trials 4382, 4373, and 4374) demonstrated the weight lowering effect of semaglutide and indicated that improvements in blood glucose, blood pressure, and lipid parameters are also expected [see Section "1.2 Efficacy"]. Semaglutide has acceptable safety, provided that appropriate precautionary statements are included in the package insert [see Section "1.3 Safety"]. Given the above findings, semaglutide can become an anti-obesity medication for patients with obesity with hypertension, dyslipidemia, or type 2 diabetes.

At the Expert Discussion, the expert advisors made the following comments and supported the above conclusion by PMDA.

- It is well recognized in clinical practice that the understanding and implementation of lifestyle intervention in diet and exercise result in weight loss and improvement of weight-related comorbidities in patients with

obesity and associated health disorders. On the other hand, especially patients with high-level obesity disease or obesity with diabetes are unable to achieve adequate weight loss with lifestyle intervention alone or may achieve weight loss temporarily, but struggle to maintain the target weight in the long-term, etc. Thus, the effects of lifestyle intervention alone are often inadequate.

- Despite the fact that the number of patients with obesity disease is increasing, there are limited options for pharmacotherapy, and a novel drug, especially, a drug that induces long-term weight loss, is needed.

1.2 Efficacy

PMDA's view:

Weight reduction effect

All 3 global phase III trials demonstrated the superiority of semaglutide 2.4 mg to placebo in the co-primary endpoints of the percent change in body weight from baseline to Week 68 and the proportion of subjects achieving ≥5% weight loss at Week 68. Also, for body weight-related secondary endpoints, all trials showed a higher proportion of subjects achieving weight loss and greater reductions in waist circumference and BMI, etc., in the semaglutide 2.4 mg group than in the placebo group. Regarding efficacy in Japanese patients, there are no major differences between Japan and overseas, in terms of the diagnosis of obesity and patients intended for pharmacotherapy being defined by BMI and obesity-related comorbidities, etc. Semaglutide exposure was higher in Japanese patients than in non-Japanese patients, and one of its factors was considered differences in body weight. Differences in some baseline subject characteristics including body weight between the Japanese subgroup and the entire trial population had no major effects on the efficacy evaluation of semaglutide, and a similar trend was seen for the primary endpoint of weight reduction in the Japanese subgroup and the entire trial population in all trials.

Beneficial effect of improving comorbidities

The 3 global phase III trials showed a trend towards improvements in blood glucose, blood pressure, and lipid parameters following administration of semaglutide. Likewise, a trend towards improvements was observed also in the Japanese subgroup. With respect to concomitant medications for hypertension, dyslipidemia, or type 2 diabetes, the proportion of subjects who increased these medications from baseline to Week 68 in the semaglutide group was similar to or lower than that in the placebo group. The proportion of subjects who decreased OAD or antihypertensive medication was higher in the semaglutide group than in the placebo group.

Given the above trial results etc., it may be interpreted that the weight reduction effect of semaglutide has been demonstrated, and semaglutide is expected to improve comorbidities (hypertension, dyslipidemia, and type 2 diabetes) in patients with obesity and hypertension, dyslipidemia, or type 2 diabetes.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.3 Safety

PMDA's view:

PMDA conducted its safety review, focusing on the incidence and rate of adverse events in the global phase III trials. The main events reported were known events with the commercially available semaglutide formulations. Also, when analyzed by glycemic status and comorbidity status (hypertension or dyslipidemia), there was no trend towards increases in specific adverse events. As to comparison between the different doses of semaglutide, although the incidences and rates of adverse events and adverse events leading to treatment discontinuation tended to be higher in the semaglutide 2.4 mg group than in the semaglutide 1.0 mg group in Trial 4374, there were no major differences in the incidence and rate of serious adverse events among the treatment groups including the placebo group. Trial 4382 showed no major differences in the incidence and rate of adverse events between the semaglutide 1.7 mg and 2.4 mg groups. In the 3 global trials, there was no trend towards differences in the incidence and rate of adverse events between the Japanese subgroup and the entire trial population.

Taking account of the mechanism of action of semaglutide, clinical trial results, etc., in addition to the above analyses etc., semaglutide at doses up to 2.4 mg has acceptable safety, provided that as with the commercially available semaglutide formulations, appropriate precautionary statements about adverse events of special interest are included in the package insert.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.4 Indication

PMDA's view:

In the 3 global phase III trials including Trial 4382, semaglutide induced weight loss, and a percent weight loss that has been reported to be useful for the treatment of obesity was observed. The global phase III trials of semaglutide showed a trend towards improvements in blood glucose, blood pressure, and lipid parameters. Given these findings etc., it may be interpreted that treatment with semaglutide is clinically meaningful to a certain extent. Semaglutide has acceptable safety, provided that as with the commercially available semaglutide formulations, appropriate precautionary statements are included in the package insert. Thus, there is no problem with the target disease of obesity with hypertension, dyslipidemia, or type 2 diabetes, taking account of the patient population of Trial 4382, which was planned based on the real situation in Japan, or the proposed indication statement reflecting the inclusion criteria as to BMI and obesity-related health disorders (weight-related comorbidities) in Trial 4382. Given the positioning of pharmacotherapy in the treatment of obesity disease, semaglutide should be used in patients who have not responded adequately to dietary and exercise therapy beforehand.

At the Expert Discussion, the expert advisors made the following comments and supported the above conclusion by PMDA.

- Dietary and exercise therapy is basic for the treatment of obesity disease, like other metabolic disorders. It should be made clear that patients should try dietary and exercise therapy prior to pharmacotherapy, so

as not to be quick to initiate pharmacotherapy. Also, in terms of obtaining the therapeutic effect of semaglutide, treatment with semaglutide should be limited to patients who have not responded adequately to dietary and exercise therapy.

- Information on the details, duration, etc., of dietary and exercise therapy that should be tried prior to the administration of semaglutide, needs to be provided appropriately.
- Since the use of semaglutide as an adjunct to dietary and exercise therapy is important also in terms of obtaining the therapeutic effect of semaglutide, it should be useful to advise that semaglutide should be used as an adjunct to continuous dietary and exercise therapy and to provide information on the details of dietary and exercise therapy performed in clinical trials.

On the basis of the comments from the Expert Discussion, PMDA requested the applicant to include the following statements in the INDICATION and PRECAUTIONS CONCERNING INDICATION sections, and the applicant responded appropriately.

Indication

Obesity

Wegovy should only be used in patients with hypertension, dyslipidemia, or type 2 diabetes mellitus who have not responded adequately to dietary and exercise therapy and have:

- a BMI of ≥27 kg/m^2 and ≥2 obesity-related health disorders, or
- a BMI of ≥35 kg/m^2

Precautions Concerning Indication

Wegovy should only be used in patients who have not responded adequately to dietary and exercise therapy, which is basic for the treatment of obesity disease, and are considered appropriate for pharmacotherapy. Refer to the characteristics of patients enrolled in the clinical trial for obesity-related health disorders.

1.5 Dosage and administration

PMDA's view:

Dosage and administration

The clinical trial results indicated that higher efficacy is expected with semaglutide 2.4 mg as compared with semaglutide 1.7 mg, and semaglutide 2.4 mg has acceptable safety, provided that appropriate precautionary statements are included in the package insert. Thus, there is no problem with the recommended clinical dose of 2.4 mg for Japanese patients with obesity disease. As in the clinical trials, patients should be initiated at a once-weekly dose of 0.25 mg and follow a fixed-dose escalation regimen, with dose increases every 4 weeks to doses of 0.5, 1.0, and 1.7 mg until 2.4 mg is reached.

Decision to continue treatment

Continuous treatment with semaglutide has sustained weight loss and improvements in blood glucose, blood pressure, and lipid parameters. However, the patient's condition, including improvement of comorbidities, should be monitored periodically to decide whether to continue treatment with semaglutide, so as not to

aimlessly continue treatment. If patients do not respond adequately to semaglutide, appropriate measures should be taken, including discontinuation of therapy. The package insert should advise these points.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA. The expert advisors made the following comments on the precautionary statements regarding patients who do not well tolerate the 2.4 mg dose and the decision to continue treatment, etc.

- According to the clinical experience with the commercially available semaglutide formulations in patients with type 2 diabetes, the incidence of gastrointestinal disorders, efficacy, etc., differ depending on individual patient's condition. Thus, the dose of the proposed product will also be adjusted according to the patient's condition in clinical practice. In addition to semaglutide 2.4 mg and 1.7 mg tested in Trial 4382, semaglutide 1.0 mg also induced clinically adequate weight loss in Trial 4374.
- While obesity is a chronic disease, and continuous treatment is needed, if patients do not respond to semaglutide or the effect of continuous treatment with semaglutide is inadequate, change of treatment, including discontinuation of semaglutide, should be considered.

On the basis of the above, PMDA requested the applicant to amend the statements in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections etc. as shown below, and the applicant responded appropriately.

Dosage and Administration

The usual adult initial dosage is 0.25 mg of semaglutide (genetical recombination) injected subcutaneously once weekly. Then the dose should be escalated every 4 weeks to 0.5, 1.0, and 1.7 mg once weekly until a dose of 2.4 mg is reached. The maintenance dose is 2.4 mg once weekly. The dose should be reduced as appropriate according to the patient's condition.

Precautions Concerning Dosage and Administration (Relevant text only)

If patients do not tolerate a dose due to gastrointestinal disorders etc., consider lowering to the previous dose or delaying dose escalation.

Important Precautions (Relevant text only)

Wegovy should be used as an adjunct to continuous dietary and exercise therapy. Body weight, blood glucose, blood pressure, lipid parameters, etc., should be measured periodically, and if there is no trend towards improvement after 3 to 4 months of treatment, treatment with Wegovy should be discontinued. Even after that, body weight, blood glucose, blood pressure, lipid parameters, etc., should be measured periodically to closely monitor the patient's condition, and if the patient do not respond adequately to Wegovy, discontinuation of Wegovy should be considered.

1.6 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA’s conclusion presented in Section "7.R.8 Post-marketing investigations" in the Review Report (1). PMDA has concluded that the risk management plan

(draft) for semaglutide should include the safety specification presented in Table 61, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 62 and 63.

Table 61. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hypoglycaemia • Gastrointestinal disorders	• Medullary thyroid cancer (thyroid C-cell tumors) • Pancreatitis acute • Pancreatic carcinoma • Intestinal obstruction • Hyperglycemia including diabetic ketoacidosis following insulin suspension • Diabetic retinopathy-related events • Embryo-fetal toxicity • Acute biliary disease	• Effect on cardiovascular risk in Japanese patients • Safety of semaglutide in patients with renal impairment
Efficacy specification		
None		

Table 62. 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 • Specified use-results survey	• Develop information materials to be distributed to healthcare professionals • Develop information materials to be distributed to patients • Disseminate data gathered during early post-marketing phase vigilance

Table 63. Outline of specified use-results survey (draft)

Objective	To evaluate the long-term safety and efficacy of semaglutide in clinical practice.
Survey method	Central registry system
Population	Patients with obesity disease
Observation period	2 years
Planned sample size	1000 patients
Main survey items	Patient characteristics, the use of semaglutide, concomitant medications/therapies, the details of dietary and exercise therapy, safety assessments (adverse events [hypoglycaemia, gastrointestinal disorders, pancreatitis acute, diabetic retinopathy, cardiovascular risk, acute biliary disease, etc.], clinical laboratory values, etc.), efficacy assessments (HbA1c, body weight, etc.)

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following condition. As the product is a drug with a new indication and a new dosage, the re-examination period is 4 years. 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

Wegovy should only be used in patients with hypertension, dyslipidemia, or type 2 diabetes mellitus who have not responded adequately to dietary and exercise therapy and have:

- a BMI of ≥27 kg/m^2 and ≥2 obesity-related health disorders, or
- a BMI of ≥35 kg/m^2

(Underline denotes changes from the proposed text.)

Dosage and Administration

The usual adult initial dosage is 0.25 mg of semaglutide (genetical recombination) injected subcutaneously once weekly. Then the dose should be escalated every 4 weeks to 0.5, 1.0, and 1.7 mg once weekly until a dose of 2.4 mg is reached. The maintenance dose is 2.4 mg once weekly. The dose should be reduced as appropriate according to the patient's condition.

(Underline denotes changes from the proposed text.)

Approval Condition

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

Appendix

List of Abbreviations

ADA	American Diabetes Association
Adverse drug reaction	An adverse event for which a causal relationship to trial drug cannot be ruled out
AgRP	Agouti-related peptide
AUC	Area under the drug plasma concentration-time curve
BMI	Body mass index
CART	Cocaine- and amphetamine-regulated transcript
CCK	Cholecystokinin
CGRP	Calcitonin gene-related peptide
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration formula
C_{max}	Maximum plasma concentration
CT	Computed Tomography
DIO	Diet induced obese
eGFR	Estimated glomerular filtration rate
FAS	Full Analysis Set
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c
HDL cholesterol	High density lipoprotein cholesterol
HLT	High Level Term
Japanese guidelines for the management of obesity disease	Guidelines for the Management of Obesity Disease 2016, edited by Japan Society for the Study of Obesity
JASSO	Japan Society for the Study of Obesity
KDIGO	Kidney Disease Improving Global Outcomes
LC-MS/MS	Liquid chromatography-tandem mass spectrometry detection
LDL cholesterol	Low density lipoprotein cholesterol
liraglutide	Liraglutide (genetical recombination)
MedDRA/J	Medical dictionary for regulatory Activities Japanese version
metformin	Metformin hydrochloride
NPY	Neuropeptide Y
PBS	Phosphate buffered saline
PMDA	Pharmaceuticals and Medical Devices Agency
POMC	Pro-opiomelanocortin
PPK	Population pharmacokinetics
PT	Preferred terms
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RIA	Radioimmunoassay
SGLT2	Sodium glucose co-transporter 2
SMQ	Standardised MedDRA queries
SOC	System organ class
SU	Sulfonylurea