Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Wegovy

Active ingredient: Semaglutide

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

November 2026

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List of abbreviations

Abbreviation	Meaning
ABI	Ankle-brachial index
ACM	Advisory Committee on Medicines
ACV	Advisory Committee on Vaccines
AE	Adverse events
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
AUC	Area under the concentration-time curve
BMI	Body mass index
Cavg	Estimated exposure
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
C_{max}	Maximum concentration
CMI	Consumer Medicines Information
CV	Cardiovascular
CV	Coefficient of variation (statistical)
CVD	Cardiovascular disease
CVOT(s)	Cardiovascular outcome trial (s)
DLP	Data lock point
EAC	Event adjudication committee
FAS	Full analysis set
FDA	Food and Drug Administration (US)
HR	Hazard ratio
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite Clinical Trials Version
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MI	Myocardial infarction
OECD	Organisation for Economic Co-operation and Development
PAD	Peripheral artery disease
PI	Product Information
PSUR	Periodic safety update report
PYE	Patient years exposure
QTc	Corrected QT interval

Abbreviation	Meaning
RMP	Risk management plan
SC	Subcutaneous
SNAC	Sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (also named salcaprozate sodium)
T1D	Type 1 diabetes
T2D	Type 2 diabetes
T2DM	Type 2 diabetes mellitus
TGA	Therapeutic Goods Administration
t_{max}	Time to maximum observed concentration
UAP	Unstable angina pectoris
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

Product submission

Submission details

Type of submission:	New pharmaceutical dosage form (major variation)
Product name:	Wegovy
Active ingredient:	Semaglutide
Decision:	Approved
Date of decision:	2 November 2026
Date of entry onto ARTG:	3 November 2026
ARTG numbers:	522753, 522757, 522758, 522759
Sponsor's name and address:	Novo Nordisk Pharmaceuticals Pty Ltd Level 10, 118 Mount Street, North Sydney, NSW 2060, Australia.
Dose form:	Tablet
Strengths:	1.5 mg, 4 mg, 9 mg, 25 mg tablets
Containers:	Blister packs: 1.5 mg, 4 mg, 9 mg and 25 mg semaglutide tablets.
Pack sizes:	All strengths: 30 and 90 tablets per pack.
Approved therapeutic use for the current submission:	***Weight Management Adults (solution for injection and tablet)*** *Wegovy is indicated as an adjunct to a reduced-energy diet and increased physical activity for chronic weight management (including weight loss and weight maintenance) in adults with an initial Body Mass Index (BMI) of* • *≥30 kg/m² (obesity), or* • *≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity (see Section 5.1 Pharmacodynamic Properties – Clinical trials).* ***Reduction in risk of major adverse cardiovascular events (solution for injection and tablet)*** *Wegovy is indicated as an adjunct to standard of care therapy to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with established cardiovascular disease, with a Body Mass Index (BMI) ≥27 kg/m², and without established Type 1 or Type 2 diabetes (see Section 5.1 Pharmacodynamic Properties – Clinical trials).*

	<u>*Concomitant use with other GLP-1 receptor agonists*</u> *Concomitant use of Wegovy (semaglutide) tablets or Wegovy (semaglutide) injection with other semaglutide-containing products or with any other GLP-1 receptor agonist is not recommended.*
Route of administration:	For oral administration.
Dosage:	The starting dose for orally administered semaglutide is 1.5 mg once daily. After one month at this dose, the dose escalation steps for orally administered semaglutide once daily are 4 mg, 9 mg and 25 mg with a minimum duration of 1 month at each dose level. The dose should be escalated until 25 mg (maintenance dose). The maximum recommended single daily dose of orally administered semaglutide is 25 mg. Orally administered semaglutide should always be used as only one tablet per day. Taking more than one tablet a day should not be done to achieve the effect of a higher dose. For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.
Pregnancy category:	**Category D** Semaglutide should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with semaglutide. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the Category 1, Type F (major variation) application by Novo Nordisk Pharmaceuticals Pty Ltd (the sponsor) to register Wegovy (Semaglutide) tablets for adults, in 4 different strengths: 1.5 mg, 4 mg, 9 mg, and 25 mg. The proposed indication for this submission is similar to the TGA approved indication for Wegovy – solution for injection:[1]

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

Weight Management <u>Adults</u> (solution for injection and tablet)

Wegovy is indicated as an adjunct to a reduced-energy diet and increased physical activity for chronic weight management (including weight loss and weight maintenance) in adults with an initial Body Mass Index (BMI) of

- *≥30 kg/m² (obesity), or*
- *≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity (see Section 5.1 Pharmacodynamic Properties – Clinical trials).*

Reduction in risk of major adverse cardiovascular events (solution for injection and tablet)

Wegovy is indicated as an adjunct to standard of care therapy to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with established cardiovascular disease, with a Body Mass Index (BMI) ≥27 kg/m², and without established Type 1 or Type 2 diabetes (see Section 5.1 Pharmacodynamic Properties – Clinical trials).

Condition

Overweight and obesity are recognized as disease states considered to be the result of interactions of genetic, metabolic, environmental and behavioural factors and are associated with increases in both morbidity and mortality. According to the World Health Organisation (WHO), overweight and obesity may be expressed in terms of the Body Mass Index (BMI = bodyweight (kilograms) / height^2 [metres^2]) with BMI between 25 and 29.9 kg/m^2 representing overweight, while obesity is defined as BMI ≥ 30 kg/m^2.

The degree of obesity is of importance with respect to the risk of morbidity and mortality, which has been shown to increase with increasing BMI.[2] The WHO defines different classes of obesity; class I (moderately obese) BMI 30-34.9 kg/m^2, class II (severely obese) BMI 35 -39.9 kg/m^2 and class III (very severely obese) BMI ≥ 40 kg/m^2. However, these cut offs may differ by geographical region, as well as for individuals who do not have a typical body composition (e.g. highly muscular subjects). The location of body fat is also a predictor of the relative health hazards of overweight and obesity. Central adiposity is known to be associated with increased risk of overweight and obesity related comorbidities and waist circumference has been shown to be an independent predictor of risk.

Some of the main health risks associated with overweight and obesity include hypertension, dyslipidaemia, insulin resistance, type 2 diabetes (T2D) mellitus and cardiovascular disease. However, other symptoms and disease states that are related to overweight and obesity, such as sleep apnoea, joint pain, urinary incontinence, impaired fertility, depression, anxiety and functional limitations can also severely impair patients' health and quality of life.

The prevalence of obesity is increasing and has reached epidemic proportions in most countries around the world with considerable medical and societal impacts as well as significant public health challenges. In Australia, 66% of adults were living with overweight or obesity in 2022 [34% overweight; 32% obese of which 13% were living with severe obesity (BMI>35kg/m^2)]. The proportion of Australians living with overweight or obesity is greater than the Organisation for Economic Co-operation and Development (OECD) average of 59% with Australia ranked

[2] Flegal KM et al. (2013) Association of all-cause mortality with overweight and obesity using standard body mass index categories: A systematic review and meta-analysis. JAMA; 309(1):71-82. https://jamanetwork.com/journals/jama/fullarticle/1555137

10th out of 21 OECD countries for the proportion of people aged 15 and over who were living with overweight or obesity, in 2022. In 2022, based on measured waist circumference, 63% of men and 72% of women aged 18 and over had a waist circumference that indicated an increased or substantially increased risk of metabolic complications.[3]

The risk of obesity-related complications increases with increasing BMI. Even a 5-10% weight loss has significant health benefits; it prevents or slows the progression to T2D and improves physical symptoms, health-related quality-of-life and other obesity-related complications. Finally, studies suggest a beneficial impact of weight loss on cardiovascular risk and mortality in both people with diabetes and people with obesity.

Current treatment options

Lifestyle modification

Lifestyle intervention in the form of diet and exercise, with or without psychological support, is the first-line treatment option for obesity, but most people with obesity struggle to achieve and maintain their weight loss without other interventions.

Pharmacological treatments

Pharmacotherapy serves as a valuable adjunct to lifestyle intervention for individuals with obesity to achieve and sustain a clinically relevant weight loss, to prevent complications, improve quality of life, and to facilitate a healthier lifestyle.

Pharmacological options may include drugs that regulate appetite via central (e.g. catecholamine and/ or serotonin) and/or peripheral (e.g. GLP-1 receptor agonism) signalling pathways. Drugs that inhibit the absorption of nutrients, promoting weight loss without having a specific effect on appetite (e.g. orlistat), might also be used in the management of overweight and obese patients.

A summary of current pharmacotherapies for obesity that are approved by the TGA and are available in Australia is provided below (Table 1). However, equity in access to these therapies remains an ongoing issue as none of these therapies are currently covered by the PBS.

Table 1. Medications approved for the treatment of obesity in Australia.

Medication	Route and form	How it supports weight loss	TGA-approved population for use
Phentermine	Oral capsule	Reduces appetite by stimulating the release of dopamine, noradrenaline and serotonin.	Adolescents and adults
Orlistat *(Xenical)*	Oral tablet	Reduces the absorption of dietary fat by inhibiting gastric and pancreatic lipases.	Adolescents and adults
Liraglutide	Subcutaneous injection	Reduces appetite by stimulating glucagon-like peptide-1 (GLP-1) receptors in the brain.	Adults only

[3] https://www.abs.gov.au/statistics/health/health-conditions-and-risks/national-health-survey/latest-release

Medication	Route and form	How it supports weight loss	TGA-approved population for use
Naltrexone–bupropion	Oral tablet	Reduces appetite by stimulating pro-opiomelanocortin (POMC) neurons in the hypothalamus.	Adults only
Semaglutide	Subcutaneous injection	Reduces appetite by stimulating GLP-1 receptors in the brain.	Adolescents and adults
Tirzepatide *(Mounjaro)*	Subcutaneous injection	Reduces appetite through dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor activity.	Adults only

Bariatric surgery

Bariatric surgery is usually reserved for patients with severe obesity with considerable peri-operative and post-operative morbidity. Surgical interventions include devices (e.g., intragastric balloon, endoscopic sleeve gastroplasty, vagal nerve blockade, hydrogels) and surgery such as laparoscopic adjustable gastric banding, Roux-en-Y gastric bypass, or biliopancreatic diversion with duodenal switch.

Clinical rationale

Semaglutide is a glucagon-like peptide 1 (GLP-1) analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that binds to and activates the GLP-1 receptor, the target for native GLP-1. GLP-1 is a physiological regulator and has multiple actions in glucose and appetite regulation. The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain[4].

The principal mechanism of protraction is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilised against degradation by the dipeptidyl peptidase-4 (DPP-4) enzyme[5].

Clinical studies show that semaglutide reduces energy intake, increases feelings of satiety, fullness and control of eating, and reduces feelings of hunger and frequency and intensity of cravings.

Animal studies show that semaglutide works in the brain through the GLP-1 receptor. Semaglutide has direct effects on areas in the brain involved in homeostatic regulation of food intake in the hypothalamus and the brainstem. Semaglutide affects the hedonic reward system through direct and indirect effects in brain areas including the septum, thalamus and amygdala. Semaglutide has shown an effect to change food intake in animals away from more rewarding

[4] Holst JJ. (2024) GLP-1 physiology in obesity and development of incretin-based drugs for chronic weight management. Nat Metab, 6: 1866-1885. https://doi.org/10.1038/s42255-024-01113-9

[5] Mahapatra MK, Karuppasamy M, & Sahoo BM. (2022) Semaglutide, a glucagon like peptide-1 receptor agonist with cardiovascular benefits for management of type 2 diabetes. Rev Endocr Metab Disord, 23: 521-539. https://doi.org/10.1007/s11154-021-09699-1

high fat, sweet items. Semaglutide orchestrates the homeostatic and hedonic contributions with executive function to regulate caloric intake, appetite, reward and food choice [6,7].

In addition, in clinical studies semaglutide have shown to reduce blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucosedependent manner. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying in the early postprandial phase. During hypoglycaemia, semaglutide diminishes insulin secretion and does not impair glucagon secretion.

The mechanism of action of semaglutide for cardiovascular risk reduction has not been established.

MASH pathogenesis is characterised by accumulation of fat in the liver leading to lipotoxicity, cellular damage and upregulation of proinflammatory cytokines, activating the immune system and pathways leading to hepatic collagen deposition (fibrosis).

The liver-specific mechanism of action of semaglutide is multifactorial and thought to be mediated through improvement in metabolic factors, including weight loss, improved glucose and lipid metabolism, and reduced inflammation. Semaglutide affects gene pathways of both inflammation and fibrosis, consequently positively changing the proteomic pattern of an individual with MASH. Moreover, semaglutide lowers liver fat deposition.

The sponsor wishes to extend the current registration for the injectable version, introducing tablets in 4 strengths: 1.5 mg, 4 mg, 9 mg, and 25 mg. Dose escalation is 1.5 mg, 4 mg, and 9 mg; maintenance dose is 25 mg. The aim is to offer adults an alternative to injections for weight management and risk reduction for major adverse cardiovascular events.

Regulatory status

Australian regulatory status

This product is considered a new pharmaceutical form (tablet) with 4 strengths 1.5 mg, 4 mg, 9 mg and 25 mg for Australian regulatory purposes.

Wegovy received initial registration in the Australian Register of Therapeutic Goods (ARTG) on 1 September 2022.[8,9,10,11,12] It was approved for the following indication:

> *Wegovy is indicated as an adjunct to a reduced-energy diet and increased physical activity for chronic weight management (including weight loss and weight maintenance) in adults with an initial Body Mass Index (BMI) of*
>
> • *≥30 kg/m² (obesity), or*

[6] Weghuber, D., Barrett, T., Barrientos-Pérez, M., Gies, I., Hesse, D., Jeppesen, O. K., Kelly, A. S., Mastrandrea, L. D., Sørrig, R., Arslanian, S., & STEP TEENS Investigators (2022). Once-Weekly Semaglutide in Adolescents with Obesity. *The New England journal of medicine*, *387*(24), 2245–2257. https://doi.org/10.1056/NEJMoa2208601

[7] Forst T, De Block C, Del Prato S, et al. (2024) The role of incretin receptor agonists in the treatment of obesity. *Diabetes Obes Metab*; 26(10): 4178-4196. doi:10.1111/dom.15796

[8] https://www.tga.gov.au/resources/artg/356285

[9] https://www.tga.gov.au/resources/artg/356286

[10] https://www.tga.gov.au/resources/artg/356287

[11] https://www.tga.gov.au/resources/artg/356288

[12] https://www.tga.gov.au/resources/artg/356270

- *≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity (see Section 5.1 of the Product Information document: Pharmacodynamic Properties – Clinical trials).*

Oral semaglutide is currently registered in Australia as a once-daily oral tablet (Rybelsus), for 3 mg, 7 mg and 14 mg to improve glycaemic control in adults with T2DM. It was approved in Australia on 22 October 2022.

International regulatory status

Semaglutide 2.4 mg subcutaneous (SC) is approved by the Food and Drug Administration (FDA - USA), Medicines and Healthcare products Regulatory Agency (MHRA - UK), Health Canada and Australia under the brand name Wegovy. Semaglutide is also approved as a subcutaneous formulation (0.5 mg, 1 mg and 2 mg Ozempic) for once-weekly administration for the treatment of type 2 diabetes (T2D) and reduction of cardiovascular (CV) risk in adults with T2D and established CV disease.

Currently, oral semaglutide (1.5 mg, 4 mg, 9 mg and 25 mg) is approved in the European Union for the treatment of type 2 diabetes under the invented name Rybelsus. (EMEA/H/C/004953). At the time the TGA considered this submission, similar submissions had been considered by other regulatory agencies. The following table provides the indications where approved (Table 2).

Table 2. International regulatory status.

Region	Status	Approved indications
United Kingdom (MHRA)	Approved 11 June 2026	*Wegovy tablets are 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/m² (obesity), or* • *≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight-related comorbidity.* *For trial results with respect to the effect on cardiovascular events, obesity-related heart failure, populations studied and background therapies see section 5.1.*
United States of America (FDA)	Approved 22 December 2025	*WEGOVY tablets are indicated in combination with a reduced calorie diet and increased physical activity:* • *To reduce the risk of major adverse CV events (CV death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established CV disease and either obesity or overweight.* • *To reduce excess body weight and maintain weight reduction long term in adults with obesity, or in adults with overweight in the presence of at least one weight-related comorbid condition.* *Limitations of Use: Concomitant use of WEGOVY (semaglutide) tablets or WEGOVY (semaglutide) injection with other semaglutide-containing products or with any other GLP-1 receptor agonist is not recommended.*

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 3. Timeline for Submission PM-2025-05799-1-2.

Description	Date
Submission dossier accepted and first round evaluation commenced	2 February 2026
Evaluation completed (End of round 2)	31 August 2026
Registration decision (Outcome)	2 November 2026
Registration in the ARTG completed	3 November 2026
Number of working days from submission dossier acceptance to registration decision*	137

*Statutory timeframe for standard submissions is 255 working days

Assessment overview

A summary of the TGA's assessment for this submission is provided below.

Quality evaluation summary

The active ingredient in Wegovy, semaglutide, was approved by the TGA in 2019 for management of poorly controlled T2DM[13,14] under the tradename Ozempic. It is manufactured by the same sponsor, Novo Nordisk Pharmaceuticals Pty Ltd.

Semaglutide for oral administration is structurally identical to the semaglutide used in Ozempic. However, its drug substance is manufactured using a different yeast strain, and the process has been optimised to support this strain and the larger production capacity required for the oral product. The new strain and manufacturing process were introduced between Phase 2 and Phase 3 clinical development.

The manufacturing process builds on prior knowledge from the approved semaglutide 3 mg, 7 mg, and 14 mg Rybelsus tablets. A robust manufacturing process was established for semaglutide 1.5 mg, 4 mg, 9 mg, and 25 mg tablets. Tablets used for primary stability studies were manufactured on the same equipment and at the same site intended for commercial production. Scale-up and process changes were controlled and shown to maintain comparable tablet quality. Process robustness and reproducibility were demonstrated through initial process validation. This is acceptable.

Stability studies verified a shelf life of 36 months for semaglutide drug substance when stored at −20°C ± 5°C:

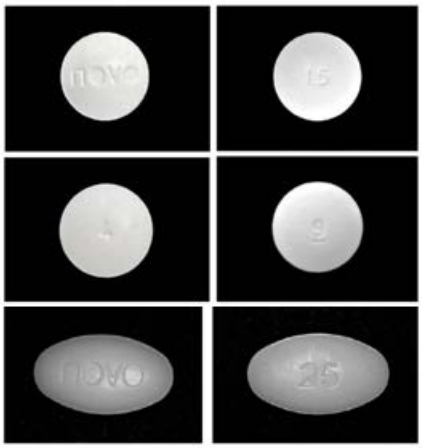
[13] OZEMPIC 1 mg semaglutide 1.34 mg/mL solution for injection pre-filled pen (315107) | Therapeutic Goods Administration (TGA)

[14] OZEMPIC 0.25/0.5 mg semaglutide 1.34 mg/mL solution for injection pre-filled pen (308324) | Therapeutic Goods Administration (TGA)

The semaglutide drug products are white to light yellow round (1.5 mg, 4 mg and 9 mg) or oval (25 mg) tablets (6.5- 6.8 mm in diameter). The tablets are debossed with a unique identification (Figure 1):

- 1.5 mg tablets: '1.5' is debossed on one side, and 'novo' on the other side of the tablet
- 4 mg tablets: '4' is debossed on one side, and 'novo' on the other side of the tablet
- 9 mg tablets: '9' is debossed on one side, and 'novo' on the other side of the tablet
- 25 mg tablets: '25' is debossed on one side, and 'novo' on the other side of the tablet.

Figure 1. The semaglutide debossed tablets.



The Module 3 Quality evaluation confirmed that there are no outstanding issues from a quality perspective.

Nonclinical evaluation summary

No new nonclinical data or further nonclinical evaluation were required for this submission. The TGA considers that previously submitted and evaluated data satisfactorily address nonclinical aspects of safety/efficacy relating to this submission.[15]

Clinical evaluation summary

Pharmacology

Pharmacokinetics

Biopharmaceutics:

The pharmacokinetics (PK) of oral semaglutide 25 mg in three different tablet formulations (Formulation C, D, and E) were evaluated in the Phase 1 study NN9924-4633 in 290 healthy males and females; the exposure of oral semaglutide at the dose levels 25 mg and 50 mg in formulations C and D, and in two additional new formulations i.e., formulations E and F which have not previously been tested in humans were evaluated in this study.

Results from this study demonstrated that for both the 25 mg and 50 mg doses, a SNAC amount (Formulation C) was optimal. For the 25 mg dose, Formulation C demonstrated a higher

[15] AusPAR for

exposure, although difference was not statistically significant compared to both Formulations D and E. For the 50 mg dose, a lower sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) amount (Formulation D) resulted in a lower bioavailability, whereas there was no benefit in increasing the amount of SNAC (Formulation E). These results support the use of Formulation C for oral semaglutide 25 mg Wegovy tablets which is the intended marketing tablet formulation.

Bioavailability

Absorption of orally administered semaglutide 25 mg is decreased if taken with food or large volumes of water. Different dosing schedules of semaglutide have been investigated. Studies show that longer pre- and post-dose fasting periods results in higher absorption.

The assessment of absolute bioavailability of oral semaglutide was based on population PK (PopPK) modelling of clinical pharmacology data and the OASIS phase 3 studies.

- Based on parameter estimates provided in clinical pharmacology PopPK report, the bioavailability in a supervised setting was 0.7 to 0.9% across oral semaglutide doses of 3 to 14 mg in the initially approved Rybelsus formulation, and 1.2-1.5% across 25 mg and 50 mg oral semaglutide in Formulation C.
- Parameter estimates from this model indicate that based on OASIS-4, the bioavailability of oral semaglutide 25 mg was 1.25%. The bioavailability of 3, 7, and 14 mg was approximately 50% less.
- The absolute bioavailability of semaglutide after administration of oral semaglutide D 1.5 mg, 4 mg, and 9 mg was estimated to 1 to 2% (Rybelsus).

Overall, the bioavailability of oral semaglutide in the intended-to-be marketed oral semaglutide tablets is only 1% to 2%. Maximum concentration of semaglutide is reached 1 hour post dose.

Based on modelling analysis of phase 3 data including OASIS-4, the estimated average (Cavg) semaglutide steady state concentration was approximately 77 nmol/L for a typical participant with obesity or overweight (BMI >27 kg/m2) treated with oral semaglutide 25 mg. The steady-state concentrations increased approximately proportionally with doses up to 25 mg once daily.

In patients with overweight or obesity without type 2 diabetes, semaglutide concentrations following once-daily administration of oral Wegovy 25 mg tablet are predicted to be comparable to Wegovy 2.4 mg once-weekly injection, although variability in semaglutide concentrations is much higher with oral compared to subcutaneous administration (90% of patients had average concentrations between 27 and 186 nmol/L with Wegovy 25 mg tablet versus 51 and 110 nmol/L with Wegovy 2.4 mg once-weekly injection).

Orally administered semaglutide has a low absolute bioavailability and a variable absorption. Daily administration according to the recommended posology in combination with a long half-life reduces day-to- day fluctuation of the exposure. Orally administered semaglutide is co-formulated with salcaprozate sodium which facilitates the absorption of semaglutide after oral administration. The absorption of orally administered semaglutide predominantly occurs in the stomach.

Following oral administration, maximum plasma concentration of semaglutide occurred 1 hour post dose. The half-life of semaglutide is approximately 1 week indicating that steady-state exposure will be reached after 4-5 weeks of once daily administration.

In patients with overweight or obesity, the average semaglutide 25 mg steady state concentration following oral administration was approximately 77 nmol/L. The steady-state concentrations increased approximately proportionally with doses up to 25 mg once daily.

The estimated absolute bioavailability of semaglutide is approximately 1-2% following oral administration. Absorption of orally administered semaglutide 25 mg is decreased if taken with

food or large volumes of water. Different dosing schedules of semaglutide have been investigated. Studies show that longer pre- and post-dose fasting periods results in higher absorption.

Steady state pharmacokinetics

The steady-state PK of oral semaglutide 25 mg was investigated in the Phase 1 study NN9924-4633, and the PK was further evaluated by modelling analysis of PK profiles from two clinical pharmacology studies and sparse sampled phase 3 studies, respectively.

Median t_{max} was approximately 1 hour in participants following the recommended dosing conditions. The steady-state exposure of oral semaglutide 25 mg was similar in healthy participants and participants with obesity, and the exposure increased with increasing dose of oral semaglutide.

Based on modelling analysis of phase 3 data including OASIS-4, estimated exposure (Cavg) was 77 nmol/L during the maintenance phase, for a typical participant with obesity treated with oral semaglutide 25 mg. Semaglutide concentrations in OASIS-4 were reasonably stable over time, with slightly higher exposure levels during the first 6 months than at the end of the study. The range of exposure levels were overlapping substantially between 25 mg (OASIS-4) and 50 mg (OASIS 1+2), and there was similar variability in Cavg levels across dose levels and studies.

Dose-proportionality

Dose proportionality of oral semaglutide was evaluated by the estimated exposure ratio (AUC and C_{max}) across oral semaglutide doses of 2.4 mg to 50 mg in study NN9924-4633, and by the estimated doubling constant derived from clinical pharmacology and Phase 3 PopPK modelling.

In study NN9924-4633, exposure was estimated to be close to dose proportional in the dose interval from 11.2 mg to 50 mg. Based on modelling analysis of studies NN9924-4564 and NN9924-4633, the estimated doubling constant for Cavg for oral semaglutide in Formulation C from doses 2.4 mg to 50 mg was 2.13 (95% CI: 2.00; 2.26) and 2.18 (1.98; 2.41) from doses 3 mg to 14 mg in the initially approved Rybelsus formulation.

Based on modelling analysis of the Phase 3 studies, exposure levels were close to dose-proportional within formulation across the 3–50 mg dose range (for 3 mg, 7 mg and 14 mg in the initially approved formulation for Rybelsus and for 25 and 50 mg in Formulation C).

Intra- inter-individual variability in semaglutide exposure

- High variability was observed for bioavailability with a total CV of 164%, which was largely driven by within or intra-individual compared to inter-individual variability (CV of 137% vs 53%). Similar intra- and inter-individual variability was observed for semaglutide exposure (AUC) following a single dose (CV of 137% vs 56%) although the contribution from several doses resulted in a considerable reduction in variability within individuals, from 137% CV for the single dose AUC, to 33% CV for Cavg at steady-state.
- The exposure in terms of Cavg obtained from off-site dosing of semaglutide in two clinical pharmacology trials was 34% and 48% lower, respectively compared to the exposure from on-site dosing with monitoring of adherence to dosing conditions.

Population pharmacokinetic data

The following results of the population pharmacokinetic *(*PopPK) analysis supported future application of this trough PopPK model to evaluate PKs based on sparse PK data from the oral semaglutide PIONEER and OASIS clinical studies:

- The trough-only PK model[16] provided high correlation (≥99.8%) to steady-state Cavg values based on the final model that included all steady-state PK data; the mean relative difference of 1.5% in steady-state Cavg in the trough-only compared to the final model was not significant.
- Estimation of Cavg based on trough-only data gave similar results to model-derived Cavg and NCA-derived Cavg based on full PK profiles.

Results of the PopPK analysis based on Phase 3 studies including OASIS-4 and PIONEER PLUS showed that: -

- Average exposure levels following oral semaglutide 25mg once daily in OASIS-4 were generally similar to those observed following SC semaglutide 2.4 mg in STEP 1 with majority of participants (82.2%) treated with oral semaglutide 25 mg in OASIS-4 achieving exposure levels within the same range as participants treated with SC semaglutide 2.4 mg in STEP 1.
- It is important to note that variability in exposure is much greater with oral semaglutide treatment [CV was 63% to 74%] compared to SC semaglutide [20 to 25%] when used for weight management. Furthermore, variability was much higher in PIONEER PLUS study with oral semaglutide in T2DM patients [90-95%]. At the at the same dose level and route of administration, lower exposure was seen in participants with T2D (STEP 2, PIONEER PLUS) versus participants without T2D (STEP 1, OASIS 1, 2, and 4).
- Although exposure levels were dose-proportional within semaglutide formulations, exposure was much higher with formulation C (dose levels of 25mg and 50mg) compared to currently marketed Rybelsus formulation (3, 7 and 14mg).

Effect of intrinsic factors on Pharmacokinetics of oral semaglutide

This was investigated in the PopPK analysis of OASIS, PIONEER and PIONEER PLUS phase 3 studies.

- Body weight was the most influential covariate, resulting in lower semaglutide exposure with higher body weight and vice versa.
- lower exposure was also observed in male participants, participants with T2D and higher exposure in participants of Asian race.

However, the above differences in exposure are unlikely to be clinically relevant and so no dose adjustment is needed for oral semaglutide 25 mg for patients based on the evaluated intrinsic factors.

- Effects of renal/hepatic impairment on PKs following oral semaglutide 25 mg was not evaluated but current recommendations for Rybelsus were included in the proposed PI for Wegovy tablets, and this is justified.
- Study NN9924-4669 with healthy lactating women evaluated concentrations of semaglutide and SNAC in breastmilk after treatment with oral semaglutide and results confirmed that breastfeeding is not recommended during treatment with oral semaglutide and reflected in the labelling for Rybelsus as well as proposed Wegovy tablets.

Effect of extrinsic factors on Pharmacokinetics of oral semaglutide

- Effects of post-dose fasting times and volume of water ingested during oral administration of semaglutide was extensively evaluated and final dosing recommendations of administration with 120 ml of water and minimum of 30 mins post-dose fasting period is justified to ensure adequate exposure to semaglutide following oral dosing.

[16] A PopPK model based on final model but re-estimated using only trough PK data and with fixed ka values, was developed.

Drug-drug interactions

- No clinically relevant drug-drug interactions related to inhibition and induction of cytochrome P450 enzymes or drug transporters by semaglutide are anticipated although delay in gastric emptying has been observed with GLP-1 RAs which may impact absorption of concomitantly administered oral medications.
- Results of the PIONEER drug-drug interaction programme demonstrated that no clinically relevant drug-drug interactions with oral semaglutide at steady state exposure were observed based on the evaluated medications (lisinopril, warfarin, metformin, digoxin, ethinylestradiol, levonorgestrel, furosemide, rosuvastatin, levothyroxine, and omeprazole). No new studies were conducted in this submission for Wegovy 25 mg tablets but extrapolation of results from PIONEER studies for current submission is acceptable.

Pharmacodynamics

Mechanism of action

Semaglutide is a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that binds to and activates the GLP-1 receptor, the target for native GLP-1 which is physiological regulator and has multiple actions in glucose and appetite regulation. The glucose and appetite effects are specifically mediated via GLP-1 receptors in the pancreas and the brain. The mechanism of action of semaglutide for cardiovascular risk reduction has not been established.

Primary pharmacodynamics effects

The Phase 1 randomised, placebo-controlled, double-blind study NN9932-4873 in 61 healthy subjects with obesity demonstrated a statistically and clinically significant 39.2% greater reduction in relative energy intake (during ad libitum lunch after 140 days) in the oral semaglutide 50 mg group compared with placebo (-33% vs 6.2%). This study also demonstrated significantly greater reduced appetite, better control of eating and less food cravings in the oral semaglutide 50 mg group compared with placebo. Greater mean reduction in body weight was also observed in the oral semaglutide 50mg group (-9.8% vs -1.5%).

In study 4873, the effect of oral semaglutide 50 mg on gastric emptying was assessed after 20 weeks using the paracetamol absorption technique. No clinically relevant effect on gastric emptying was observed during the early and full postprandial period with oral semaglutide 50 mg compared to placebo.

Although this study provided important information regarding potential mechanism of action of oral semaglutide for weight management, interpretation was limited by the fact that only the higher 50 mg dose (not proposed for registration in this submission) was evaluated.

Secondary pharmacodynamics effects

Consistent with the potentially immunogenic properties of medicinal products containing proteins or peptides, patients may develop antibodies following treatment with semaglutide. The proportion of patients testing positive for anti-semaglutide antibodies at any time post-baseline in the SC semaglutide studies was low (2.9%) and no patients had anti-semaglutide neutralising antibodies or anti-semaglutide antibodies with endogenous GLP-1 neutralising effect at end-of-trial. In the OASIS-4 study, ADA samples were not analysed as there were no safety reasons or unexpected PK/PD results (as was pre-specified in the study protocol).

No prolongation of the QTc interval was observed, no exposure-QTc relationship was found in a previous thorough QTc study (NN9535-3652) in healthy participants administered up to 1.5 mg SC semaglutide. As the exposure levels in OASIS 1, 2 and 4 with oral semaglutide (25mg and 50 mg) showed overlapping exposure with that observed in study NN9535-3652, it can be assumed

that QTc prolongation is unlikely following oral semaglutide 25mg in patients with overweight/ obesity. Similar lack of effect of SNAC on QTc prolongation can be deemed unlikely based on results of the prior study from the PIONEER programme (NN9924-4247) which did not show any prolongation of QTc interval.

Exposure-response analyses

Exposure-response relationships for the change from baseline in body weight indicate increased body weight reductions with increasing exposure of both oral and SC semaglutide after 64- 68 weeks of treatment in a range of studies, with a clinically relevant response associated with the exposure of oral semaglutide 25 mg (OASIS-4).

Treatment with oral semaglutide 25 mg from OASIS-4 resulted in exposure levels that were similar and overall comparable to exposure levels with semaglutide SC 2.4 mg in STEP 1 with majority (82.2%) of participants treated with oral semaglutide 25 mg in OASIS-4 achieved exposure levels within the same range as participants treated with semaglutide SC 2.4 mg in STEP 1 (section 5.2.3.1). As expected, there was greater variability in exposure with oral semaglutide treatment compared to SC semaglutide treatment. However, the similar exposure levels obtained with oral semaglutide 25 mg in OASIS-4 and 2.4 mg semaglutide SC translate into similar treatment difference to placebo, as seen by the overlapping exposure-response relationships for OASIS-4 and STEP 1.

The exposure-response relationship for the proportion of participants reporting nausea and vomiting over the first 6 months of treatment in the weight management studies was similar for oral and SC administration with a marginally higher adverse events reporting detected in the OASIS studies with oral semaglutide.

Based on modelling analysis of expected exposure change in phase 3 studies, switching between treatment with oral semaglutide 25 mg and semaglutide SC 2.4 mg is considered safe. The two treatments provide overlapping exposure, and a substantial proportion of patients will obtain comparable exposure with both treatments.

The simulated MACE hazard ratio (HR) for oral semaglutide 25 mg [HR=0.79 (95% CI: 0.67-0.90)] was predicted to be comparable to the published hazard ratio for SC 2.4 mg semaglutide in the SELECT study [0.80 (0.72-0.90)] in patients with overweight or obesity and established cardiovascular disease (CVD).

Efficacy

Dose finding for the pivotal studies

Background studies

The data from the semaglutide SC 2.4 mg in STEP development programme (NN9536, Wegovy, STEP 1–4) was used as confirmatory evidence for efficacy (data from STEP 1) and supportive evidence for safety data (all STEP 1–4 studies) to support the weight management indication for oral semaglutide 25 mg.

The safety data also supported by results from the phase 3 study, PIONEER PLUS (NN9924-4635), evaluating once-daily oral semaglutide of 14 mg, 25 mg, and 50 mg in participants with T2D and a BMI of at least 25 kg/m2.

The weight management indication was supported by nonclinical and clinical pharmacology data from the oral semaglutide T2D PIONEER development programme (NN9924, Rybelsus). Population PK and exposure-response models were developed using data from phase 3 studies

in the OASIS, STEP, PIONEER, and SUSTAIN (NN9535 Ozempic SUSTAIN 1–3, SUSTAIN JPN OAD, and SUSTAIN FORTE) development programmes.

Dose finding studies

PopPK modelling showed that exposure levels of 50 mg reasonably match the exposure levels following 2.4 mg semaglutide SC (STEP) and that the proposed 25 mg oral dose of semaglutide is expected to provide lower exposure levels than 50 mg oral semaglutide and 2.4 mg semaglutide SC

The sponsor has provided the following justification for evaluating the 25 mg dose only in the pivotal NN9932-4954 (OASIS 4) study as an additional, lower-dose option to the 50 mg dose evaluated in the OASIS 1 and OASIS 3 studies:

- Due to variability in exposure levels following oral administration, some subjects taking 25 mg oral semaglutide are expected to achieve exposure levels in the same range as 2.4 mg semaglutide SC The treatments with oral semaglutide 25 mg and semaglutide SC 2.4 mg are expected to result in overlapping exposure, and a substantial number of patients are likely to experience similar exposure with both treatments.
- The multifactorial aetiology of obesity contributes to variation in treatment responses and some people with obesity will achieve their weight loss goal with a lower dose.
- Therefore, 25 mg oral semaglutide has been selected for the current study as maintenance dose in order to add more flexibility to the treatment by providing an additional, lower treatment dose option to the 50 mg treatment dose.

However, it should be noted that due to the same increased variability in semaglutide exposures following oral dosing (compared to SC), it is equally likely that some patients may achieve much lower semaglutide exposures (and potentially reduced efficacy) especially if some patients are not consistently compliant with the dosing instructions (to be taken fasting with only 120 ml of water and minimum of 30 min post-dose fasting).

Pivotal study for weight management indication: OASIS-4

This was a Phase 3b, randomised, placebo-controlled, double-blind two-armed, multi-centre, multinational, 64-week clinical study comparing the efficacy of once daily 25 mg oral semaglutide versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in adults with overweight and weight-related comorbidities, or with obesity (Figure 2). The study was conducted from 11 Oct 2022 to 7 May 2024 at 22 sites in 4 countries (Canada, USA, Germany and Poland).

Figure 2. Study design OASIS-4.



The main inclusion criteria were:

- male or female aged ≥ 18 years at time of signing informed consent,

- overweight [BMI of ≥ 27.0 kg/m^2] with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or CV disease OR Obese [BMI ≥ 30.0 kg/m^2].
- history of at least one self-reported unsuccessful dietary effort to lose body weight.

The main exclusion criteria were:

- self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records
- Treatment with any medication indicated for weight management within 90 days prior to screening.
- Previous or planned (during the study period) obesity treatment with surgery or a weight loss device with some exceptions.[17]

Efficacy variables and outcomes

The co-primary endpoints were: Relative change in body weight (from baseline to week 64) and achievement of ≥ 5% reduction in body weight (at week 64).

Body weight was measured on a digital scale, preferably using the same scale throughout the study. The scale must be calibrated yearly as a minimum, unless the manufacturer or local requirements certifies that calibration of the scale is valid for the duration of the study. Measurement must be performed without shoes, on an empty bladder, and only wearing light clothing and recorded in the eCRF in kilogram [kg] or pounds [lb] with the precision of 1/10 unit (e.g., 75.3 kg /166.0 lb).

Proportion of patients with achievement of body weight reduction of ≥ 10%, ≥15% and ≥ 20% at end of treatment (week 64) were the confirmatory secondary endpoints. Another confirmatory secondary endpoint was the change in physical function domain (5-items) score from the Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT, version 1.0) measure.

The sample size of 300 participants (200 randomised to 25 mg oral semaglutide and 100 randomised to placebo) provides more than 99% power for confirming superiority for both co-primary endpoints, and 71% power for confirming superiority for all confirmatory endpoints at 5% significance level using 2:1 randomisation.

Participant flow

Of the 346 participants who were screened, 37 were screen failures and 2 withdrew prior to randomisation. Overall, 307 participants were randomised to study treatment (oral semaglutide 25 mg vs placebo: 205 vs 102) of which 243 (79.2%) were on study treatment at end of study visit, i.e., treatment completers (81.5% vs 74.5%) and 290 (94.5%) completed end study visit, i.e.., study completers (95.6% vs 92.2%). Overall, proportion of participants who permanently discontinued study treatment was lower in the oral semaglutide 25 mg compared to placebo group (18% vs 25.5%) with main reasons being AEs (6.8% vs 5.9%) or protocol violation (1.5% vs 2%).

The mean age of all study participants was 48 years, mean body weight was 106 kg, mean BMI was 37.6 kg/ m2, mean waist circumference was 114 cms, mean HbA1c was 5.7% and mean FPG was 5.3 mmol/L with no differences between treatment groups.

[17] However, the following are allowed: (1) liposuction and/or abdominoplasty, if performed >1 year prior to screening, (2) lap banding, if the band has been removed >1 year prior to screening, (3) intragastric balloon, if the balloon has been removed >1 year prior to screening or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed >1 year prior to screening

Results for the primary efficacy outcome

Results for the co-primary endpoints by treatment policy estimand showed statistically significant superiority of oral semaglutide 25 mg compared to placebo at week 64 (end of treatment) as per:

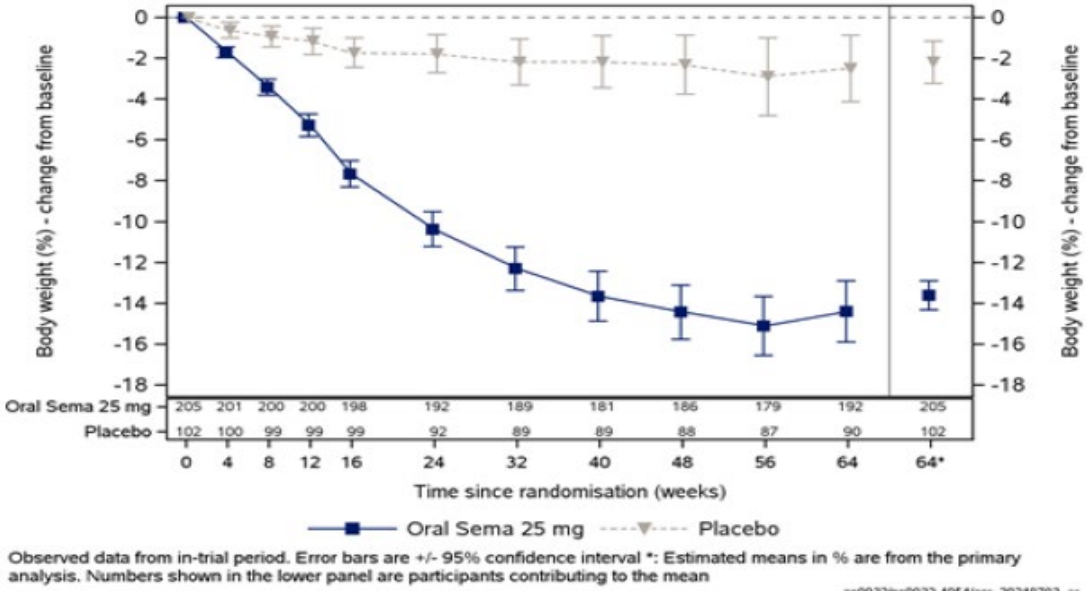
- the estimated mean change in body weight in the oral semaglutide 25 mg compared to placebo group was -13.61% vs -2.18% [ETD=-11.43% (95% CI: -13.88, -8.98), p<0.0001].
- the estimated proportion of participants achieving body weight reduction ≥5% was 76.3% vs 30.5% [EOR=7.34 (4.22, 12.76), p<0.0001].

Results for the co-primary endpoints by hypothetical strategy estimand also showed statistically significant superiority of oral semaglutide 25 mg compared to placebo at week 64.

- the estimated mean change in body weight was -16.62% vs -2.75% [ETD=-13.87 (-16.53, -11.21), p<0.0001].
- the estimated proportion of participants achieving body weight reduction ≥5% was 90.8% vs 28.2% [EOR=25.23 (13.24, 48.07), p<0.0001].

Onset of efficacy was rapid with ≥ 5% reduction in mean body weight from baseline seen by 12 weeks in the oral semaglutide 25 mg group with further reductions observed over the treatment period (Figure 3).

Figure 3. Body weight (%) change from baseline by week-mean plot–treatment policy strategy FAS.

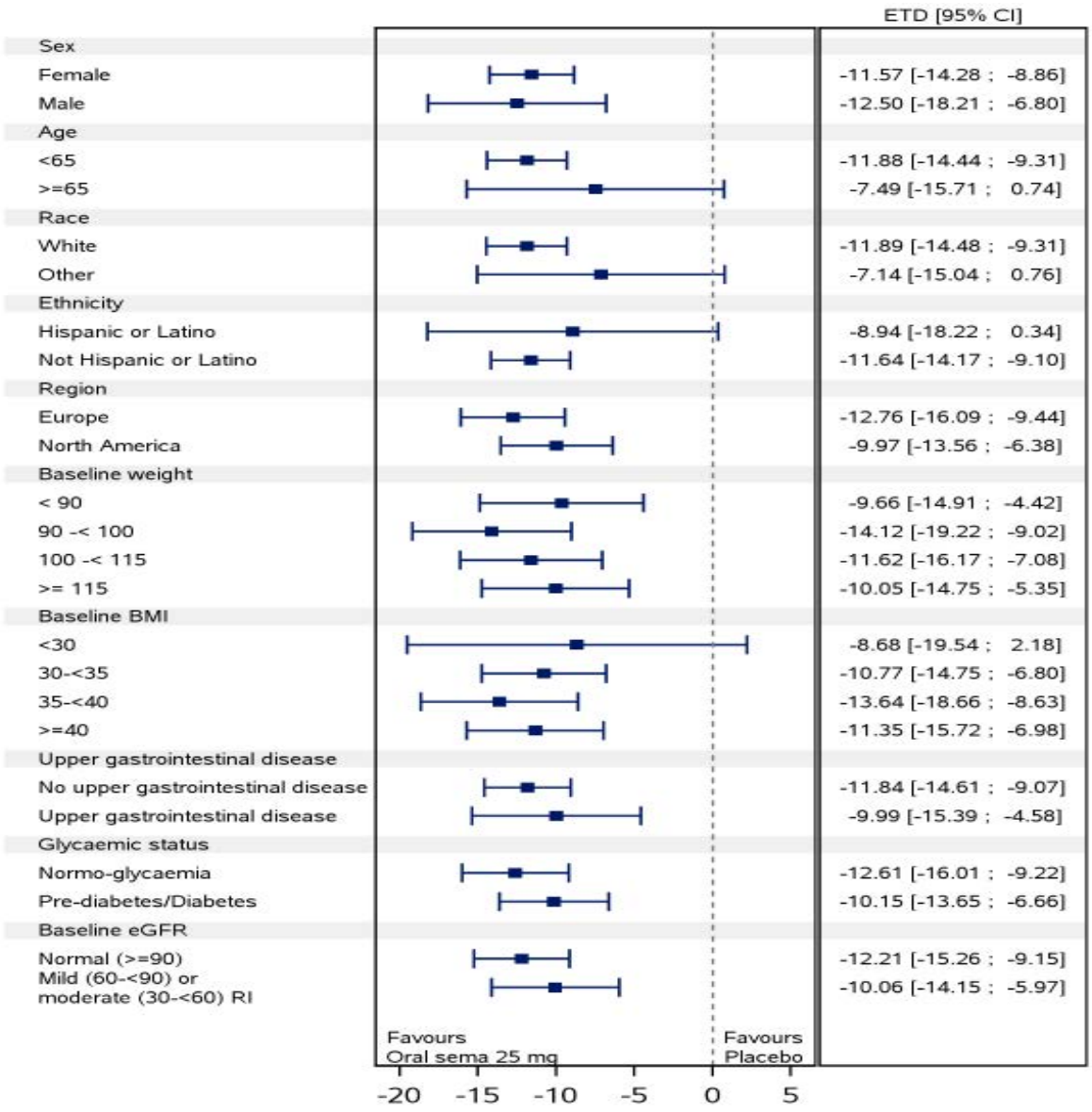


The results were confirmed in the sensitivity analysis**.** The efficacy was greater in treatment completers compared to participants who had returned for week 64 assessment after permanent discontinuation, i.e. retrieved participant. The efficacy response (% body weight change) for oral semaglutide 25 mg compared to placebo was consistent and beneficial across subgroups (Figure 4).

Results for confirmatory secondary endpoints:
Results for the confirmatory secondary endpoints by treatment policy estimand showed statistically significant superiority of oral semaglutide 25mg compared to placebo at week 64 (end of treatment) as follows:

- the estimated proportion of participants achieving body weight reduction ≥10% was (oral semaglutide 25mg vs placebo) 59.8% vs 14.1% [EOR=4.74 (4.74, 17.29), p<0.0001].
- the estimated proportion of participants achieving body weight reduction ≥15% was 47.0% vs 5.4% [EOR=15.74 (6.16, 40.24), p<0.0001].
- the estimated proportion of participants achieving body weight reduction ≥20% was 27.5% vs 3.0% [12.24 (3.72, 40.26), p<0.0001].
- the estimated mean change in IWQOL-Lite-CT Physical Function score was 16.18 vs 8.45 [ETD=7.73 (3.30, 12.16), p=0.0006].
- the improvement in physical function was significantly higher in the oral semaglutide 25 mg group compared to placebo from week 32 to week 64 with no overlap between the 95% CIs.

Figure 4. Body weight (%) change from baseline by subgroups- estimated treatment difference - forest plot - treatment policy strategy – FAS.



BMI: Body mass index GI: Gastrointestinal, eGFR: Estimated glomerular filtration rate RI: Renal impairment, ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period.

Supportive studies for weight management indication:

Supportive evidence of efficacy for proposed oral semaglutide 25mg once daily was also provided by:

- The data from the semaglutide SC 2.4 mg in STEP development programme (NN9536, Wegovy, STEP 1−4) especially the STEP 1 study which had similar patient population to that evaluated in the pivotal OASIS-4 study also provided confirmatory evidence of efficacy of 25 mg oral semaglutide. the weight loss observed with oral semaglutide 25 mg is consistent with the weight loss observed with semaglutide SC 2.4 mg in the STEP programme. This magnitude of weight loss has shown to result in the clinically relevant improvements in glucose metabolism, cardiovascular risk, general health, and physical functioning in patients with obesity or overweight.
- The weight management indication was also supported by nonclinical and clinical pharmacology data from the oral semaglutide T2D PIONEER development programme (NN9924, Rybelsus).
- Population PK and exposure-response models were developed using data from phase 3 studies in the OASIS, STEP, PIONEER, and SUSTAIN (NN9535 Ozempic SUSTAIN 1−3, SUSTAIN JPN OAD, and SUSTAIN FORTE) development programmes. The treatments with oral semaglutide 25 mg and semaglutide SC 2.4 mg are expected to result in overlapping exposure, and a substantial number of patients are likely to experience similar exposure with both treatments.

Safety data from all STEP 1−4 studies was used to support the safety of oral semaglutide 25 mg for the weight management indication. The safety data will also be supported by results from the phase 3 study, PIONEER PLUS (NN9924-4635), evaluating once-daily oral semaglutide of 14 mg, 25 mg, and 50 mg in participants with T2D and a BMI of at least 25 kg/m2.

Body weight loss in patients with T2DM

The % body weight change from baseline to week 68 in STEP 2 and to week 52 in PIONEER PLUS was numerically lower with 25mg oral semaglutide compared to 2.4 mg SC with the 50 mg oral dose showing comparable % body weight reduction. Furthermore, the observed proportion of participants with body weight loss of ≥ 5% in STEP 2 was 68.8% vs 28.5% (2.4 mg SC vs placebo) while it was 58.5% and 65.7% with oral semaglutide 25 mg and 50 mg, respectively (vs 42.2% with 14 mg oral semaglutide) in the PIONEER PLUS study. Despite limitation of comparisons across different studies, the clinically relevant endpoint of ≥5% body weight loss responders also showed slightly reduced efficacy with the proposed 25 mg oral dose with comparable efficacy between 2.4 mg SC and 50 mg oral doses.

Sustaining weight loss and withdrawal effect

Effect of withdrawal of oral semaglutide 25 mg on ability to retain body weight loss was not evaluated.

The semaglutide SC 2.4 mg study, STEP 4, assessed sustained weight loss and the effect of treatment withdrawal on body weight. All participants in STEP 4 were first treated with semaglutide for a 20-week run-in period (including 16 weeks of dose escalation). Participants who had reached the maintenance dose of semaglutide SC 2.4 mg were then randomised at week 20 to either continue semaglutide treatment or to switch to placebo for the remaining 48 weeks of treatment. Participants in the semaglutide SC 2.4 mg group continued to lose weight until the end of the treatment period while participants randomised to placebo gradually regained weight, without returning to the weight level at week 0 (baseline).

With comparable exposure and efficacy across semaglutide SC 2.4 mg and oral semaglutide 25 mg administration, it is assumed that the efficacy and the effect of treatment withdrawal from

STEP 4 can be extrapolated to the oral semaglutide development programme for weight management.

Overall, the evidence for efficacy of proposed oral semaglutide 25 mg once daily as an adjunct to diet and exercise for weight management indication was adequate. However, there was some evidence to suggest potential usefulness of the higher oral semaglutide 50 mg once daily dose in certain patient populations (including Asian populations and those with T2DM) which has not been explored in this submission.

Cardiovascular risk reduction: efficacy data

SOUL study

The SOUL study was a Phase 3b randomised, double-blind, parallel-group, placebo-controlled study comparing oral semaglutide versus placebo both administered once daily and added to standard of care in patients with T2DM at high risk of cardiovascular events. Patients were randomised 1:1 to receive either oral semaglutide 14 mg or placebo. The study was conducted from 17 June 2019 to 23 Aug 2024 at 441 centres in 34 countries (in Europe, USA and Asia).

The main inclusion criteria were:

- Male or female, age ≥50 years at the time of signing informed consent
- Diagnosed with T2DM, HbA1c 6.5% - 10.0% (47 - 86 mmol/mol) (both inclusive).
- At least one of the following conditions:
    1. Coronary heart disease defined as at least one of the following:
        i. Prior myocardial infarction (MI)
        ii. Prior coronary revascularisation procedure
        iii. ≥50% stenosis in coronary artery documented by cardiac catheterisation, computerized tomography coronary angiography
        iv. Coronary heart disease with ischaemia documented by stress test with any imaging modality.
    2. Cerebrovascular disease defined as at least one of the following:
        i. Prior stroke
        ii. Prior carotid artery revascularisation procedure
        iii. ≥50% stenosis in carotid artery documented by X-ray angiography, magnetic resonance angiography, computerized tomography angiography or Doppler ultrasound.
    3. Symptomatic peripheral artery disease (PAD) defined as at least one of the following:
        i. Intermittent claudication with an ankle-brachial index (ABI) < 0.85 at rest
        ii. Intermittent claudication with a ≥50% stenosis in peripheral artery (excluding carotid) documented by X-ray angiography, magnetic resonance angiography, computerized tomography angiography or Doppler ultrasound
        iii. Prior peripheral artery (excluding carotid) revascularization procedure
        iv. Lower extremity amputation at or above ankle due to atherosclerotic disease (excluding e.g., trauma or osteomyelitis).

4. Chronic kidney disease defined as eGFR < 60 mL/min/1.73 m^2 .

The main exclusion criteria were:

- MI, stroke, hospitalisation for unstable angina pectoris (UAP) or transient ischaemic attack within the past 60 days prior to the day of screening.
- Planned coronary, carotid or peripheral artery revascularisation known at screening.
- Heart failure presently classified as being in New York Heart Association Class IV.
- Treatment with any GLP-1 receptor agonist within 30 days before screening.

Dosing was once daily with escalation every 4th week until maintenance dose of 14 mg once daily was reached. Dosing instructions were similar to those discussed in detail in the OASIS-4 study. Matching placebo tablets were used. Three doses of oral semaglutide (3 mg, 7 mg and 14 mg once daily) had been evaluated in the Phase 3a development program, and the maximum treatment dose of 14 mg oral semaglutide was compared to placebo in this cardiovascular outcome trial (CVOT). Eligible subjects were centrally randomised in a 1:1 manner to one of the two treatment groups (oral semaglutide 14 mg or placebo).

Efficacy variables and outcomes

The primary endpoint in this trial was time from randomisation to first occurrence of a composite MACE endpoint consisting of CV death, non-fatal MI and non-fatal stroke. The primary analysis addressed the primary estimand (intention-to-treat); the HR for comparing oral semaglutide versus placebo was estimated from a Cox proportional hazards model with treatment group (oral semaglutide, placebo) as fixed factor together with the 2-sided 95% CI and one-sided fixed design p-value for hypothesis testing. If superiority was established for the primary endpoint, sensitivity and supplementary analyses were to be performed. Furthermore, the consistency in the treatment effect for the primary endpoint was also explored by subgroup analyses based on baseline information.

Given superiority for the primary endpoint, the superiority hypothesis stated below were to be tested for each of the confirmatory secondary endpoints under multiplicity control via a stagewise hierarchical testing scheme using the below order:

- Time from randomisation to first occurrence of 5-component composite CKD endpoint
- Time from randomisation to CV death
- Time from randomisation to first occurrence of MACE endpoint

All subjects had T2DM according to study protocol with similar mean duration of diabetes in both treatment groups (oral semaglutide vs placebo: 15.32 vs 15.44 years). Majority of the subjects were male (71.1%), White (68.9%) or Asian (23.4%) and not Hispanic/Latino (84.7%). The mean age was 66.1 years with 58.2% aged >65 years (14.2% were > 75 years). Majority of subjects were overweight or obese; 34.6%, 30.0%, 14.9% and 7.4% had BMI of 25 to <30, 30 to <35, 35 to <40 and >40kg/m2, respectively with similar distribution in both treatment groups. Majority of subjects had CHD (70.1%) and CKD (42.4%) with similar distribution of individual CVD or CKD disease in both treatment groups.

Overall, the baseline characteristics were well-balanced across both treatment groups and treatment compliance was generally similar in both groups.

Results: Primary endpoints

A total of 1,474 MACEs in 1,247 subjects (of which not all were first events) were confirmed during the in-trial observation period. MACE occurred less frequently and at a lower rate with

oral semaglutide than with placebo. The proportion of subjects with first EAC-confirmed MACE was lower with oral semaglutide (12.0%) than with placebo (13.8%) and was mainly driven by a smaller number of first non-fatal MI with oral semaglutide than with placebo (4.0% vs 5.2%); the other components of the MACE composite endpoint (non-fatal stroke and CV death) were also lower in the oral semaglutide group (Table 4).

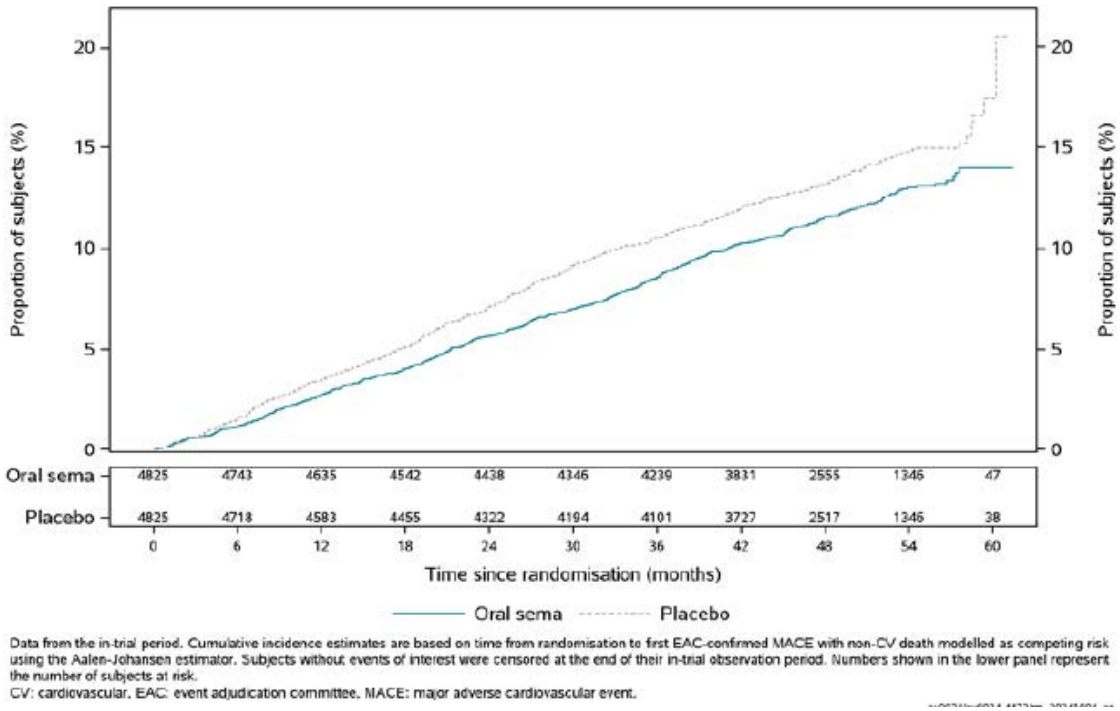
Table 4. EAC-confirmed MACE (all events) – summary – FAS in-trial.

	Oral Sema					Placebo				
	N	(%1)	E	(%2)	R	N	(%1)	E	(%2)	R
Number of subjects	4825					4825				
Observation time (years) all events	19188					18984				
All EAC-confirmed MACE	579	(12.0)	683	(100)	3.6	668	(13.8)	791	(100)	4.2
Non-fatal MI	191	(4.0)	218	(31.9)	1.1	253	(5.2)	292	(36.9)	1.5
Non-fatal stroke	144	(3.0)	164	(24.0)	0.9	161	(3.3)	179	(22.6)	0.9
CV death	301	(6.2)	301	(44.1)	1.6	320	(6.6)	320	(40.5)	1.7

Notes: Data from in-trial period. CV death includes undetermined cause of death. MI comprise acute MIs. Silent MIs are not part of the non-fatal MI component. %1 = percentage of subjects with at least one event. %2 = percentage of total number of events.
Abbreviations: CV = cardiovascular; E = number of events; EAC = event adjudication committee; FAS = full analysis set; MACE = major adverse cardiovascular event; MI = myocardial infarction; N = number of subjects with at least one event; R = events per 100 years of observation; sema = semaglutide.

The estimated risk of experiencing a first MACE within any certain time from randomisation was lower for oral semaglutide compared with placebo as reflected in the separation of the curves from shortly after trial initiation, and throughout the trial (Figure 5).

Figure 5. Time from randomisation to first EAC-confirmed MACE – cumulative incidence plot – FAS in-trial



Data from the in-trial period. Cumulative incidence estimates are based on time from randomisation to first EAC-confirmed MACE with non-CV death modelled as competing risk using the Aalen-Johansen estimator. Subjects without events of interest were censored at the end of their in-trial observation period. Numbers shown in the lower panel represent the number of subjects at risk.
CV: cardiovascular, EAC: event adjudication committee, MACE: major adverse cardiovascular event.

There was a 14% lower relative risk of MACE with oral semaglutide compared to placebo [HR=0.86 (95% CI: 0.77, 0.96), p=0.0028]. The absolute risk difference between oral semaglutide and placebo at week 156 was -0.020 (95 % CI: -0.032; -0.0008).

The primary analysis was confirmed by the sensitivity analysis.

Supportive secondary endpoints

The estimated risk of experiencing a first EAC-confirmed non-fatal MI within any certain time from randomisation was lower for oral semaglutide compared with placebo as reflected in the separation of the curves from shortly after trial initiation, and throughout the trial**;** estimated HR (oral semaglutide vs placebo) was 0.74 (95% CI: 0.61, 0.89). Similar results were observed for time from randomisation to first EAC-confirmed all MI events (fatal or non-fatal) with an estimated HR of 0.73 (95% CI: 0.61; 0.88).

The estimated risk of experiencing a first EAC-confirmed non-fatal stroke within any certain time from 6 months after trial initiation was lower for oral semaglutide compared with placebo as reflected in the separation of the curves from 6 months after trial initiation, and throughout the trial with estimated HR of 0.88 (0.70; 1.11). Similar results were observed for time from randomisation to first EAC-confirmed all stroke events (fatal or non-fatal) although the 95% CI for estimated HR included unity [0.95 (95% CI: 0.76, 1.17)].

A total of 930 composite kidney endpoint[18] events in 838 subjects (of which not all were first events) had onset during the in-trial observation period. Composite kidney endpoint events occurred less frequently and at a lower rate with oral semaglutide than with placebo.

Effect of oral semaglutide 25mg on MACE

Effect of oral semaglutide 25mg once daily on MACE was not specifically evaluated. The proposed CV indication is supported by the combined evidence from cardiovascular outcome trials (CVOTs) that demonstrated the superiority of semaglutide (both SC and oral) compared to placebo in reducing cardiovascular risk.

The CVOT, EX9536-4388 (SELECT) demonstrated superiority of SC semaglutide 2.4 mg (Wegovy) compared to placebo with a clinically relevant risk reduction of 20% in MACE in participants with established CVD and obesity or overweight without history of T1D or T2D. Semaglutide was the first weight management medication to show CV risk reduction and the first GLP-1 RA to demonstrate CV risk reduction in a population with established CVD and obesity or overweight, without history of T1D or T2D.

An event driven pre-approval CVOT (NN9924-4221, denoted PIONEER 6) for oral semaglutide (Rybelsus), designed to rule out excess cardiovascular risk, demonstrated improved CV risk factors in participants with T2D and confirmed non-inferiority for MACE in participants with T2D at high CV risk. Subsequently, the CVOT (EX9924-4473, denoted SOUL) demonstrated superiority of oral semaglutide 14 mg versus placebo in CV risk reduction, in participants with T2D at high CV risk (% risk reduction).

A beneficial effect of SC semaglutide (Ozempic) on MACE was demonstrated with a statistically significant estimated risk reduction when added to standard-of-care therapy in participants with T2D and high CV risk (NN9535-3744, denoted SUSTAIN 6). Ozempic is approved for CV risk reduction in several countries (including the US) in people with T2D and established CV disease. Furthermore, data obtained from the literature on GLP-1 RA class effect on CV risk reduction support the substantial evidence of effectiveness generated from the semaglutide outcomes trials (SELECT, SOUL, SUS-TAIN 6, PIONEER 6 and FLOW).

[18] Composite kidney endpoint consisted of events including CV death, kidney death, onset of persistent ≥50% reduction in eGFR (CKD-EPI) compared with baseline, onset of persistent eGFR (CKD-EPI) <15 mL/min/1.73 m2 and initiation of chronic kidney replacement therapy (dialysis or kidney transplantation). Events not related to eGFR (kidney death, CV death and kidney replacement therapy) had to be EAC-confirmed

Although not specifically evaluated, the effect on MACE with oral semaglutide 25 mg is likely to be consistent with the effect observed with SC semaglutide 2.4 mg in SELECT, oral semaglutide 14 mg in the SOUL study and SC semaglutide 0.5 and 1.0 mg in SUSTAIN 6.

A model-based analysis extrapolating the effect on MACE from 2.4 mg SC semaglutide in SELECT to 25 mg oral semaglutide is described in CV Modelling Report. This showed that the exposure-response relationship between semaglutide and MACE risk appeared identical for oral and SC semaglutide. The simulated 21% MACE risk reduction for a SELECT population randomised to oral semaglutide 25 mg [HR=0.79 (95% CI 0.67-0.90)] was similar to the risk reduction observed for the actual SELECT trial [HR=0.80 (95% CI 0.72-0.90)].

Safety

Overall, 603 participants in the oral semaglutide 25 mg treatment group were exposed for at least one year which was considered adequate for evaluation of safety in compliance with EMA and FDA guidelines requirement of one year of treatment to evaluate safety for medicinal products for weight management.

Overall, the demographic characteristics, comorbidities and concomitant medications for the participants evaluated for safety in the OASIS-4 and PIONEER PLUS studies for oral semaglutide 25 mg was representative of the target patient population in Australia.

Special populations that were excluded from each of the studies for safety reasons in line with other studies investigating GLP-1 RAs included pregnant women, children, patients with T1DM, congestive heart failure NYHA class IV, and patients with a history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma. These patient populations were adequately highlighted in the proposed Australian PI.

The safety and efficacy of Wegovy was not evaluated in patients being treated with other products for weight management, with type 1 diabetes or with NYHA class IV congestive heart failure. The proposed Australian PI recommends that semaglutide should not be used in these patients. Furthermore, there is limited evidence of efficacy/safety of semaglutide in patients with inflammatory bowel disease, diabetic gastroparesis or in those aged over 85 years; use with caution is recommended in these patients.

A similar proportion of participants in OASIS-4 reported any adverse events (AE) during the on-treatment period (OASIS-4: 93.1% at an event rate of 493.5 events per 100 patient years exposure - PYE) and in STEP phase 3a pool: (88.5% at an event rate of 521.0 events per 100 PYE). In PIONEER PLUS, the overall proportion of participants in the oral semaglutide groups reporting any AE during the treatment period was similar between 25 mg and 50 mg oral semaglutide treatment arms. Both of these treatment arms were higher than the 14 mg oral semaglutide group, with no placebo control in this study (79.0% at an event rate of 317.6 events per 100 PYE for 25 mg group, and 80.1% at an event rate of 319.9 events per 100 PYE for 50 mg group).

Although some AEs are exposure-dependent, such as gastrointestinal AEs which were reported more frequently for OASIS-4 participants with high exposure (>147 nmol/L), overall safety and tolerability of oral semaglutide 25 mg in OASIS-4 were similar to that of oral semaglutide 50 mg in OASIS 1 (91.9% of participants reporting any AE during the on-treatment period at an event rate of 561.3 events per 100 PYE). This is consistent with the overall and well-established safety profile of semaglutide and the GLP-1 RA drug class in general.

The overall safety profile for oral semaglutide 25 mg administered once daily, as an adjunct to a reduced-calorie diet and increased physical activity in OASIS-4, was consistent with the safety profile of semaglutide and the GLP-1 RA drug class in general.

The PIONEER PLUS study compared 25 mg and 50 mg oral doses of semaglutide with the currently used 14 mg dose in adults with T2DM. Results from this study showed higher incidence of overall AEs including commonly reported gastrointestinal AEs in the 25 mg and 50 mg dose groups compared to the 14 mg dose but the increase in AEs was comparable in the proportion of participants reporting AEs between the 25 mg and 50 mg doses.

The Phase 3a, 68-week, randomised, placebo-controlled, double-blind study OASIS 2 was conducted in 200 East Asian (Japanese/South Korean) overweight (with at least 2 comorbidities) or obese participants (with at least 1 comorbidity) while the OASIS 3 study was a Phase 3a, 44-week, randomised placebo-controlled study in 199 Chinese adults. The overall safety profile for oral semaglutide 50 mg was consistent with the safety profile for semaglutide in weight management (SC and oral) and the GLP-1 RA class of drugs.

The overall safety profile for oral semaglutide 50 mg observed in OASIS 2 and OASIS 3 studies conducted in Japanese/South Koren and Chinese overweight/obese adults, respectively was consistent with the safety profile observed in the OASIS-4 study, PIONEER PLUS study and STEP program. However, it is important to note that the 50 mg was evaluated in Caucasians only in the PIONEER PLUS study which did not have a placebo control (it compared 25 mg and 50 mg oral doses with 14 mg dose) and was conducted only adults with in T2DM.

Recommendation following the clinical evaluation

Overall, the evidence to support CV risk indication for proposed 25 mg oral semaglutide is acceptable. The safety and tolerability or proposed oral semaglutide 25 mg once daily was consistent with the overall and well-established profile of semaglutide (oral and SC).

Risk management plan

The sponsor is required to comply with product vigilance and risk minimisation requirements.

See TGA's guidance on 'when an RMP is required'.

The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit analysis

Delegate's considerations

Efficacy

The average exposure levels observed in OASIS-4 following oral semaglutide 25 mg once daily were generally similar to those observed following SC semaglutide 2.4 mg in STEP 1, as indicated by the results of the PopPK analysis based on Phase 3 studies, including PIONEER PLUS and OASIS-4. The exposure levels of most participants (82.2%) who were treated with oral semaglutide 25 mg in OASIS-4 were within the same range as those who were treated with SC semaglutide 2.4 mg in STEP 1. In order to substantiate the proposed indication of CV risk reduction for oral semaglutide 25 mg in this submission, E-R modelling and analysis were implemented.

The pivotal study for weight management indication (OASIS-4) was a Phase 3b randomised, double-blind, placebo-controlled, multinational study that was well conducted. The trial included 307 participants with obesity or overweight and at least one obesity-related comorbidity. The study was devised in accordance with the EMA guidelines for the evaluation of medicinal products for weight management that were adopted by the TGA. From the baseline to week 64, oral semaglutide 25 mg was superior to the placebo in all tests within the statistical test hierarchy.

- Primary endpoint, %-change in body weight: -13.61% vs -2.18% [ETD=-11.43% (95% CI: -13.88, -8.98), p<0.0001].
- Primary endpoint, ≥5% weight loss: 76.3% vs 30.5% [EOR=7.34 (4.22, 12.76), p<0.0001].

Robustness of results was confirmed in the sensitivity analysis. The efficacy response (% body weight change) for oral semaglutide 25 mg compared to placebo was consistent, and beneficial across subgroups.
The Phase 3b, 68-week, randomised, active-controlled, double-blinded, three-armed (oral semaglutide 14 mg, 25 mg, and 50 mg od), multi-centre, multinational study PIONEER PLUS, which included 1606 adults with T2DM, provides supportive evidence of efficacy in weight management. In comparison to the 14 mg oral semaglutide dose, the higher oral semaglutide doses (25 mg and 50 mg) resulted in greater improvements in weight-related and glycaemic parameters.
The SOUL study demonstrated evidence of a decrease in cardiovascular risk associated with oral semaglutide. The impact of oral semaglutide 25 mg once daily on MACE was not specifically assessed. The SOUL study was conducted exclusively on T2DM patients at a high risk of cardiovascular events and evaluated 14 mg oral semaglutide (RYBELSUS, which is an oral medication available for T2DM). The relative risk of MACE was 14% lower with oral semaglutide compared to placebo [HR=0.86 (95% CI: 0.77, 0.96), p=0.0028]. At week 156, the absolute risk difference between oral semaglutide and placebo was -0.020 (95% confidence interval: -0.032; -0.0008). The sensitivity and supplementary analyses verified the robustness of the primary analysis. Although not specifically evaluated in a clinical study, the effect on MACE with oral semaglutide 25 mg is likely to be consistent with the effect observed with SC semaglutide 2.4 mg in SELECT, oral semaglutide 14 mg in the SOUL study and SC semaglutide 0.5 and 1.0 mg in SUSTAIN 6.

Safety

Overall, the safety and tolerability or proposed oral semaglutide 25 mg once daily was consistent with the overall and well-established profile of semaglutide (oral and SC).

Proposed action

In the context of the substantial and increasing global burden of obesity and associated cardiovascular risk, and in light of the magnitude and range of the benefits, as well as the manageable and well-characterized risks as previously discussed and overall, based on the review of data on quality, safety and efficacy, the Delegate considers that the benefit-risk balance of Wegovy (semaglutide) tablets is favorable.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Wegovy (semaglutide) 1.5mg, 4mg, 9mg, 25mg tablets, indicated for:

Weight Management
Adults (solution for injection and tablet)
Wegovy is indicated as an adjunct to a reduced-energy diet and increased physical activity for chronic weight management (including weight loss and weight maintenance) in adults with an initial Body Mass Index (BMI) of

- ≥30 kg/m2 (obesity), or
- *≥27 kg/m2 to <30 kg/m2 (overweight) in the presence of at least one weight-related comorbidity (see Section 5.1 Pharmacodynamic Properties – Clinical trials).*

Reduction in risk of major adverse cardiovascular events (solution for injection and tablet)

Wegovy is indicated as an adjunct to standard of care therapy to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with established cardiovascular disease, with a Body Mass Index (BMI) ≥27 kg/m2, and without established Type 1 or Type 2 diabetes (see Section 5.1 Pharmacodynamic Properties –Clinical trials).

Concomitant use with other GLP-1 receptor agonists

Concomitant use of WEGOVY (semaglutide) tablets or WEGOVY (semaglutide) injection with other semaglutide-containing products or with any other GLP-1 receptor agonist is not recommended.

Specific conditions of registration

Laboratory testing & compliance with Certified Product Details (CPD)

i. All batches of **WEGOVY semaglutide (Tablet)** supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

ii. When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

Certified Product Details

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

A template for preparation of CPD for biological prescription medicines can be obtained from the TGA website

[for the form] https://www.tga.gov.au/form/certified-product-details-cpdbiological-prescription-medicines

[for the CPD guidance] https://www.tga.gov.au/guidance-7-certified-productdetails

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

Reference/Publication #