Mounjaro®▼ (tirzepatide)

Weight Management

Clinical Summary & Formulary Pack

Indication:

Mounjaro is indicated for weight management, including weight loss and weight maintenance, as an adjunct to a reduced-calorie diet and increased physical activity in adults with an initial Body Mass Index (BMI) of:[1]

- ≥ 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 comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus).

Adverse events and product complaints should be reported. Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events and product complaints should also be reported to Lilly: please call Lilly UK on 01256 315 000.

Prescribing information can be found at the end of the document.

For healthcare professionals and relevant decision makers in Great Britain only
PP-TR-GB-0373 | March 2024

Lilly

once weekly mounjaro®▼ tirzepatide

Purpose of this document

This document has been designed to support healthcare professionals or other authorised persons who are involved with formulary and guideline decision-making.

The information provided is not intended as a substitution for local data regarding patients and services, but to provide additional background information to support cases for local implementation. Depending on local circumstances, the content of any given application may vary, and this document is designed to be used flexibly to suit local formulary application requirements.

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Introducing Mounjaro

Mechanism of Action & Licensed Indication

Mounjaro is a long-acting dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist.[1] Both receptors are present on the pancreatic α and β endocrine cells, heart, vasculature, immune cells (leukocytes), gut and kidney.[1] GIP receptors are also present on adipocytes.[1] Mounjaro lowers body weight and body fat mass.[1] The mechanisms associated with body weight and body fat mass reduction involve decreased food intake through the regulation of appetite and modulation of fat utilisation.[1] Clinical studies show that Mounjaro reduces energy intake and appetite by increasing feelings of satiety (fullness),decreasing feelings of hunger, and decreasing food cravings.[1]

Mounjaro is licensed for weight management, including weight loss and weight maintenance, as an adjunct to a reduced-calorie diet and increased physical activity in adults with an initial 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 comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus).[1]

Safety & Efficacy

For more information on SURMOUNT-1 and SURMOUNT-2 please see the Mounjaro Clinical Programme section.

The safety and efficacy of Mounjaro for weight management in combination with a reduced calorie intake and increased physical activity were evaluated in two randomised double-blinded, placebo-controlled phase 3 studies in patients without diabetes mellitus (SURMOUNT-1) and with diabetes mellitus (SURMOUNT-2).[1] A total of 3,477 patients (2,519 randomised to treatment with Mounjaro) were included in the trials.[1] All patients treated with Mounjaro started with 2.5 mg for 4 weeks.[1] Then the dose of Mounjaro was increased by 2.5 mg every 4 weeks until they reached their assigned dose.[1]

In SURMOUNT-1 the dose of Mounjaro or matching placebo was escalated to 5 mg, 10 mg, or 15 mg subcutaneously once weekly during a 20-week period followed by the maintenance period.[1] In SURMOUNT-2, the dose of Mounjaro or matching placebo was escalated to 10 mg or 15 mg subcutaneously once weekly during a 20-week period followed by the maintenance period.[1] For SURMOUNT-1 and SURMOUNT-2, the co-primary endpoints for Mounjaro 10 mg and/or 15 mg once weekly were the mean percent change in body weight from baseline and the percentage of participants achieving ≥5% reduction in body weight from baseline.

Co-primary objectives were to show superiority to placebo at Week 72 for these endpoints.[3,4]

In SURMOUNT-1 and SURMOUNT-2, Mounjaro 10 mg and 15 mg demonstrated sustained, superior and clinically meaningful weight reduction vs placebo.[3,4]

The most common adverse events with Mounjaro were gastrointestinal in nature and were mostly mild to moderate in severity.[1]

Dosing Schedule

The starting dose of Mounjaro is 2.5 mg once weekly. After 4 weeks, the dose should be increased to 5 mg once weekly. If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose.[1]

The recommended maintenance doses are 5, 10 and 15 mg.[1]

The maximum dose is 15 mg once weekly.[1]

Mounjaro pre-filled KwikPen® device

Please note devices shown in this guide are for illustrative purposes only and are not actual size

Table 1: KwikPen®: Product Specifications and Technical Prescribing Codes

Approved Dose (4-weeks treatment)	UK List Price[2]	PIP Code	Barcode (GTIN)
2.5 mg	£92.00	540-2268	5014602102029
5 mg	£92.00	540-2292	5014602102036
7.5 mg	£107.00	540-2300	5014602102043
10 mg	£107.00	540-2318	5014602102074
12.5 mg	£122.00	540-2326	5014602102050
15 mg	£122.00	540-2334	5014602102067

Product Specifications (same for all doses)	
Pack Size	1 Pen
Dimensions: Height (mm)	38
Dimensions: Length (mm)	146
Dimensions: Width (mm)	55
Pack Weight (g)	93.75

Product Profile

Name of the medicinal product

Mounjaro® (tirzepatide)[1]

Clear, colourless to slightly yellow solution.[1]

Licensed indication for weight management

Mounjaro is indicated for weight management, including weight loss and weight maintenance, as an adjunct to a reduced-calorie diet and increased physical activity in adults with an initial BMI of:[1]

- ≥ 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 comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus).

Posology and method of administration

Posology

The starting dose of Mounjaro is 2.5 mg once weekly.[1] After 4 weeks, the dose should be increased to 5 mg once weekly. If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose.[1]

- The recommended maintenance doses are 5, 10 and 15 mg.[1]
- The maximum dose is 15 mg once weekly.[1]
- For weight management, if patients have been unable to lose at least 5% of their initial body weight 6 months after titrating to the highest tolerated dose, a decision is required on whether to continue treatment, taking into account the benefits of treatment against risk profile in the individual patient.[1]

When tirzepatide is added to existing metformin and/or sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy, the current dose of metformin and/or SGLT2i can be continued.

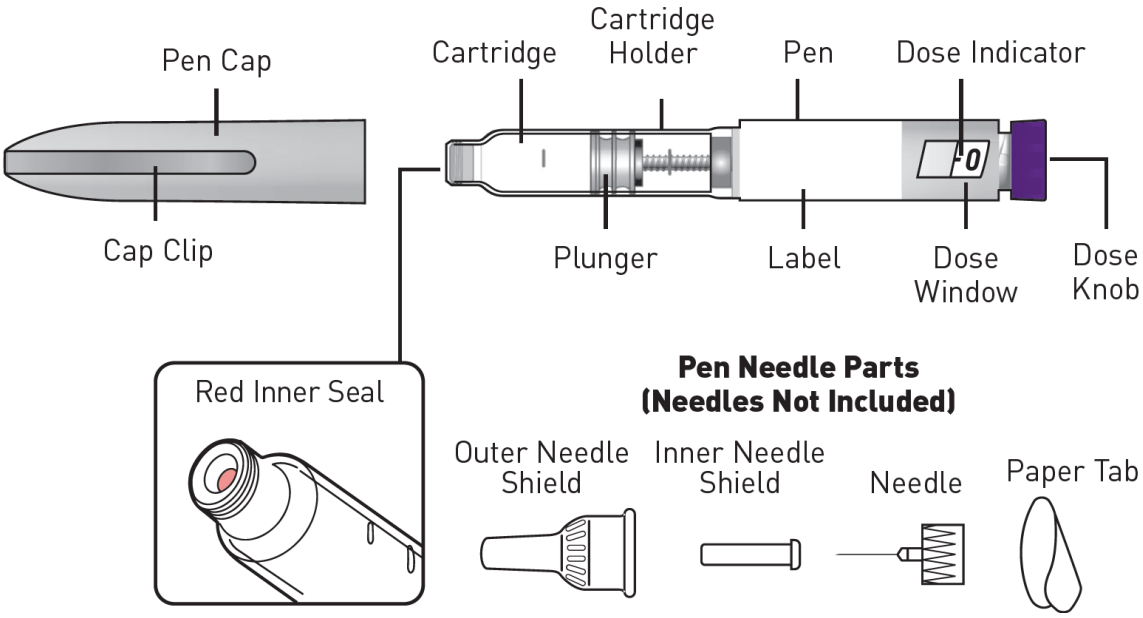
When tirzepatide is added to existing therapy of a sulphonylurea and/or insulin, a reduction in the dose of sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia. Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea and insulin. A stepwise approach to insulin reduction is recommended.

Method of administration

- Mounjaro is to be injected subcutaneously in the abdomen, thigh or upper arm.[1]
- The dose can be administered at any time of day, with or without meals.[1]
- Injection sites should be rotated with each dose. If a patient also injects insulin, they should inject Mounjaro into a different injection site.[1]

Patients should be advised to carefully read the instructions for use and the package leaflet for the pre-filled Kwikpen before administering the medicinal product.[1]

Figure 1: Parts of the Mounjaro KwikPen[5]



Special populations

Elderly, gender, race, ethnicity or body weight.[1]

No dose adjustment is needed based on age, gender, race, ethnicity or body weight.[1]

Renal impairment

No dose adjustment is required for patients with renal impairment including end stage renal disease (ESRD). [1] Experience with the use of Mounjaro in patients with severe renal impairment and ESRD is limited. Caution should be exercised when treating these patients with Mounjaro.[1]

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment. Experience with the use of Mounjaro in patients with severe hepatic impairment is limited.[1] Caution should be exercised when treating these patients with Mounjaro.[1]

Paediatric population

The safety and efficacy of Mounjaro in children aged less than 18 years have not yet been established. No data are available.[1]

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the Summary of Product Characteristics (SmPC).[1]

Special warnings and precautions for use

Acute pancreatitis

Mounjaro has not been studied in patients with a history of pancreatitis and should be used with caution in these patients.[1]

Acute pancreatitis has been reported in patients treated with Mounjaro.[1]

Patients should be informed of the symptoms of acute pancreatitis.[1] If pancreatitis is suspected, Mounjaro should be discontinued.[1] If the diagnosis of pancreatitis is confirmed, Mounjaro should not be restarted. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.[1]

Hypoglycaemia in patients with type 2 diabetes mellitus

Patients receiving Mounjaro in combination with an insulin secretagogue (for example, a sulphonylurea) or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of the insulin secretagogue or insulin.[1]

Gastrointestinal effects

Mounjaro has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhoea.[1] These adverse reactions may lead to dehydration, which could lead to a deterioration in renal function including acute renal failure.[1] **Patients treated with Mounjaro should be advised of the potential risk of dehydration, due to the gastrointestinal adverse reactions and take precautions to avoid fluid depletion and electrolyte disturbances.[1] This should particularly be considered in the elderly, who may be more susceptible to such complications.[1]**

Severe gastrointestinal disease

Mounjaro has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and should be used with caution in these patients.[1]

Diabetic retinopathy

Mounjaro has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy or diabetic macular oedema, and should be used with caution in these patients with appropriate monitoring.[1]

Elderly

Only very limited data are available from patients aged ≥ 85 years.[1]

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.[1]

Benzyl Alcohol [E1519]

This medicine contains 5.4 mg Benzyl Alcohol [E1519] in each 0.6 ml dose. Benzyl alcohol may cause allergic reactions. **Patients with hepatic or renal impairment should be informed of the potential risk of metabolic acidosis due to accumulation of benzyl alcohol over time.**[1]

Interaction with other medicinal products and other forms of interaction

Mounjaro delays gastric emptying and thereby has the potential to impact the rate of absorption of concomitantly administered oral medicinal products.[1] This effect, resulting in decreased maximum plasma concentration (C_{max}) and a delayed time to peak drug concentration (t_{max}), is most pronounced at the time of Mounjaro treatment initiation.[1]

Based on the results from a study with paracetamol, which was used as a model medicinal product to evaluate the effect of Mounjaro on gastric emptying, no dose adjustments are expected to be required for most concomitantly administered oral medicinal products.[1] However, it is recommended to monitor patients on oral medicinal products with a narrow therapeutic index (e.g., warfarin, digoxin), especially at initiation of Mounjaro treatment and following dose increase. The risk of delayed effect should also be considered for oral medicinal products for which a rapid onset of effect is of importance.[1]

Paracetamol

No dose adjustment of paracetamol is necessary when administered with Mounjaro. Following a 5 mg single dose of Mounjaro, the C_{max} of paracetamol was reduced by 50%, and the median t_{max} was delayed by 1 hour.[1] The effect of Mounjaro on the oral absorption of paracetamol is dose and time dependent.[1] At low doses (0.5 and 1.5 mg), there was only a minor change in paracetamol exposure.[1] After four consecutive weekly doses of Mounjaro (5/5/8/10 mg), no effect on the paracetamol C_{max} and t_{max} was observed.[1] The overall exposure (AUC [area under the curve]) was not influenced.[1]

Oral contraceptives

Administration of a combination oral contraceptive (0.035 mg ethinyl estradiol plus 0.25 mg norgestimate, a prodrug of norelgestromin) in the presence of a single dose of Mounjaro (5 mg) resulted in a reduction of oral contraceptive C_{max} and area under the curve (AUC).[1] Ethinyl estradiol C_{max} was reduced by 59% and AUC by 20% with a delay in t_{max} of 4 hours. Norelgestromin C_{max} was reduced by 55% and AUC by 23% with a delay in t_{max} of 4.5 hours. Norgestimate C_{max} was reduced by 66%, and AUC by 20% with a delay in t_{max} of 2.5 hours.[1] This reduction in exposure after a single dose of Mounjaro is not considered clinically relevant. No dose adjustment of oral contraceptives is required in women with normal BMI.[1]

There is limited information about the effect of Mounjaro on the pharmacokinetics and efficacy of oral contraceptives in women who are

overweight or women with obesity.[1] Since reduced efficacy of oral contraceptives cannot be excluded, it is advised switching to a non-oral contraceptive method, or add a barrier method of contraception upon initiating Mounjaro therapy (for 4 weeks), or after each dose escalation (for 4 weeks).[1]

Fertility, pregnancy and lactation

Pregnancy

There are no or a limited amount of data from the use of Mounjaro in pregnant women.[1] Studies in animals have shown reproductive toxicity. Mounjaro is not recommended during pregnancy and in women of childbearing potential not using contraception.[1] If a patient wishes to become pregnant, Mounjaro should be discontinued at least 1 month before a planned pregnancy due to the long half-life of Mounjaro.[1] Mounjaro should not be used during pregnancy.[1]

Breast-feeding

It is unknown whether Mounjaro is excreted in human milk. A risk to the newborn/infant cannot be excluded.[1]

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Mounjaro therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.[1]

Fertility

The effect of Mounjaro on fertility in humans is unknown.[1]

Animal studies with Mounjaro did not indicate direct harmful effects with respect to fertility.[1]

Shelf life and storage

14 Months.[1]

Store in a refrigerator (2 °C – 8 °C).[1]

Do not freeze.[1]

Store in original package in order to protect from light.[1]

Mounjaro may be stored unrefrigerated for up to 30 days at a temperature not above 30 °C and then the pre-filled KwikPen must be discarded. [1]

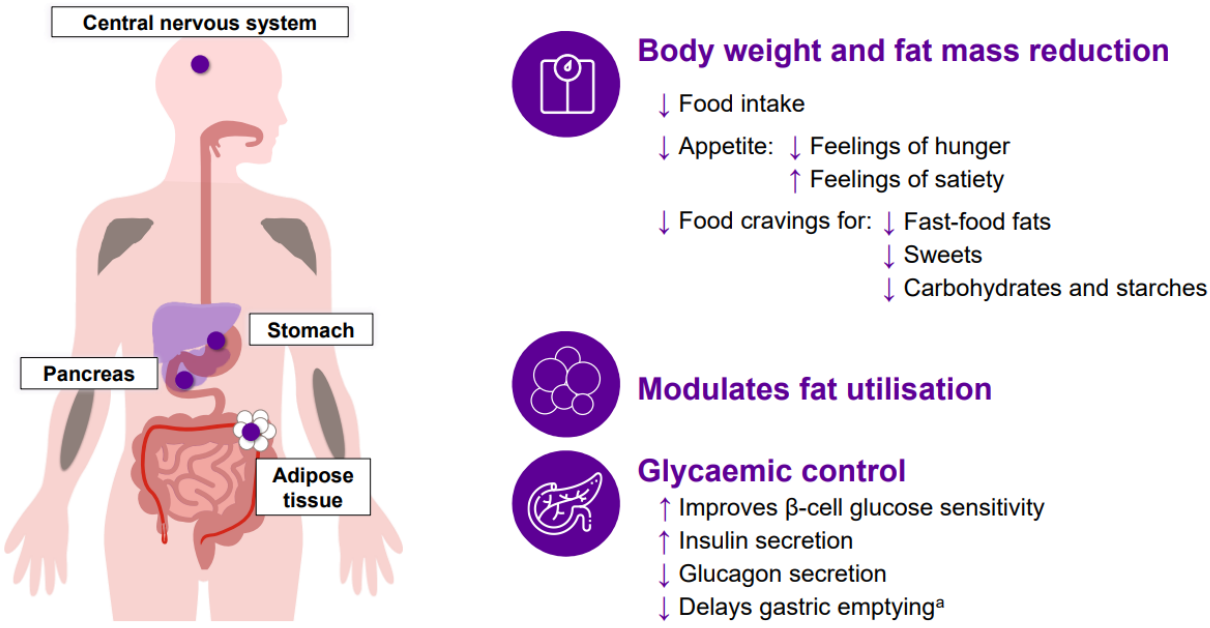
Mode of Action

Mounjaro is a long-acting dual GIP and GLP-1 receptor agonist. Both receptors are present on the pancreatic α and β endocrine cells, heart, vasculature, immune cells (leukocytes), gut and kidney. GIP receptors are also present on adipocytes.[1]

In addition, both GIP and GLP-1 receptors are expressed in the areas of the brain important to appetite regulation.[1]

Mounjaro is highly selective to human GIP and GLP-1 receptors. Mounjaro has high affinity to both the GIP and GLP-1 receptors.[1] The activity of Mounjaro on the GIP receptor is similar to native GIP hormone.[1] The activity of Mounjaro on the GLP-1 receptor is lower compared to native GLP-1 hormone.[1]

Figure 2: The pharmacodynamics of Mounjaro[1]



[a]Mounjaro-induced delay in gastric emptying diminishes over time.

Appetite regulation and energy metabolism

Mounjaro lowers body weight and body fat mass.[1] The mechanisms associated with body weight and body fat mass reduction involve decreased food intake through the regulation of appetite and modulation of fat utilisation.[1] Clinical studies show that Mounjaro reduces energy intake and appetite by increasing feelings of satiety (fullness), decreasing feelings of hunger, and decreasing food cravings.[1]

Mounjaro significantly decreased the amount of food consumed and calorie intake during ad libitum lunch, dinner and combined compared to placebo in people living with obesity.[1] Mounjaro significantly lowered overall appetite as measured by retrospective visual analogue scale (VAS) throughout an 18-week period compared to placebo.[1] Mounjaro decreased hunger and prospective food consumption starting at week 1 of the treatment and increased satiety starting at week 3.[1] Mounjaro significantly decreased craving for fast-food fats, sweets, carbohydrates and starches, except cravings for vegetables and fruit, compared to placebo in people living with obesity.[1]

Insulin secretion

Mounjaro increases pancreatic β-cell glucose sensitivity. It enhances first- and second-phase insulin secretion in a glucose dependent manner.

In a hyperglycaemic clamp study in patients with type 2 diabetes, Mounjaro was compared to placebo and the selective GLP-1 receptor agonist semaglutide 1 mg for insulin secretion. Mounjaro 15 mg enhanced the first and second-phase insulin secretion rate by 466 % and 302 % from baseline, respectively. There was no change in first- and second-phase insulin secretion rate for placebo.[1]

Insulin sensitivity

Mounjaro improves insulin sensitivity.

Mounjaro 15 mg improved whole body insulin sensitivity by 63 %, as measured by M-value, a measure of glucose tissue uptake using hyperinsulinemic euglycaemic clamp. The M-value was unchanged for placebo.

Mounjaro lowers body weight in patients with type 2 diabetes and in patients who are overweight or have obesity, which may contribute to improvement in insulin sensitivity. Reduced food intake with Mounjaro contributes to body weight loss. The body weight reduction is mostly due to reduced fat mass.[1]

Glucagon concentration

Mounjaro reduced the fasting and postprandial glucagon concentrations in a glucose dependent manner.[1] Mounjaro 15 mg reduced fasting glucagon concentration by 28% and glucagon AUC after a mixed meal by 43%, compared with no change for placebo.[1]

Gastric emptying

Mounjaro delays gastric emptying which may slow post meal glucose absorption and can lead to a beneficial effect on postprandial glycaemia.[1] Mounjaro-induced delay in gastric emptying diminishes over time.[1]

Mounjaro Clinical Programme

Overview of the Clinical Programme

The safety and efficacy of Mounjaro for weight management (weight reduction and maintenance) in combination with a reduced calorie intake and increased physical activity were evaluated in two randomised double-blinded, placebo-controlled phase 3 studies in patients without diabetes mellitus (SURMOUNT-1) and with diabetes mellitus (SURMOUNT-2). A total of 3,477 patients (2,519 randomised to treatment with Mounjaro) were included in the trials.[1]

SURMOUNT-1 included a total of 2,539 patients (1,896 randomised to treatment with Mounjaro), while a total of 938 patients (623 randomised to treatment with Mounjaro) were included in SURMOUNT-2.[1]

All patients treated with Mounjaro started with 2.5 mg for 4 weeks. Then the dose of Mounjaro was increased by 2.5 mg every 4 weeks until they reached their assigned dose.[1]

In SURMOUNT-1 the dose of Mounjaro or matching placebo was escalated to 5 mg, 10 mg, or 15 mg subcutaneously once weekly during a 20-week period followed by the maintenance period. In SURMOUNT-2, the dose of Mounjaro or matching placebo was escalated to 10 mg or 15 mg subcutaneously once weekly during a 20-week period followed by the maintenance period.[1]

Treatment with Mounjaro demonstrated clinically meaningful, statistically significant and sustained weight reduction compared with placebo in overweight patients (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) with at least one weight-related comorbidity and in patients with obesity (BMI ≥ 30 kg/m^2). Furthermore, across the trials, a higher proportion of patients achieved ≥ 5%, ≥ 10%, ≥ 15% and ≥ 20% weight loss with Mounjaro compared with placebo. Treatment with Mounjaro also showed improvements in waist circumference, systolic blood pressure and lipid parameters compared to placebo.[1]

Table 2: Key clinical trials supporting the efficacy and safety profile of Mounjaro for weight management

Name	Study Duration	Comparator	Population Size	Primary Objectives
SURMOUNT 1	72 weeks	Placebo	N=2,539	Mounjaro 10 mg and 15 mg demonstrated superiority in mean percent change in body weight vs placebo at Week 72.[1,4] Mounjaro 10 mg and 15 mg demonstrated superiority for percentage of participants with ≥5% weight reduction vs placebo at Week 72.[1,4]
SURMOUNT 2	72 weeks	Placebo	N=938	Mounjaro 10 mg and 15 mg demonstrated superiority in mean percent change in body weight vs placebo at Week 72.[1,3] Mounjaro 10 mg and 15 mg demonstrated superiority for percentage of participants with ≥5% weight reduction vs placebo at Week 72.[1,3]

SURMOUNT-1

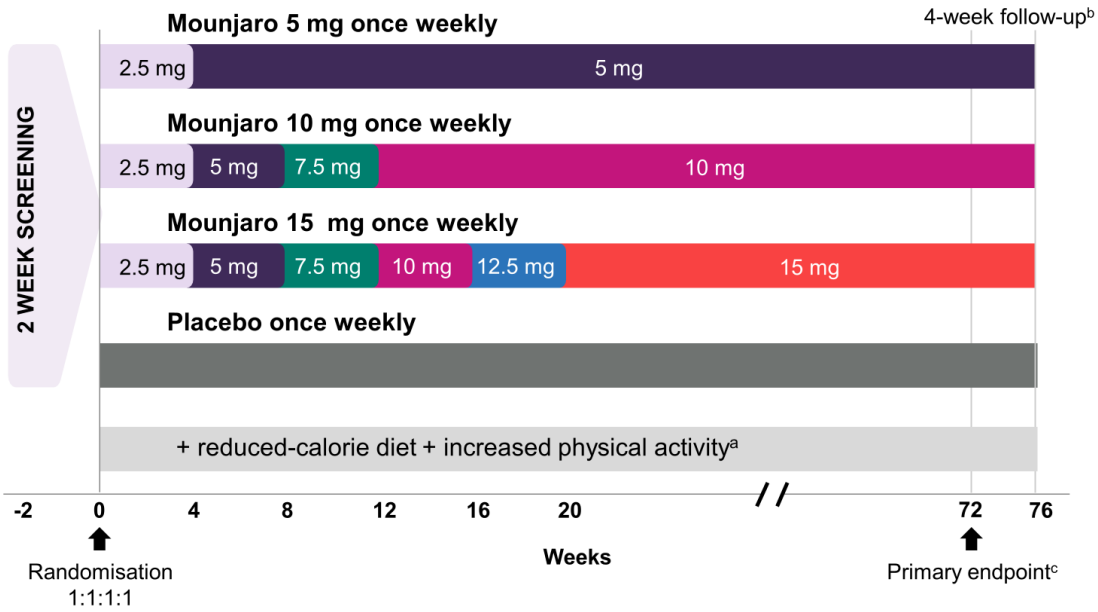
In a 72-week double blind placebo-controlled study, 2,539 adult patients with obesity (BMI ≥30 kg/m^2), or with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) and at least one weight-related comorbid condition, such as treated or untreated dyslipidaemia, hypertension, obstructive sleep apnoea, or cardiovascular disease, were randomised to Mounjaro 5 mg, 10 mg or 15 mg once weekly or placebo. Patients with type 2 diabetes mellitus were excluded. Patients had a mean age of 45 years and 67.5 % were women. At baseline 40.6 % of patients had prediabetes. Mean baseline body weight was 104.8 kg and mean BMI was 38 kg/m^2.[1] The study design is represented diagrammatically in Figure 3.

The co-primary objective was to establish whether Mounjaro 10 mg and/or 15 mg once weekly demonstrated superiority to placebo at Week 72 for:[4]

- Percentage change in body weight.
- Percentage of participants with ≥5% body weight reduction.

A key secondary objective was to establish whether Mounjaro 5 mg once weekly demonstrated superiority to placebo at Week 72 in the same parameters. Other key secondary objectives included whether Mounjaro 10 mg and 15 mg demonstrated superiority versus placebo at week 72 for body weight reduction percentages of ≥10% ≥15% and ≥20% and change in waist circumference, followed by mean change in body weight (kg) from baseline at week 20, SF-36v2 physical function scores at week 72, and cardiovascular and lipid parameter improvements (including systolic blood pressure, triglycerides, non-high-density lipoprotein (HDL) and HDL cholesterol) at week 72 in a pooled analysis.[4]

Figure 3: SURMOUNT-1 study design[4]



[a]Included counselling by a dietitian or qualified healthcare professional, a deficit of 500 calories per day, and at least 150 minutes of physical activity per week.
[b]No prediabetes at screening.
[d]End of treatment for participants without prediabetes at screening.

SURMOUNT-1 Trial Limitations[4]:

- The enrolled participants may represent a subpopulation with a greater commitment to weight-management efforts than the general population living with overweight/obesity
- The measured baseline cardiometabolic risk factors in the trial population, such as blood pressure and lipids, were relatively normal, possibly attenuating the potential to show improvement, though meaningful changes in these variables were observed
- Only 5.5% of trial participants with overweight (BMI of ≥27 to <30 kg/m^2) were included; further studies would be needed in such patients

Efficacy

Change in body weight

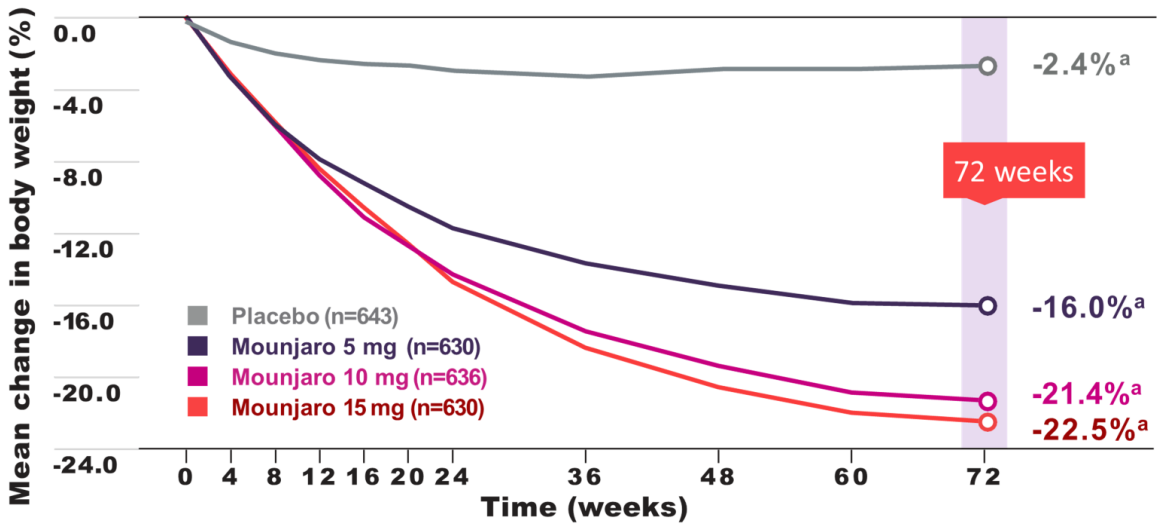
In SURMOUNT-1, Mounjaro 10 mg and 15 mg demonstrated superiority in mean percent change in body weight vs placebo at Week 72 ($p<0.001$ vs placebo, adjusted for multiplicity).[4] Mounjaro 5 mg also demonstrated superiority in mean percent change in body weight vs placebo at Week 72 ($p<0.001$ vs placebo, adjusted for multiplicity), measured as a key secondary objective.[4]

Mean weight reduction at 72 weeks was 21.4% in the 10 mg group and 22.5% in the 15 mg group compared to 2.4% with placebo.

Mean weight reduction was 16.0% in the 5 mg group compared to 2.4% with placebo.[4] The results can be seen in Figure 4.

Figure 4: Change from baseline in body weight at 72 weeks in SURMOUNT-1[4]

Difference from placebo in change in body weight, % (95% confidence interval [CI]) at Week 72[1]	Mounjaro 5 mg	Mounjaro 10 mg	Mounjaro 15 mg
	-13.5 (-14.6 to -12.5)[b]	-18.9 (-20.0 to -17.8)[b]	-20.1 (-21.2 to -19.0)[b]



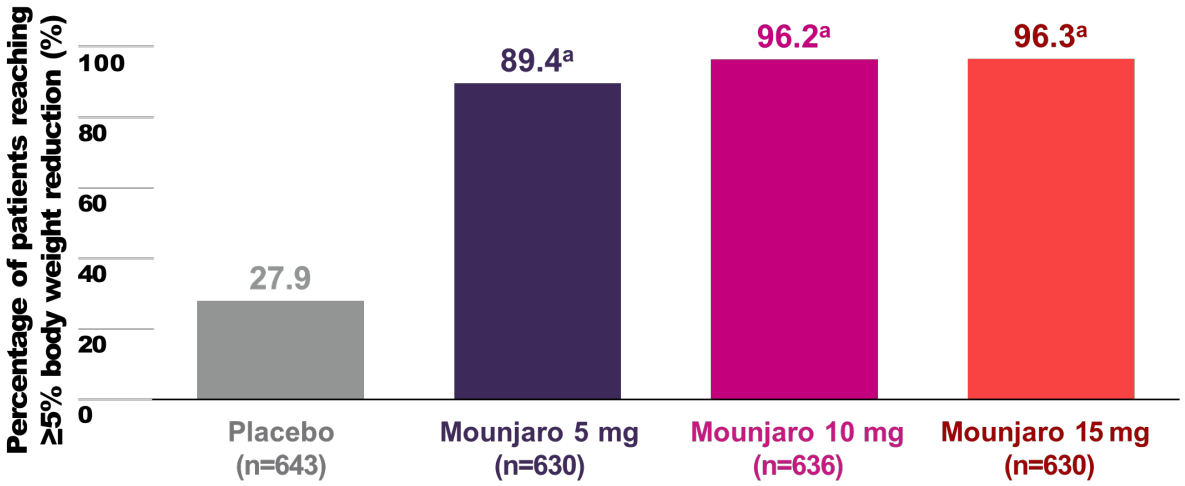
Mean baseline body weight: 104.8 kg[4]

[a]p<0.001 vs placebo vs baseline [b]p<0.001 vs placebo, adjusted for multiplicity. [1]
Efficacy estimand, mixed model for repeated measures (MMRM) analysis, mITT population (efficacy analysis set). Data are least squares means [4]
All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity

Mounjaro 10 mg and 15 mg demonstrated superiority for percentage of participants with ≥5% weight reduction vs placebo at week 72 (p<0.001 vs placebo, adjusted for multiplicity).[4] The percentage of participants who achieved a body weight reduction of ≥5% at week 72 was 96.2% in the 10 mg group and 96.3% in the 15 mg group, compared to 27.9% of participants in the placebo group.[1,4]

Mounjaro 5 mg also demonstrated superiority for percentage of participants with ≥5% weight reduction vs placebo at Week 72 (p<0.001 vs placebo, adjusted for multiplicity).[1,4] The percentage of participants who achieved a body weight reduction of ≥5% at week 72 was 89.4% in the 5 mg group compared to 27.9% of participants in the placebo group.[4,1] The results can be seen in Figure 5.

Figure 5: Percentage of patients who achieved clinically meaningful weight loss of ≥5% from baseline at Week 72 in SURMOUNT-1[1]

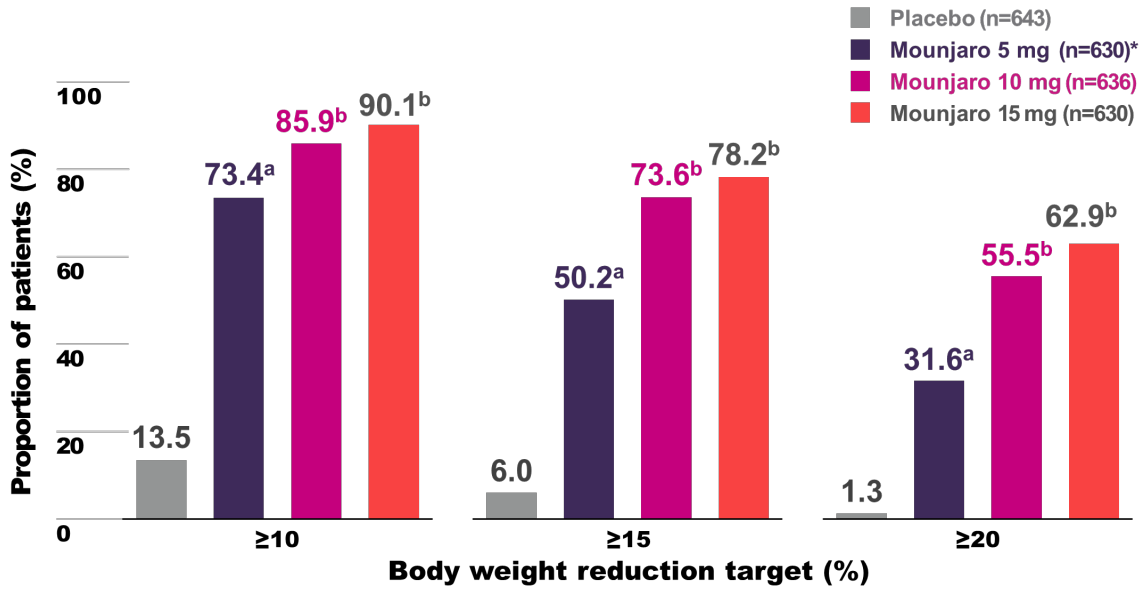


Mean baseline body weight: 104.8 kg[4]

[a]p<0.001 vs placebo, adjusted for multiplicity. [1]
Efficacy estimand, logistic regression analysis, mITT population (efficacy analysis set).
All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity[4]

Mounjaro 10 mg and 15 mg demonstrated superior and clinically meaningful body weight reduction of ≥10%, ≥15%, and ≥20% vs placebo at Week 72 (p<0.001 vs placebo, adjusted for multiplicity).[4,1] The results can be seen in Figure 6 (key secondary objective).

Figure 6: Percentage of patients achieving weight reduction of ≥10%, ≥15%, and ≥20% at Week 72 in SURMOUNT-1[1,4]



Mean baseline body weight: 104.8 kg[4]

[a]p<0.001 vs placebo, not adjusted for multiplicity. [b]p<0.001 vs placebo, adjusted for multiplicity. [1]
Efficacy estimand, logistic regression analysis, mITT population (efficacy analysis set).
All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity. [4]
*The specified weight-reduction targets in the Mounjaro 5 mg group were not key secondary end points and were analysed as additional secondary end points. Hypothesis testing was not conducted; confidence intervals were not adjusted for multiplicity, and no definite conclusions can be drawn.[4]

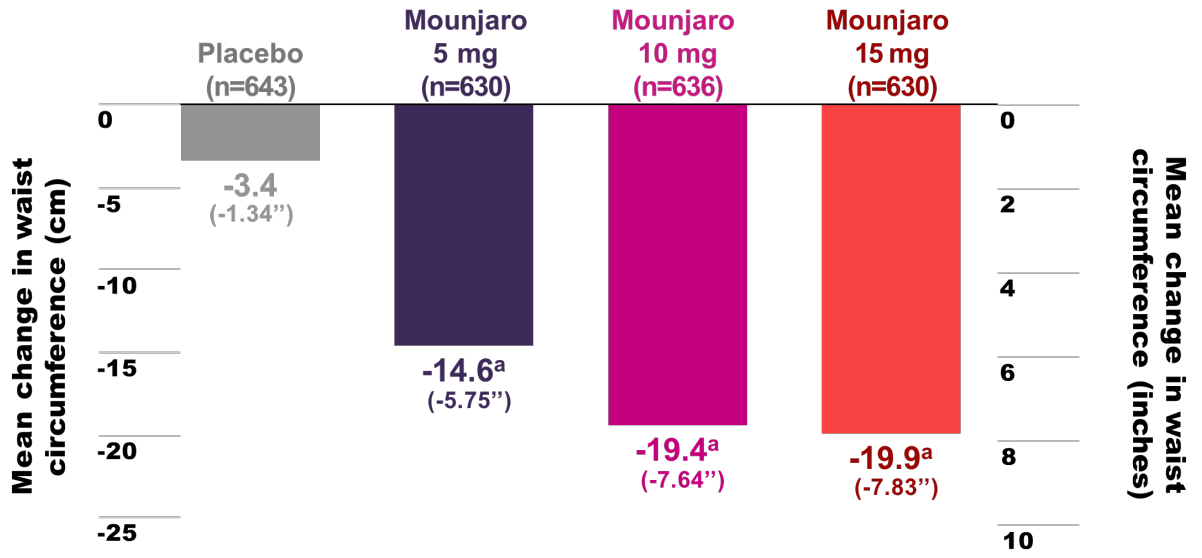
Change in waist circumference

Mounjaro 10 mg and 15 mg demonstrated superiority for waist circumference vs placebo at Week 72 ($p<0.001$ vs baseline).[4,1]

Participants achieved 19.4 and 19.9 cm (7.64 and 7.83”) waist circumference reduction from baseline with Mounjaro 10 mg and 15 mg at Week 72, compared with 3.4 cm (1.34”) reduction with placebo.[1] The results can be seen in Figure 7 (key secondary objective).

Figure 7: Mean change in waist circumference from baseline with Mounjaro 10 mg and 15 mg at Week 72 in SURMOUNT-1.[1,4]

Difference from placebo in change in waist circumference, % (95% CI)[1]	Mounjaro 5 mg	Mounjaro 10 mg	Mounjaro 15 mg
	-11.2 (-12.3 to -10.0)[b]	-16.0 (-17.2 to -14.9)[c]	-16.5 (-17.7 to -15.4)[c]



Mean baseline waist circumference: 114.1 cm (44.9”)[4]

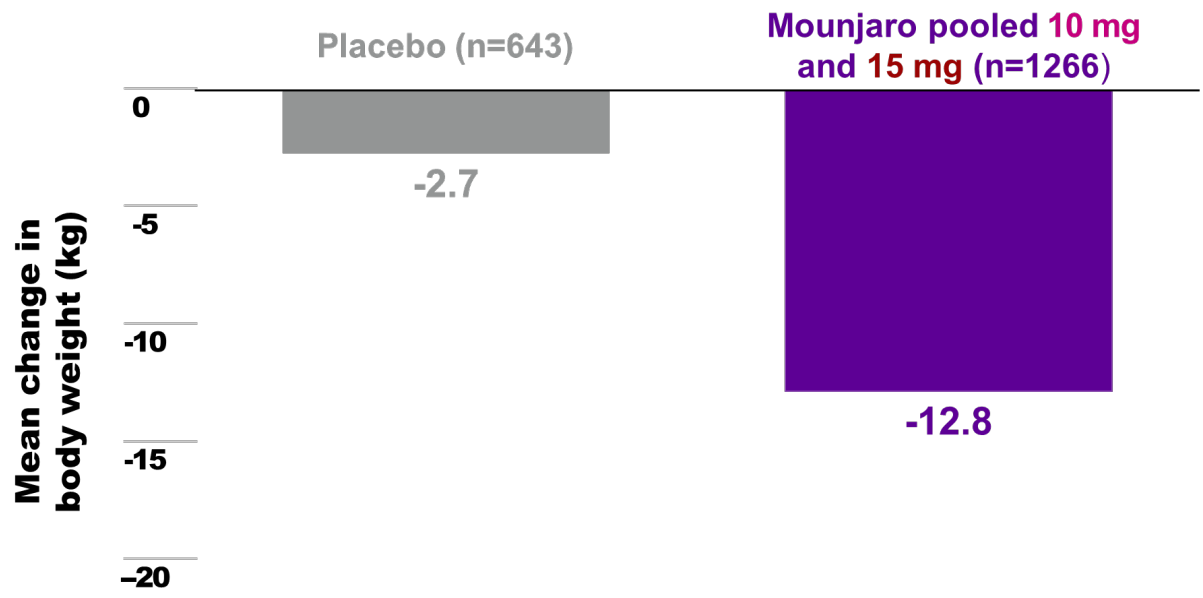
[a]$p<0.001$ vs baseline [b]$p<0.001$ vs placebo, not adjusted for multiplicity [c]$p<0.001$ vs placebo, adjusted for multiplicity[1]
Efficacy estimand, MMRM analysis, mITT population (efficacy analysis set). Data are least squares means.
All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity.[1,4]

Early weight reduction (change from baseline at Week 20)

Pooled Mounjaro (10 mg and 15 mg) demonstrated superiority for body weight vs placebo at Week 20 (p<0.001 vs placebo, adjusted for multiplicity)[4], measured by the treatment regimen estimand, as shown in Figure 8 (key secondary objective).

Figure 8: Early weight reduction (change from baseline at Week 20) in SURMOUNT-1.[4]

Difference from placebo in mean change in body weight at Week 20, kg (95% CI)[4]	Mounjaro pooled 10 mg and 15 mg
	-10.1 (-10.7 to -9.6)[a]



Mean baseline body weight: 104.8 kg[4]

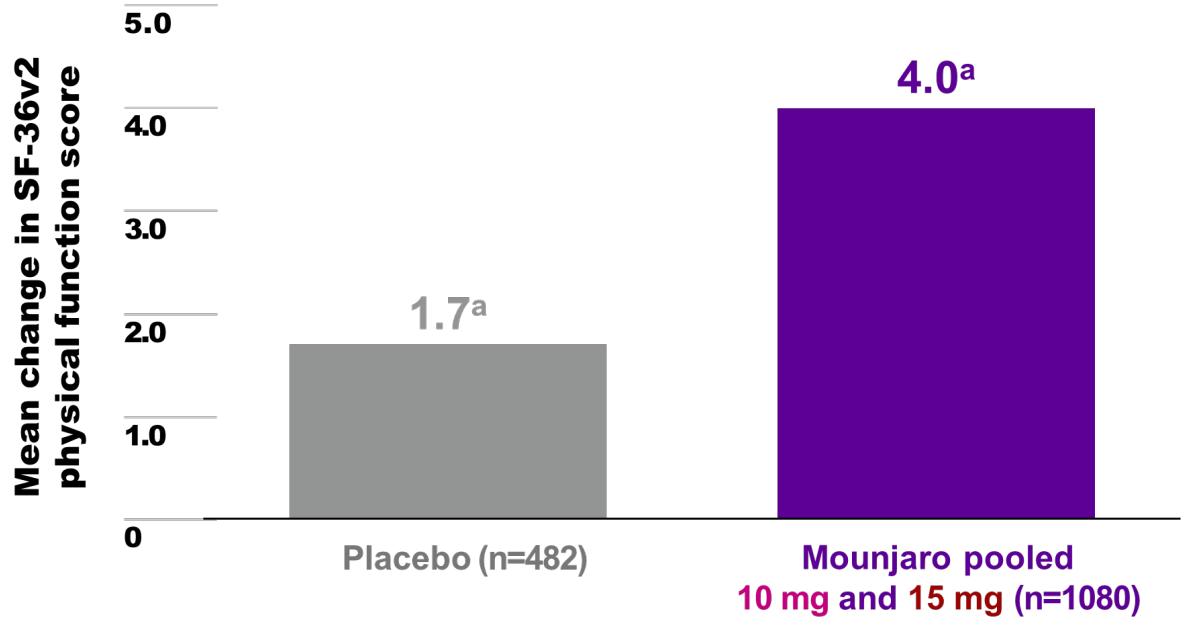
[a]p<0.001 vs placebo, adjusted for multiplicity[4]
Analysis of covariance (ANCOVA) analysis, mITT population, (full analysis set). Data are least squares means.
All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity[4]
CI=confidence interval; mITT=modified intent-to-treat.

Mean change from baseline in SF-36v2 physical function score

Pooled Mounjaro (10 mg and 15 mg) demonstrated superiority for SF-36v2 physical function score vs placebo at Week 72 ($p<0.001$ vs placebo, adjusted for multiplicity)[1,4], shown in Figure 9 (key secondary objective).

Figure 9: Mean change from baseline in SF-36v2 physical function score at week 72 in SURMOUNT-1.[4]

Difference from placebo in SF-36v2 physical function score at Week 72, score (95% CI)[1]	Mounjaro pooled 10 mg and 15 mg
	2.3 (1.6 to 2.9)[b]



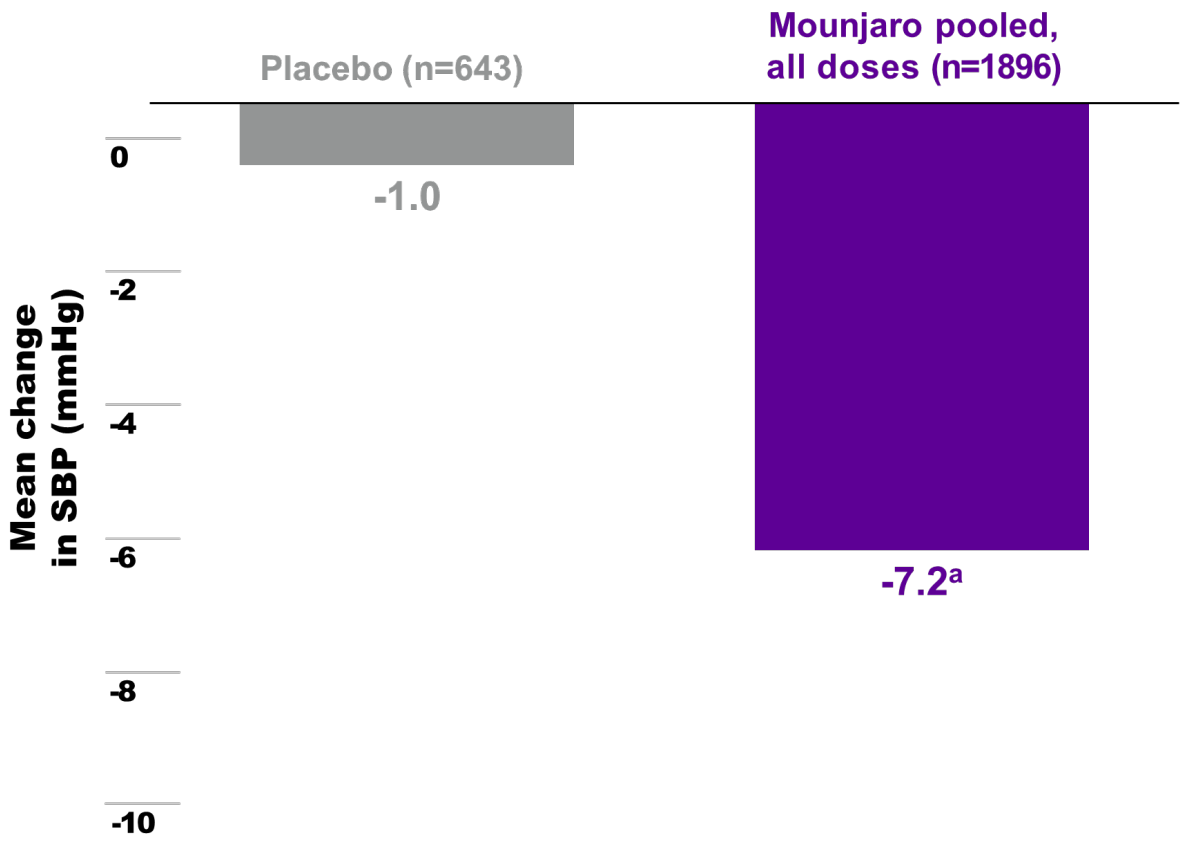
Mean baseline SF-36v2 physical function score[4]
- **Placebo: 49.7**
- **Pooled Mounjaro: 49.6**

[a]$p<0.001$ vs baseline, [b]$p<0.001$ vs placebo, adjusted for multiplicity[1]
Efficacy estimand, MMRM analysis, mITT population (efficacy analysis set). Data are least squares means
All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity.[1,4]
CI=confidence interval; mITT=modified intent-to-treat; MMRM=mixed model for repeated measures; SF-36v2=short-form-36 health survey version 2

Mean change from baseline in systolic blood pressure

Pooled Mounjaro (all doses) had a mean 7.2 mmHg reduction in systolic blood pressure from baseline, compared with a mean 1.0 mmHg reduction in the placebo group at Week 72 ($p<0.001$ vs placebo, adjusted for multiplicity)[4], measured by the treatment regimen estimand, as shown in Figure 10 (key secondary objective)

Figure 10: Mean change from baseline in systolic blood pressure at week 72 in SURMOUNT-1.[4]



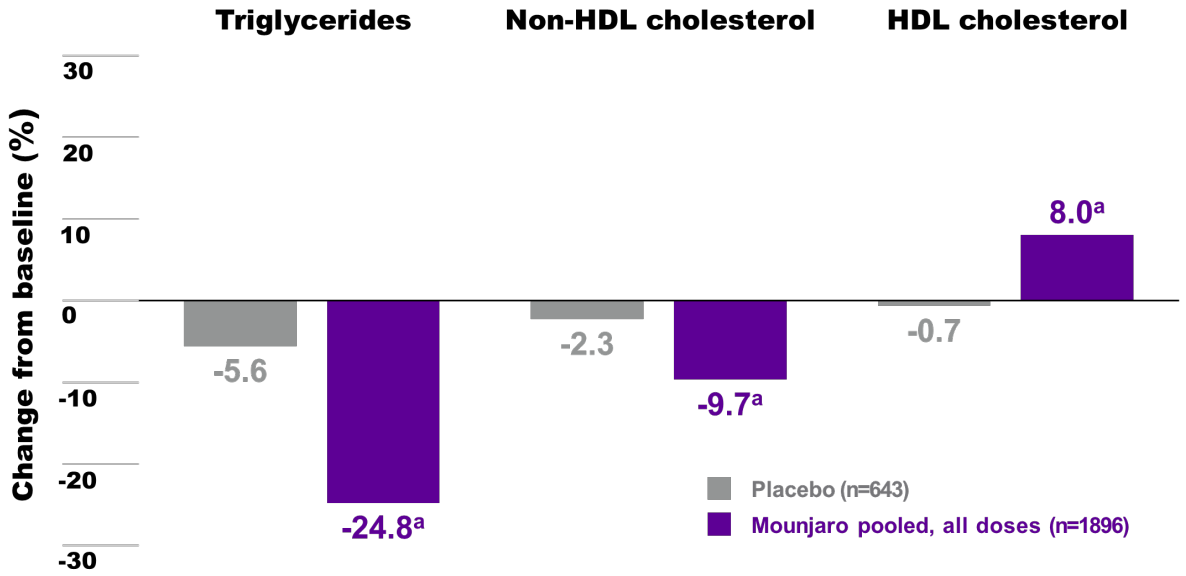
Mean baseline systolic blood pressure: 123.3 mmHg[4]

[a]$p<0.001$ vs placebo, adjusted for multiplicity[4]
All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity.[4]
mITT=modified intent-to-treat; SBP=systolic blood pressure.

Mean change from baseline in triglycerides, HDL cholesterol and non-HDL cholesterol

Pooled Mounjaro (all doses) demonstrated larger reductions in triglycerides and in non-HDL cholesterol from baseline vs placebo, and an increase in HDL cholesterol from baseline vs placebo at Week 72 ($p<0.001$ vs placebo, adjusted for multiplicity)[4], measured by the treatment regimen estimand, as shown in Figure 11 (key secondary objective)

Figure 11: Mean change from baseline in triglycerides at week 72 in SURMOUNT-1.[4]



Mean baseline triglycerides: 128.4 mg/dL[4]
Mean baseline non-HDL: 138.0 mg/dL[4]
Mean baseline HDL cholesterol: 47.3 mg/dL[4]

[a]$p<0.001$ vs placebo, adjusted for multiplicity[4]
ANCOVA analysis, mITT population (full analysis set). Lipid levels were analysed with the use of log transformation.[4]

All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity. [4]
ANCOVA=analysis of covariance; HDL=high-density lipoprotein; mITT=modified intent-to-treat.

Safety

Common adverse events

In SURMOUNT-1, the most common adverse events were gastrointestinal in nature, mostly mild or moderate in severity, and occurred during the dose-escalation period.[4]

Severe adverse events

Serious adverse events were reported in 6.3% of participants overall, with similar percentages in the Mounjaro and placebo groups.[4]

Treatment discontinuation rates

Treatment discontinuation rates due to adverse events were 4.3% in the 5 mg group, 7.1% in the 10 mg group, 6.2% in the 15 mg group, and 2.6% in the placebo group.[4]

The selected safety information for SURMOUNT-1 can be seen in Table 3.

Table 3: SURMOUNT-1 selected safety information[4]

Adverse events in SURMOUNT-1[1]				
PERCENTAGE OF PATIENTS	**Placebo (n=643)**	**Mounjaro 5 mg (n=630)**	**Mounjaro 10 mg (n=636)**	**Mounjaro 15 mg (n=630)**
Patients with ≥1 treatment-emergent adverse event (TEAE)	72.0%	81.0%	81.8%	78.9%
Serious adverse events	6.8%	6.3%	6.9%	5.1%
Death[a]	0.6%	0.6%	0.3%	0.2%
Adverse events leading to discontinuation[b]	2.6%	4.3%	7.1%	6.2%
TEAEs occurring in ≥5% of patients in any treatment group[b]				
Nausea	9.5%	24.6%	33.3%	31.0%
Diarrhoea	7.3%	18.7%	21.2%	23.0%
Coronavirus disease 2019 (COVID-19)	14.0%	14.9%	15.4%	13.0%
Constipation	5.8%	16.8%	17.1%	11.7%
Dyspepsia	4.2%	8.9%	9.7%	11.3%
Vomiting	1.7%	8.3%	10.7%	12.2%
Decreased appetite	3.3%	9.4%	11.5%	8.6%
Headache	6.5%	6.5%	6.8%	6.5%
Abdominal pain	3.3%	4.9%	5.3%	4.9%
Alopecia	0.9%	5.1%	4.9%	5.7%
Dizziness	2.3%	4.1%	5.5%	4.1%
Eructation	0.6%	3.8%	5.2%	5.6%
Injection-site reaction[c]	0.3%	2.9%	5.7%	4.6%

Adverse events of special interest occurring in ≥1% of patients in any treatment group[1]				
PERCENTAGE OF PATIENTS	**Placebo (n=643)**	**Mounjaro 5 mg (n=630)**	**Mounjaro 10 mg (n=636)**	**Mounjaro 15 mg (n=630)**
Cancer	1.1%	1.4%	0.5%	0.8%
GI events[d]	1.1%	1.7%	3.1%	3.3%
Gallbladder disease[d]	0.8%	0.8%	1.7%	1.0%
Hypoglycaemia[e]	0.2%	1.4%	1.6%	1.6%

[a]All deaths were adjudicated by an external committee of physicians, who determined whether the death was CV-related.
[b]Adverse events are listed according to Medical Dictionary for Regulatory Activities, version 24.1, preferred terms.
[c]None of the events were reported as severe or serious.
[d]Events were classified as severe or serious adverse events.
[e]Hypoglycaemia defined as blood glucose 3.0 mmol/L (<54 mg/dL).

SURMOUNT-2

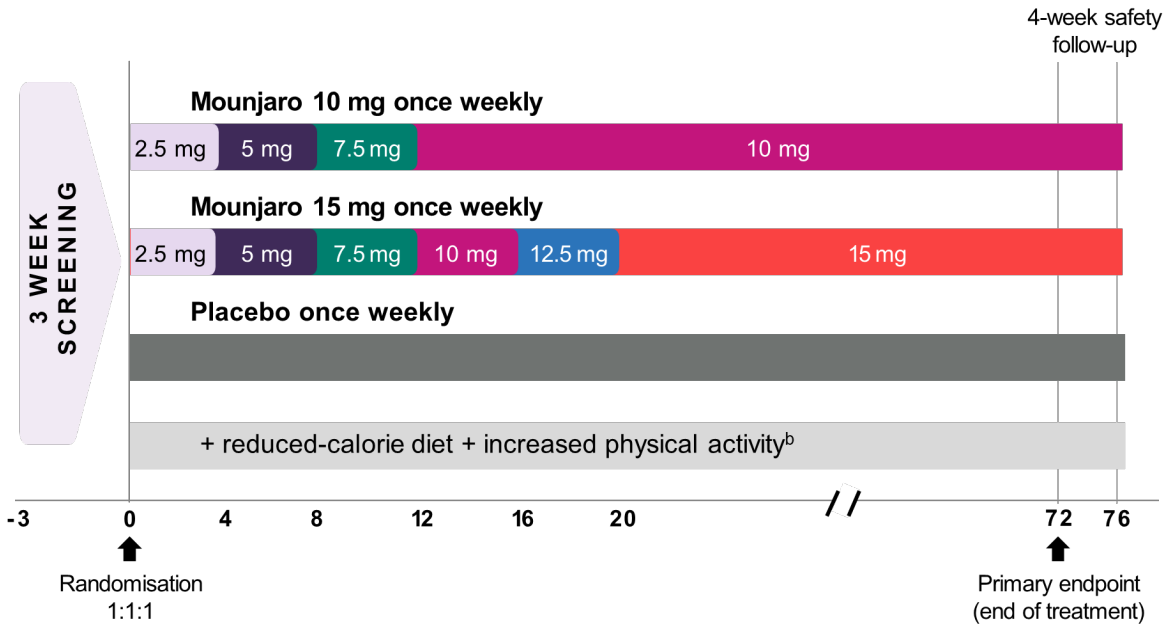
In a 72-week double blind placebo-controlled study, 938 adult patients with BMI ≥27 kg/m^2 and type 2 diabetes mellitus, were randomised to Mounjaro 10 mg or 15 mg once weekly or placebo. Patients had a mean age of 54 years and 50.7% were women. Mean baseline body weight was 100.7 kg and mean BMI was 36.1 kg/m^2.[1,3] The study design is represented in Figure 12.

The co-primary objective was to establish whether Mounjaro 10 mg and/or 15 mg once weekly (dose analysis) demonstrated superiority to placebo at Week 72 for:[3]

- Percent change in body weight.
- Percentage of participants with ≥5% body weight reduction.

Other key secondary objectives included whether Mounjaro 10 mg and 15 mg demonstrated superiority versus placebo at week 72 for body weight reduction, change in waist circumference and glycaemic control, followed by cardiovascular parameters (systolic blood pressure) and lipid parameter (triglycerides, non-HDL cholesterol, and HDL cholesterol) improvements in a pooled analysis.[3]

Figure 12: SURMOUNT-2 study design[3]



[a]Along with minimum 1 self-reported unsuccessful dietary effort for weight reduction.
[b]Included regular lifestyle counselling by a dietitian or qualified healthcare professional. The counselling sessions were focused on healthy, balanced meals with a recommended caloric deficit of 500 calories per day relative to the estimated total daily energy expenditure and at least 150 min per week of physical activity.

SURMOUNT-2 Trial Limitations[3]:

- The efficacy of Mounjaro 5 mg, an licensed dose for the treatment of type 2 diabetes, was not evaluated
- Over a third of screened individuals were not enrolled into the study; most (56%) did not meet diabetes-related entry criteria

- Gastrointestinal adverse events were self-reported, and although this is standard practice in most clinical trials, it could contribute to reporting bias. A “nocebo” effect related to participant expectations of adverse gastrointestinal effects could not be ruled out
- People treated with insulin were excluded; however, Mounjaro has been evaluated in patients with type 2 diabetes treated with insulin in the SURPASS clinical trials

Efficacy

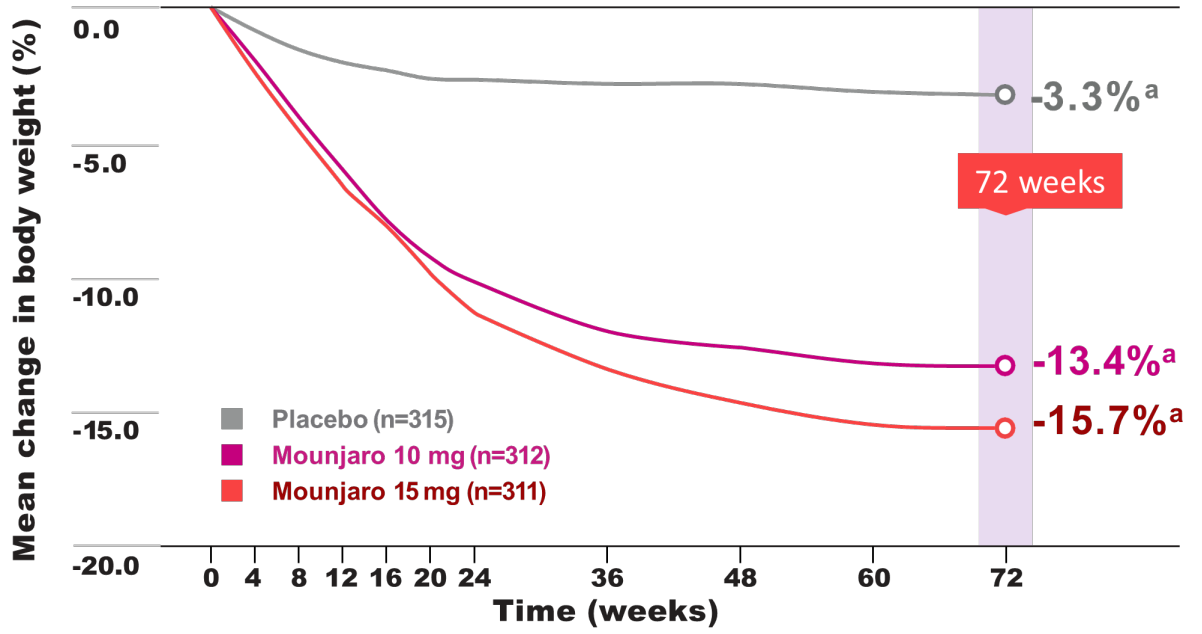
Change in body weight

In SURMOUNT-2, Mounjaro 10 mg and 15 mg demonstrated superiority in mean percent change in body weight vs placebo at Week 72 (p<0.001 vs placebo, adjusted for multiplicity).[3]

Mean change in bodyweight at 72 weeks was -13.4% in the 10 mg group and -15.7% in the 15 mg group compared to -3.2% with placebo.[1,3] The results can be seen in Figure 13.

Figure 13: Change from baseline in body weight at 72 weeks in SURMOUNT-2[1,3]

Difference from placebo in change in body weight, % (95% CI) at Week 72[1]	Mounjaro 10 mg	Mounjaro 15 mg
	-10.1 (-11.5 to -8.8)[b]	-12.4 (-13.7 to -11.0)[b]

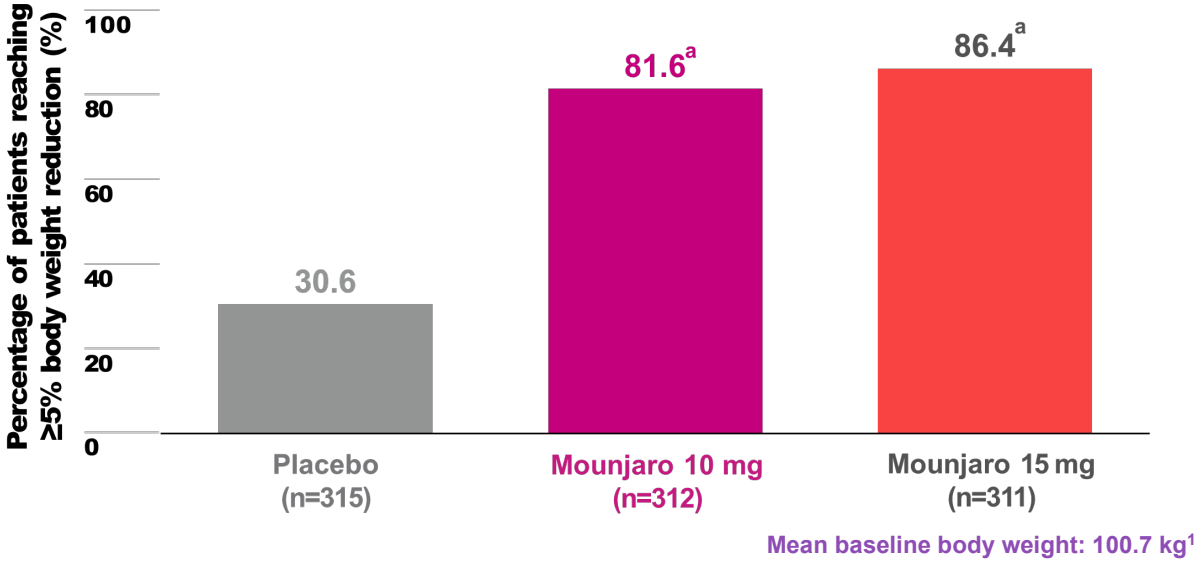


Mean baseline body weight: 100.7 kg[1]

[a]p<0.001 vs baseline.[1] [b]p<0.001 vs placebo, adjusted for multiplicity.[1]
Efficacy estimand, MMRM analysis, mITT population (efficacy analysis set). Data are least squares means. All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity. [3]

Mounjaro 10 mg and 15 mg demonstrated superiority for percentage of participants with ≥5% weight reduction vs placebo at Week 72 (p<0.001 vs placebo, adjusted for multiplicity).[1,3] The percentage of patients who achieved clinically meaningful ≥5% weight reduction from baseline at Week 72 was 81.6% with Mounjaro 10 mg and 86.4% with Mounjaro 15 mg compared to 30.6% of patients on placebo.[1] The results can be seen in Figure 14.

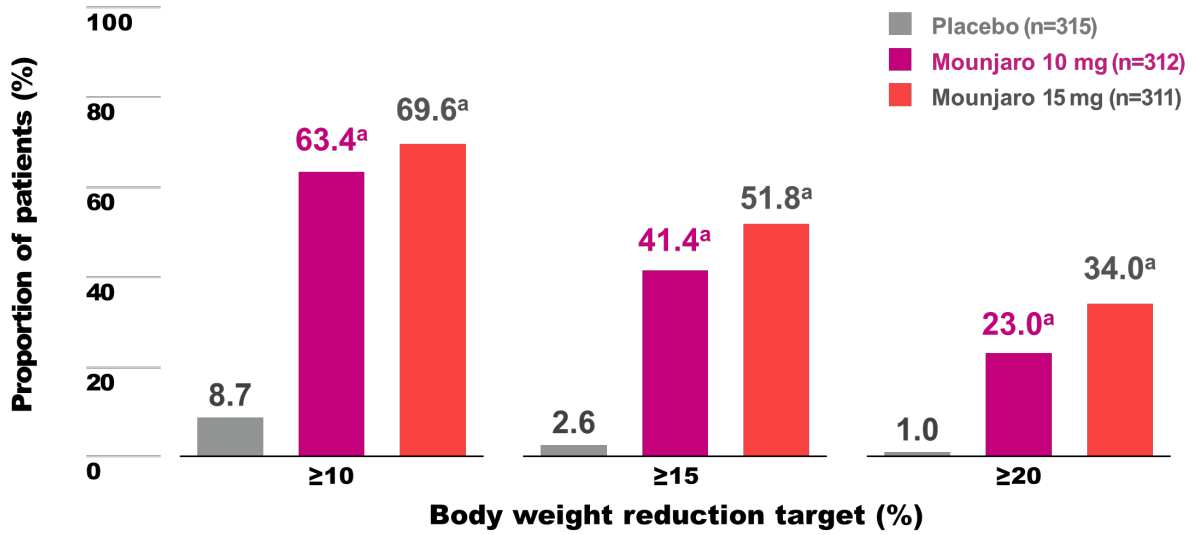
Figure 14: Percentage of patients achieving body weight reduction target of ≥5% at 72 weeks in SURMOUNT-2[1,3]



[a]p<0.001 vs placebo, adjusted for multiplicity.[1]
Efficacy estimand, logistic regression analysis, mITT population (efficacy analysis set). Data are least squares means. All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity. [3]

Furthermore, Mounjaro 10 mg and 15 mg demonstrated superior and clinically meaningful weight reduction of ≥10%, ≥15%, and ≥20% from baseline at Week 72 vs placebo ($p<0.001$ vs placebo, adjusted for multiplicity).[1,3] The results can be seen in Figure 15 (key secondary objective).

Figure 15: Percentage of achieving weight reduction of ≥10%, ≥15%, and ≥20% at Week 72 in SURMOUNT-2[1]



Mean baseline body weight: 100.7 kg[1]

[a]$p<0.001$ vs placebo, adjusted for multiplicity.[1]
Efficacy estimand, logistic regression analysis, mITT population (efficacy analysis set). Data are least squares means. All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity.[3]

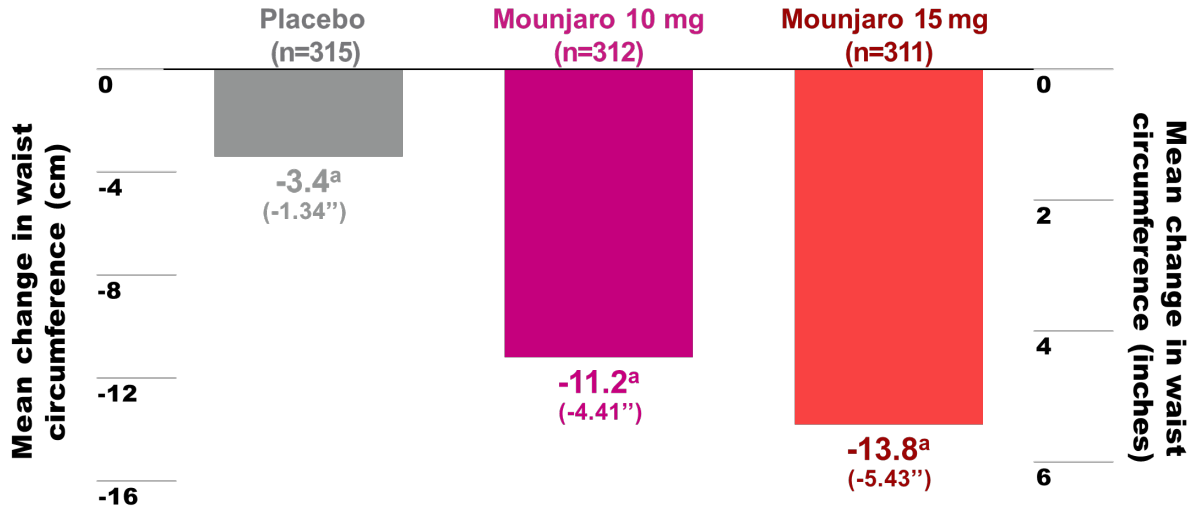
Change in waist circumference

Mounjaro 10 mg and 15 mg demonstrated superiority for change in waist circumference vs placebo at Week 72 ($p<0.001$ vs placebo, adjusted for multiplicity)[1,3]

Participants achieved a waist circumference reduction from baseline of 11.2 cm (4.41”) with Mounjaro 10 mg and 13.8 cm (5.43”) with Mounjaro 15 mg, compared to 3.4 cm (1.34”) reduction with placebo at week 72.[1,3] The results can be seen in Figure 16 (key secondary endpoint).

Figure 16: Change in waist circumference from baseline to week 72 in SURMOUNT-2[1]

Difference from placebo in change in waist circumference, cm (95% CI)[1]	Mounjaro 10 mg	Mounjaro 15 mg
	-7.8[b] (-9.2 to -6.4)	-10.4[b] (-11.8 to -8.9)



Mean baseline waist circumference, cm (inches): 114.9 (45.2)[3]

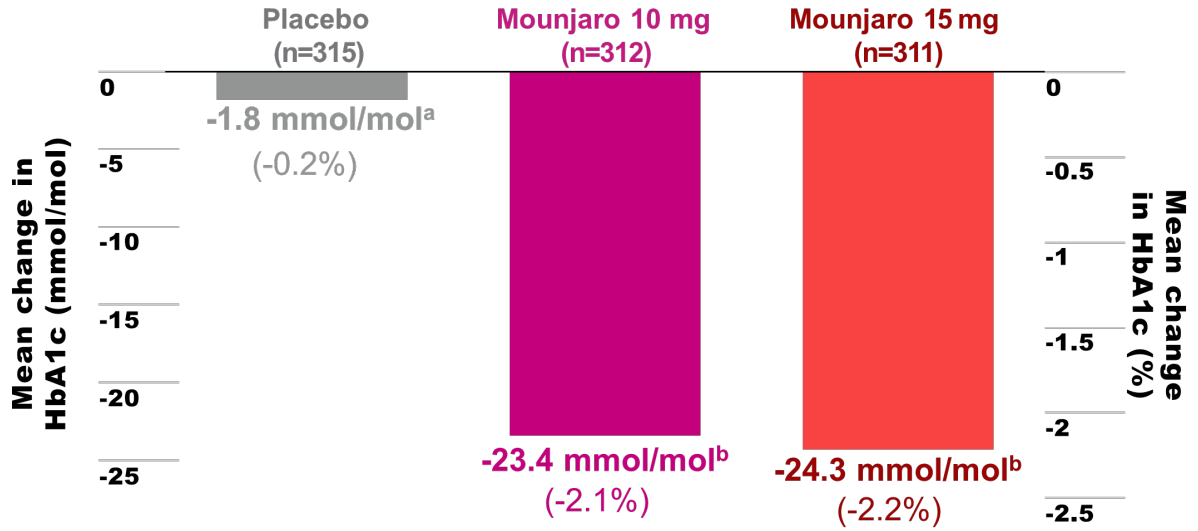
[a]$p< 0.001$ vs baseline.[1] [b]$p< 0.001$ vs placebo, adjusted for multiplicity.[1]
Efficacy estimand, MMRM analysis, mITT population (efficacy analysis set). Data are least squares means. All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity. [3]

Mean change from baseline in glycaemic control

Mounjaro 10 mg and 15 mg significantly improved glycaemic control from baseline at Week 72 vs placebo (p<0.001 vs placebo, adjusted for multiplicity)[1,3], as shown in Figure 17 (key secondary objective)

Figure 17: Mean change from baseline in glycaemic control at week 72 in SURMOUNT-2.[3]

Difference from placebo in HbA1c (%) (95% CI)[3]	Mounjaro 10 mg	Mounjaro 15 mg
	-2.0[c] (-2.2 to -1.8)	-2.1[c] (-2.2 to -1.9)



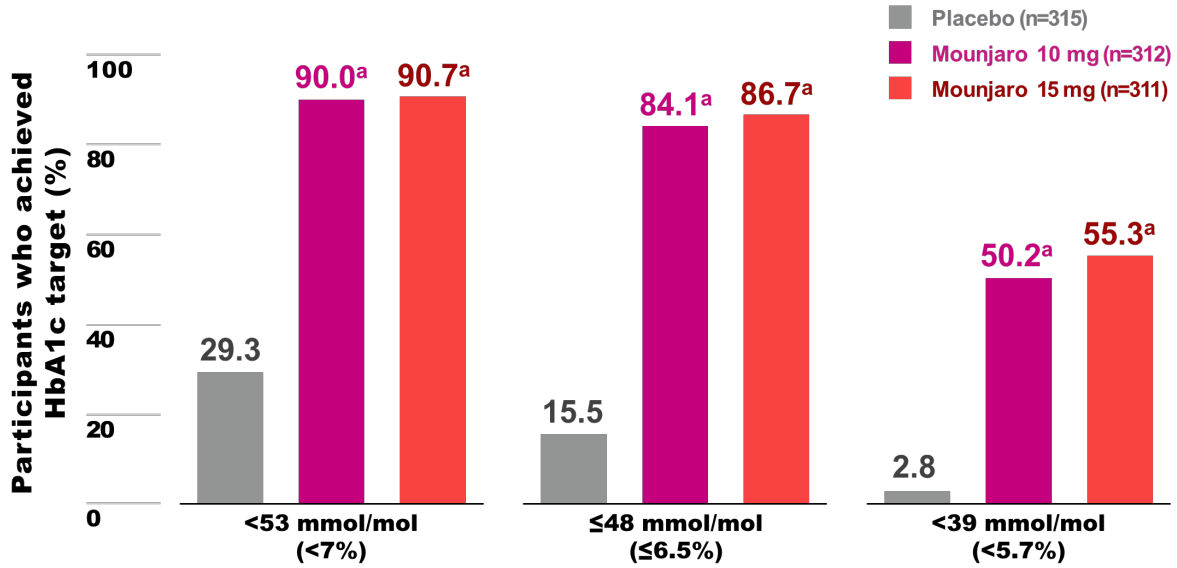
Mean baseline HbA1c: 64.1 mmol/mol (8.02%)[3]

[a]p<0.05 vs baseline, [b]p<0.001 vs baseline, [c]p<0.0001 vs placebo, adjusted for multiplicity.
Efficacy estimand, MMRM analysis, mITT population (efficacy analysis set). Data are least squares means.
All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity.
CI=confidence interval; HbA1c=glycated haemoglobin; mITT=modified intent-to-treat; MMRM=mixed model for repeated measures.

HbA1c treatment goal achievement

90.0-90.7% of patients on Mounjaro 10 mg and 15 mg achieved the HbA1c treatment goal of <53 mmol/mol (<7%) at Week 72, compared with 29.3% in the placebo group, as shown in Figure 18 (key secondary objective)[1,3]

Figure 18: HbA1c treatment goal achievement week 72 in SURMOUNT-2.[3]



Mean baseline HbA1c: 64.1 mmol/mol (8.02%)[3]

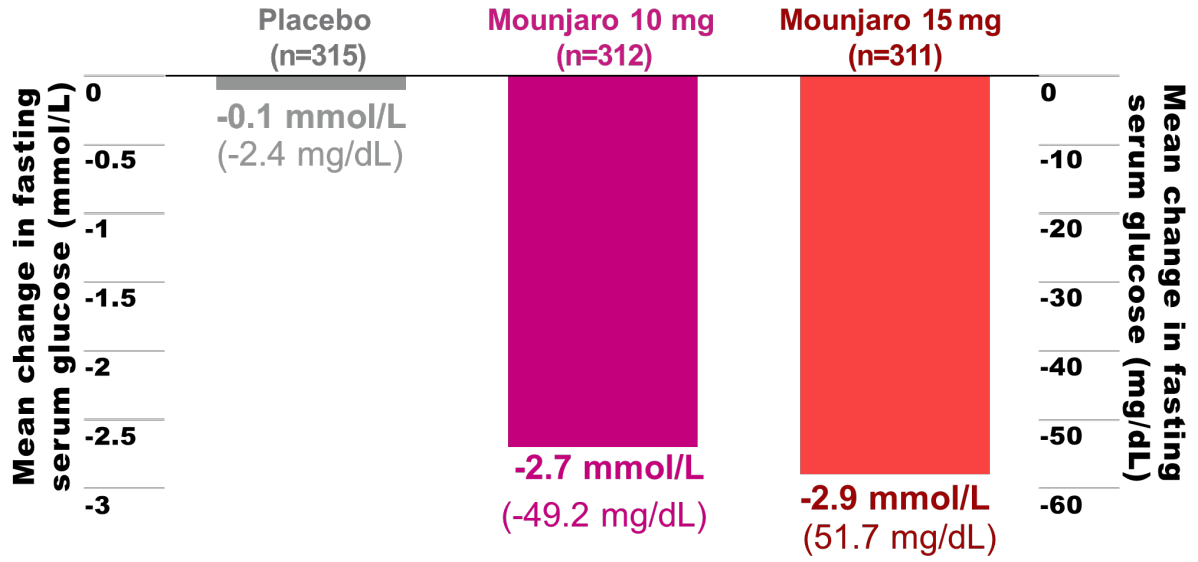
[a]p<0.0001 vs placebo, adjusted for multiplicity. [1]
Efficacy estimand, logistic regression analysis. mITT population (efficacy analysis set).
All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity. [3]
HbA1c=glycated haemoglobin; mITT=modified intent-to-treat.

Mean change from baseline in fasting serum glucose

Mounjaro 10 mg and 15 mg significantly improved fasting serum glucose at Week 72 vs placebo (p<0.0001 vs placebo, adjusted for multiplicity)[1,3], as shown in Figure 19 (key secondary objective)

Figure 19: Mean change from baseline in fasting serum glucose at week 72 in SURMOUNT-2.[3]

Difference from placebo in fasting serum glucose (mg/dL) (95% CI)[3]	Mounjaro 10 mg	Mounjaro 15mg
	-46.8[a] (-52.7 to -40.9)	-49.3[a] (-55.2 to -43.3)



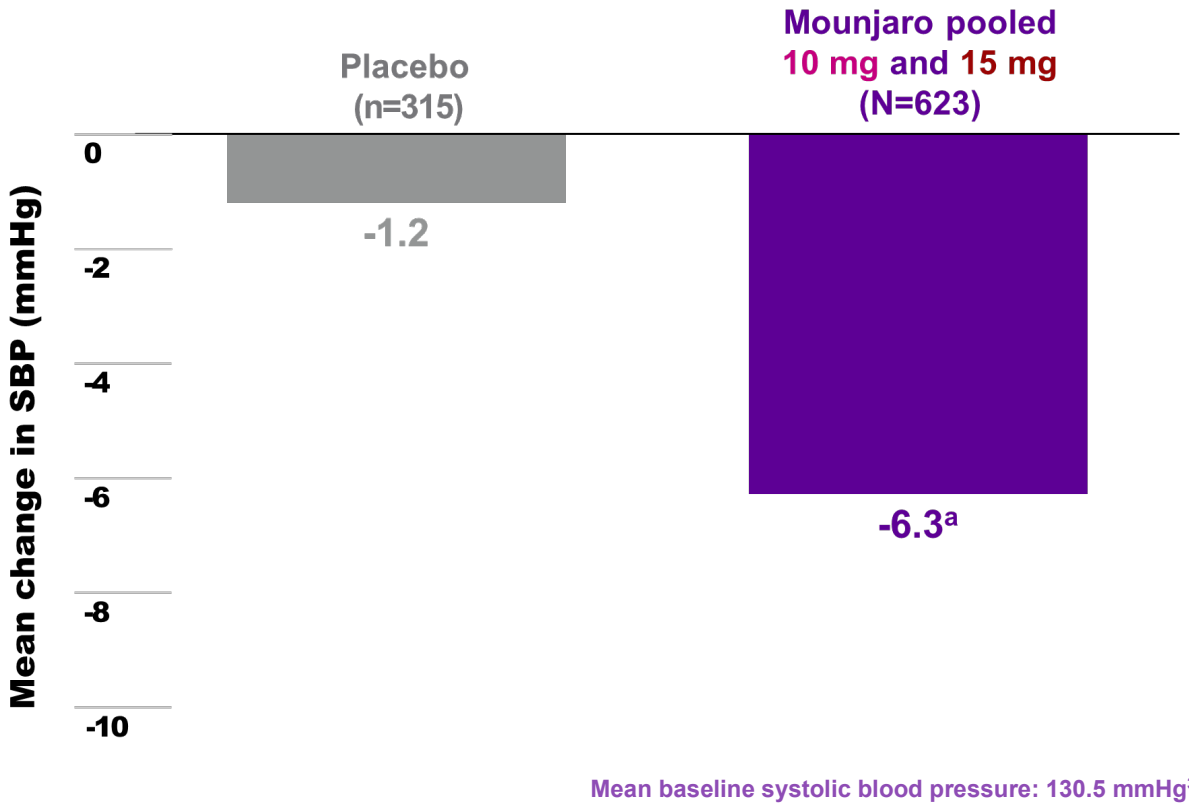
Mean baseline fasting serum glucose: 8.8 mmol/L (159.3 mg/dL)1[3]

[a]p<0.0001 vs placebo, adjusted for multiplicity. [3]
Efficacy estimand, MMRM analysis. mITT population (efficacy analysis set). Data are least squares means.
All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity. [3]
CI=confidence interval; mITT=modified intent-to-treat; MMRM=mixed model for repeated measures.

Mean change from baseline in systolic blood pressure

Mounjaro (pooled 10 mg and 15 mg) demonstrated a 6.3 mmHg mean reduction in systolic blood pressure from baseline, vs a 1.2 mmHg reduction with placebo at week 72 ($p<0.0001$ vs placebo, adjusted for multiplicity)[3], measured by the treatment regimen estimand, as shown in Figure 20 (key secondary objective)

Figure 20: Mean change from baseline in systolic blood pressure at week 72 in SURMOUNT-2.[3]

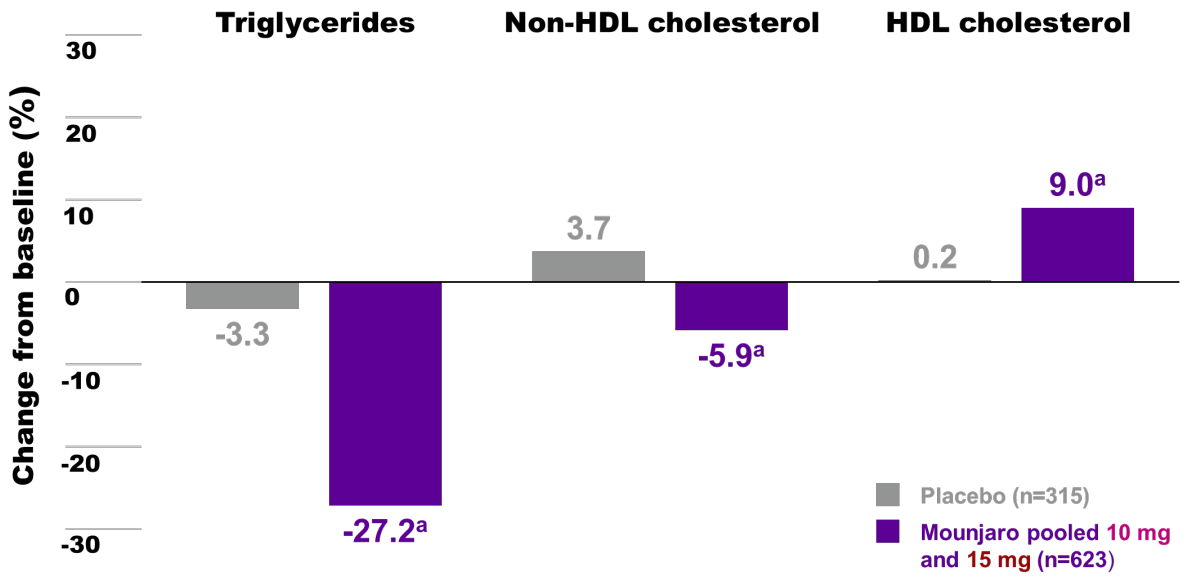


[a]$p<0.0001$ vs placebo, adjusted for multiplicity. [3]
ANCOVA analysis. mITT population (full analysis set). Data are estimated means.
All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity. [3]
mITT=modified intent-to-treat; MMRM=mixed model for repeated measures;

Mean change from baseline in triglycerides, HDL cholesterol and non-HDL cholesterol

Mounjaro (pooled 10 mg and 15 mg) demonstrated larger reductions in triglycerides and in non-HDL cholesterol, and a larger increase in HDL cholesterol vs placebo at Week 72 ($p<0.0001$ vs placebo, adjusted for multiplicity)[3], measured by the treatment regimen estimand, as shown in Figure 21 (key secondary objective)

Figure 21: Mean change from baseline in triglycerides at week 72 in SURMOUNT-2.[3]



Mean baseline triglycerides: 185.9 mg/dL[4]
Mean baseline non-HDL: 131.2 mg/dL[4]
Mean baseline HDL cholesterol: 46.3 mg/dL[4]

[a]$p<0.0001$ vs placebo [3]
ANCOVA analysis. mITT population (full analysis set). Data are estimated means.
All participants received lifestyle intervention, including a reduced-calorie diet and increased physical activity. [3]
ANCOVA=analysis of covariance; HDL=high-density lipoprotein; mITT=modified intent-to-treat

Safety

Common adverse events

In SURMOUNT-2, the most frequent adverse events were gastrointestinal in nature and mostly mild or moderate in severity.[3]

Severe adverse events

Serious adverse events were reported by 7% of participants overall.[3]

Treatment discontinuation rates

Treatment discontinuation rates due to adverse events were 4% in the Mounjaro 10 mg group, 7% in the Mounjaro 15 mg group, and 4% in the placebo group.[3]

The selected safety information for SURMOUNT-2 can be seen in Table 4.

Table 4: SURMOUNT-2 selected safety information[3]

Adverse events in SURMOUNT-2[1]			
PERCENTAGE OF PATIENTS	**Placebo (n=315)**	**Mounjaro 10 mg (n=312)**	**Mounjaro 15 mg (n=311)**
Patients with ≥1 TEAE	76%	78%	71%
Any serious adverse events[a]	7%	6%	9%
Death[a]	0%	1%	0%
AEs leading to treatment discontinuation	4%	4%	7%
TEAEs occurring in ≥5% of patients in any treatment group, according to preferred term			
Diarrhoea	9%	20%	22%
Nausea	6%	20%	22%
COVID-19	17%	17%	11%
Vomiting	3%	11%	13%
Decreased appetite	2%	10%	10%
Constipation	4%	8%	9%
Dyspepsia	3%	7%	7%
Hyperglycaemia	14%	2%	1%
Upper respiratory tract infection	7%	3%	4%
Abdominal pain	2%	4%	7%
Headache	3%	5%	5%
Nasopharyngitis	5%	3%	3%
Eructation	1%	6%	4%
Dizziness	2%	5%	3%

Adverse events of special interest occurring in ≥1% of patients in any treatment group[1]			
PERCENTAGE OF PATIENTS	**Placebo (n=315)**	**Mounjaro 10 mg (n=312)**	**Mounjaro 15 mg (n=311)**
Hepatic events[b]	0%	1%	0%
Malignancies	2%	<1%	1%
Pancreatitis (adjudication-confirmed)	<1%	0%	1%
Major adverse cardiovascular event (MACE; adjudication-confirmed)	1%	1%	1%
Cardiac disorders[c]	<1%	1%	<1%
Gastrointestinal events[b]	1%	2%	3%
Gallbladder disease[b]	1%	1%	1%
Renal events[b]	<1%	1%	0%

[a]Deaths were also included as serious adverse events. All deaths were adjudicated by an external committee of physicians, who determined whether the death was cardiovascular-related.
[b]Adverse events are listed according to Medical Dictionary for Regulatory Activities, version 24.1, preferred terms.
[c]Events were classified as severe or serious adverse events.
[d]Events were classified as severe or serious arrhythmias and cardiac conduction disorders.

Summary of Adverse Reactions

A summary of adverse reactions with Mounjaro can be seen in Table 5. For full details, please refer to section 4.8 of the Mounjaro Summary of Product Characteristics.[1]

Table 5: Summary of adverse reactions[1]

Table of adverse reactions				
System organ class	**Very common** (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1 000 to <1/100)	**Rare** (≥1/10 000 to <1/1 000)
Immune system disorders		Hypersensitivity reactions		Anaphylactic reaction[a], angioedema[a]
Metabolism and nutrition disorders	Hypoglycaemia[b,c], when used with sulphonylurea or insulin	Hypoglycaemia[b,c], when used with metformin and sodium-glucose cotransporter 2 inhibitor (SGLT2i), decreased appetite	Hypoglycaemia[b,c], when used with metformin, weight decreased[b]	
Nervous system disorders		Dizziness[d]		
Vascular disorders		Hypotension-related events[d,e]		
Gastrointestinal disorders	Nausea, diarrhoea, vomiting[d], consitipation[d]	Abdominal pain, vomiting[b], dyspepsia, constipation[b], abdominal distention, eructation, flatulence, gastroesophageal reflux disease	Cholelithiasis, acute pancreatitis, cholecystitis[d]	
Skin and subcutaneous administration site conditions		Hair loss[d]		
General disorders and administration site conditions		Fatigue[f], injection site reactions	Injection site pain	
Investigations		Heart rate increased[b], lipase increased, amylase increased[b]	Blood calcitonin increased, amylase increased[d], heart rate increased[d]	

[a]From post-marketing reports.
[b]Frequency reported in clinical trials supporting the T2D indication.
[c]Hypoglycaemia defined as: clinically significant hypoglycaemia (blood glucose <3.0 mmol/L [<54 mg/dL]), or severe hypoglycaemia (requiring the assistance of another person).
[d]Frequency reported in clinical trials supporting the weight management indication.
[e]Includes the terms: "blood pressure decreased", "hypotension", and "orthostatic hypotension"; in weight management trials, 94% of hypotension-related events were mild to moderate in severity.
[f]Includes the terms fatigue, asthenia, malaise and lethargy

Rationale for Mounjaro use

Mounjaro has demonstrated superior body weight reductions compared with placebo in SURMOUNT-1 and SURMOUNT-2 clinical trials. [3,4] In SURMOUNT-1, mean weight reduction at 72 weeks was 21.4% in the 10 mg group and 22.5% in the 15 mg group compared to 2.4% with placebo. Mean weight reduction was 16.0% in the 5 mg group compared to 2.4% with placebo.[4]

With a body-weight reduction of 5% or more often being considered the threshold for clinically meaningful effect on the basis of improved metabolic health, weight

reductions of up to 20% provide additional clinical benefits to patients and may allow improvement in weight-related complications.[3,4]

The most common adverse events with Mounjaro were gastrointestinal in nature and were mostly mild to moderate in severity.[3,4]

Mounjaro is administered as a once-weekly dose from a pre-filled KwikPen. It can be administered at any time of the day, with or without meals.[1]

Mounjaro is available in 6 doses (2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg), allowing the clinician to tailor dosing to meet the requirements of individual patient needs, whilst achieving weight reductions across the 3 maintenance doses.[1]

References

1. EMC. Mounjaro® (tirzepatide) KwikPen® Summary of Product Characteristics. 2024 Available at: https://www.medicines.org.uk/emc/product/14203/smpc/print. Accessed March 2024.
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3. Garvey WT et al. Lancet. 2023:402:613-626 (incl Suppl Mat)
4. Jastreboff AM et al. N Engl J Med. 2022;205-216 (incl Suppl Mat)
5. Mounjaro KwikPen [GB] Instruction for Use

Mounjaro® ▼ (KwikPen®) (tirzepatide)

PRESCRIBING INFORMATION United Kingdom (Great Britain)

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section below for how to report adverse reactions. **Presentation:** Mounjaro solution for injection in a four-dose pre-filled pen containing 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg or 15 mg of tirzepatide in 0.6 ml solution. Each pre-filled Kwikpen contains 3 ml of solution. Mounjaro is a clear, colourless to slightly yellow solution. **Uses:** Type 2 diabetes. Mounjaro is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise either as monotherapy when metformin is considered inappropriate due to intolerance or contraindications, or in addition to other medicinal products for the treatment of diabetes. Weight management. Mounjaro is indicated for weight management, including weight loss and weight maintenance, as an adjunct to a reduced-calorie diet and increased physical activity 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 comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus). **Dosage and administration:** Posology: The starting dose of Mounjaro is 2.5 mg once weekly. After 4 weeks, the dose should be increased to 5 mg once weekly. If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose. The recommended maintenance doses are 5, 10 and 15 mg. The maximum dose is 15 mg once weekly. When Mounjaro is added to existing metformin and/or sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy, the current dose of metformin and/or SGLT2i can be continued. When Mounjaro is added to existing therapy of a sulphonylurea and/or insulin, a reduction in the dose of sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia. Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea and insulin. A stepwise approach to insulin reduction is recommended. *For weight management,* if patients have been unable to lose at least 5 % of their initial body weight 6 months after titrating to the highest tolerated dose, a decision is required on whether to continue treatment, taking into account the benefit/risk profile in the individual patient. (See SmPC for full information). Method of administration: Mounjaro is to be injected subcutaneously in the abdomen, thigh or upper arm. The dose can be administered at any time of day, with or without meals. Injection sites should be rotated with each dose. If a patient also injects insulin, they should inject Mounjaro into a different injection site. (See SmPC for full information). Missed doses: If a dose is missed, it should be administered as soon as possible within 4 days after the missed dose. If more than 4 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule. *Changing the dosing schedule:* The day of weekly administration can be changed, if necessary, as long as the time between two doses is at least 3 days. Special populations: *Elderly, gender, race, ethnicity or body weight:* No dose adjustment is needed. *Renal impairment:* No dose adjustment is required for patients with renal impairment including end stage renal disease (ESRD). Experience with the use of tirzepatide in patients with severe renal impairment and ESRD is limited. Caution should be exercised when treating these patients with tirzepatide. *Hepatic impairment:* No dose adjustment is required for patients with hepatic impairment. Experience with the use of tirzepatide in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with tirzepatide. *Paediatric population:* The safety and efficacy of tirzepatide in children aged less than 18 years have not yet been established. No data are available. (see SmPC for full information) **Contra-indications:** Hypersensitivity to the active substance or to any of the excipients listed in the SmPC. **Special warnings and precautions:** *Acute pancreatitis:* Tirzepatide has not been studied in patients with a history of pancreatitis, and should be used with caution in these patients. Acute pancreatitis has been reported in patients treated with tirzepatide. Patients should be informed of the symptoms of acute pancreatitis. If pancreatitis is suspected, tirzepatide should be discontinued. If the diagnosis of pancreatitis is confirmed, tirzepatide should not be restarted. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis. *Hypoglycaemia in patients with type 2 diabetes:* Patients receiving tirzepatide in combination with an insulin secretagogue (for example, a sulphonylurea) or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of the insulin secretagogue or insulin. *Gastrointestinal effects:* Tirzepatide has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhoea. These adverse reactions may lead to dehydration, which could lead to a deterioration in renal function including acute renal failure. Patients treated with tirzepatide should be advised of the potential risk of dehydration, due to the gastrointestinal adverse reactions and take precautions to avoid fluid depletion and electrolyte disturbances. This should particularly be considered in the elderly, who may be more susceptible to such complications. *Severe gastrointestinal disease:* Tirzepatide has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and should be used with caution in these patients. *Diabetic retinopathy:* Tirzepatide has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy or diabetic macular oedema, and should be used with caution in these patients with appropriate monitoring. *Elderly:* Only very limited data are available from patients aged ≥ 85 years. *Sodium content:* This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium free'. *Benzyl Alcohol:* This medicine contains 5.4 mg Benzyl Alcohol [E1519] in each 0.6 ml dose. Benzyl alcohol may cause allergic reactions. Patients with hepatic or renal impairment should be informed of the potential risk of metabolic acidosis due to accumulation of benzyl alcohol over time. **Interactions:** Tirzepatide delays gastric emptying and thereby has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. This effect, resulting in decreased C_{max} and a delayed t_{max}, is most pronounced at the time of tirzepatide treatment initiation. Based on the results from a study with paracetamol, no dose adjustments are expected to be required for most concomitantly administered oral medicinal products. However, it is recommended to monitor patients on oral medicinal products with a narrow therapeutic index especially at initiation of tirzepatide and following dose increase. The risk of delayed effect should also be considered for oral medicinal products for which a rapid onset of effect is of importance. *Paracetamol:* No dose adjustment of paracetamol is necessary when administered with tirzepatide. *Oral contraceptives:* No dose adjustment of oral contraceptives is required in women with normal BMI. There is limited information about the effect of tirzepatide on the pharmacokinetics and efficacy of oral contraceptives in women with obesity or overweight. Switching is advised to a non-oral contraceptive method, or add a barrier method of contraception upon initiating tirzepatide therapy (for 4 weeks) or after each dose escalation (for 4 weeks). **Fertility, pregnancy and lactation:** *Pregnancy:* Tirzepatide is not recommended during pregnancy and in women of childbearing potential not using contraception. If a patient wishes to become pregnant, tirzepatide should be discontinued at least 1 month before a planned pregnancy due to the long half-life of tirzepatide. Tirzepatide should not be used during pregnancy. *Breast feeding:* It is unknown whether tirzepatide is excreted in human milk. A risk to the newborn/infant cannot be excluded. *Fertility:* The effect of tirzepatide on fertility in humans is unknown, animal studies with tirzepatide did not indicate direct harmful effects with respect to fertility. (see SmPC for full information) **Effects on ability to drive and use machines:** Tirzepatide has no or negligible influence on the ability to drive or use machines. When tirzepatide is used in combination with a sulphonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines. (see SmPC for full information). **Undesirable Effects:** *Serious side effects:* Acute pancreatitis (uncommon ≥ 1/1 000 to < 1/100), anaphylactic reaction (rare ≥ 1/10 000 to < 1/1 000), angio-oedema (rare). *Frequency of other side effects:* Very common (≥ 1/10): Hypoglycaemia when used with sulphonylurea or insulin (type 2 diabetes), nausea, diarrhoea, constipation (weight management) vomiting (weight management). Common (≥ 1/100 to < 1/10): Hypersensitivity reactions, dizziness (weight management), hypotension related events (weight management), hypoglycaemia when used with metformin and SGLT2i (type 2 diabetes), decreased appetite (type 2 diabetes), abdominal pain, vomiting (type 2 diabetes), dyspepsia, constipation (type 2 diabetes), abdominal distention, eructation, flatulence, gastroesophageal reflux disease, hair loss (weight management), fatigue, injection site reactions, heart rate increased (type 2 diabetes), lipase increased, amylase increased (type 2 diabetes). Prescribers should consult the SmPC for further information in relation to other adverse reactions. *For full details of these and other side-effects, please see the Summary of Product Characteristics, which is available at http://www.medicines.org.uk/emc/.* **Legal Category:** POM **Marketing Authorisation Numbers (or Product Licence Numbers) and Holder:** PLGB 14895/0340, PLGB 14895/0341, PLGB 14895/0342, PLGB 14895/0343, PLGB 14895/0344, PLGB 14895/0345. Eli Lilly Nederland B.V. Papendorpseweg 83 3528 BJ Utrecht The Netherlands. **Cost (GB Only):** 1 x 2.5 mg pre-filled KwikPen: £92.00, 1 x 5 mg pre-filled KwikPen: £92.00, 1 x 7.5 mg pre-filled KwikPen: £107.00, 1 x 10 mg pre-filled KwikPen: £107.00, 1 x 12.5 mg pre-filled KwikPen: £122.00, 1 x 15 mg pre-filled KwikPen: £122.00. **Date of Preparation or Last Review:** 25 January 2024. **Further Information is Available From:** Eli Lilly and Company Limited, Lilly House, Basing View, Basingstoke, Hampshire, RG21 4FA. Telephone: **UK (Great Britain):** + 44-(0) 1256 315000, E-mail: ukmedinfo@lilly.com, Website: www.lilly.co.uk

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Adverse events and product complaints should be reported. Reporting forms and information can be found at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Adverse events and product complaints should also be reported to Lilly: please call Lilly UK on 01256 315 000.