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- This Lecture is sponsored by Eli Lilly
- I have no actual or potential conflict of interest in relation to this presentation

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- Take screenshots of the slides presented during this meeting
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Indications and Limitations of Use

Indication

► Type 2 diabetes mellitus

Mounjaro is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

► Weight Management

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

- ≥ 30 kg/m2 (obesity) or
- ≥ 27 kg/m2 to < 30 kg/m2 (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).

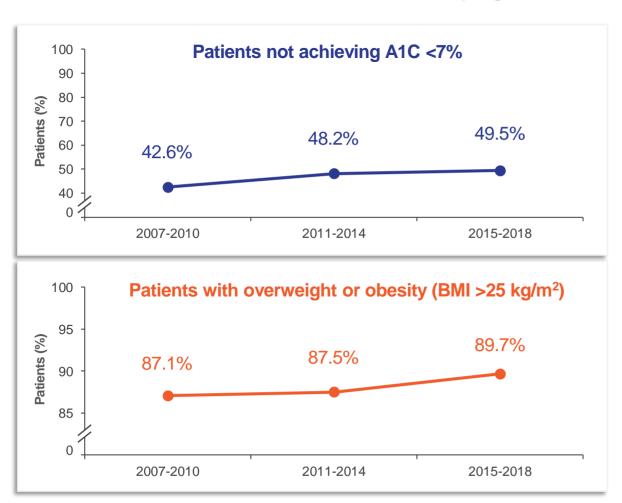


Addressing Type 2 Diabetes:

A1C and Excess Weight

US: Despite Recent Advances in Treatment Options, HbA1c and BMI Are Not Improving in People With Diabetes¹*

US adults with diabetes in the NHANES program



According to the latest **NHANES** data on adults with diabetes (2015-2018),[†]

~50% of patients did not achieve an A1C <7%

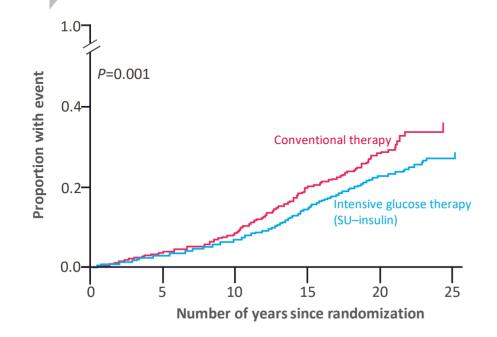
~90% of patients had overweight or obesity

*Over 90% of people with diabetes in the US have T2D; therefore, these data largely reflect trends in glycemic control among individuals with T2D. †NHANES participants from 2015-2018 who were nonpregnant, ≥20 years of age, and reported having ever received a diagnosis of diabetes from a physician, aside from gestational diabetes (n=6653).A1C=glycated hemoglobin; BMI=body mass index; NHANES=National Health and Nutrition Examination Survey; T2D=type 2 diabetes; US=United States. 1. Fang M, et al. N Engl J Med. 2021;384(23):2219-2228.

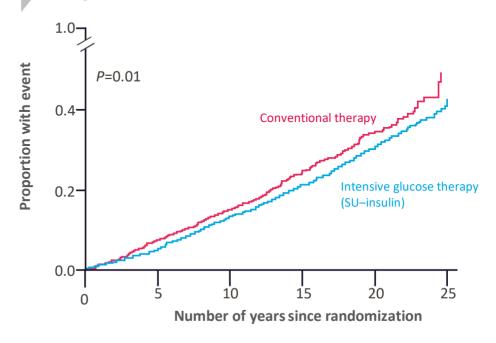
Early Intensive Glycemic Control Is Associated With **Decreased** Risk of T2D-Related Complications¹²

- In the UKPDS trial, early intensive glucose therapy in newly diagnosed patients with T2D reduced the risk of microvascular complications (25%) over 10 years compared to the conventional group¹
- Results from the 10-year posttrial follow-up showed that reductions were sustained for microvascular risk (24%), and emergent risk reductions for MI (15%) were observed²

Microvascular disease²



Myocardial infarction²



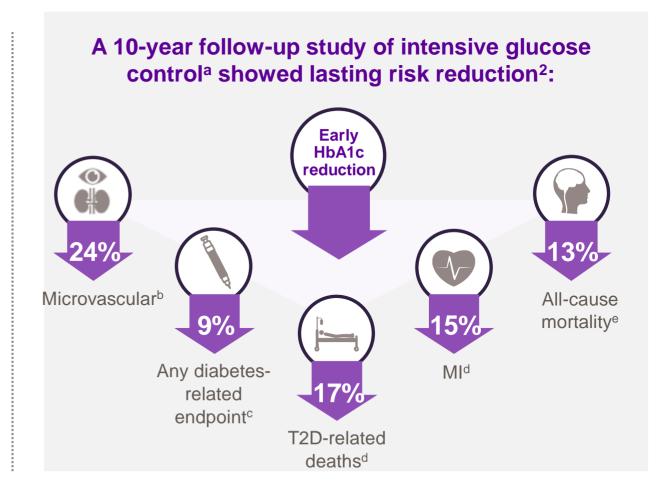
Improved Glycaemic Control Lowers the Risk of Complications

UKPDS Legacy Effect: Complications in People With T2D

Prospective RCT-enrolled People With Newly Diagnosed T2D From 1977-1991

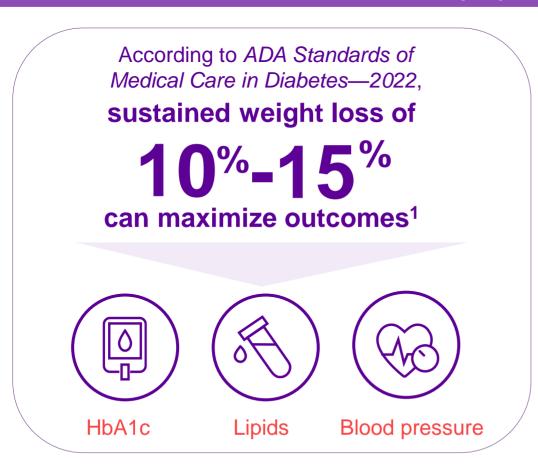
10-year study of intensive glucose control¹

- Median HbA1c:
 - Intensive therapy: 7.0%
 - Conventional therapy: 7.9%
- Macrovascular events:
 - No significant difference between in MI rates between therapy groups (P=.052)
- Microvascular events:
 - Intensive therapy resulted in a 25% risk reduction compared to conventional therapy (P<.01)



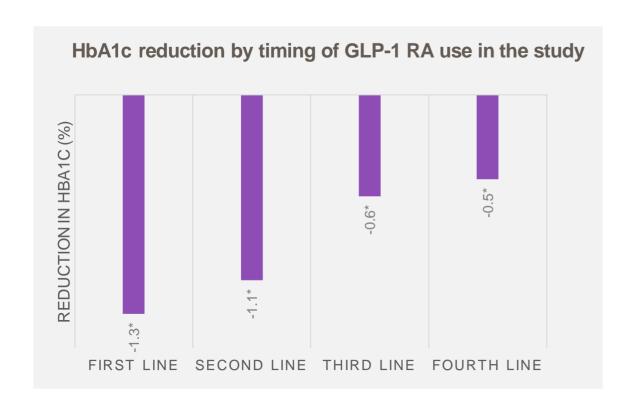
Diabetes guidelines emphasize the importance of weight management in T2D

Lifestyle intervention to achieve and maintain >5% weight loss is recommended for most people with T2D and excess weight¹



ADA 2024: When choosing glucose-lowering medications for people with type 2 diabetes and overweight or obesity, prioritize medications with beneficial effect on weight.²

Earlier Initiation of GLP-1 RAs Is Associated With Significantly Greater HbA1c Reduction



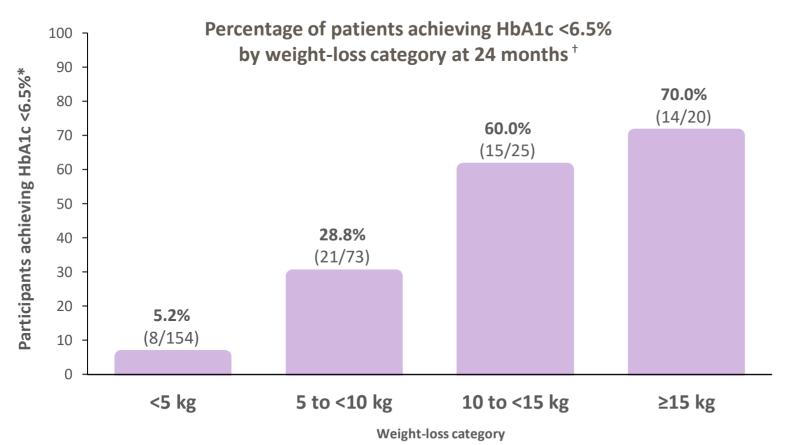
In 1122 patients with type 2 diabetes, the last HbA1c result prior to GLP-1 RA initiation was compared with the last HbA1c result 2 years after initiation

- At the end of the study, patients who initiated a GLP-1 RA first-line had an average HbA1c 1.3% lower than the reference group (P<0.0001)[†]
- First-line patients were 390% more likely than the reference group[†] to achieve an HbA1c <7%

^{*}P<0.05 vs the reference group.

[†]Reference group was comprised of patients who took ≥4 classes of glucose-lowering therapies prior to GLP-1 RA initiation. GLP-1 RA=Glucagon-like Peptide 1 Receptor Agonist; HbA1C=Glycated Hemoglobin. Boye KS, et al. *Clin Ther.* 2020;42(9):1812-1817

Weight Reduction Is Associated With Improvement in HbA1c Levels



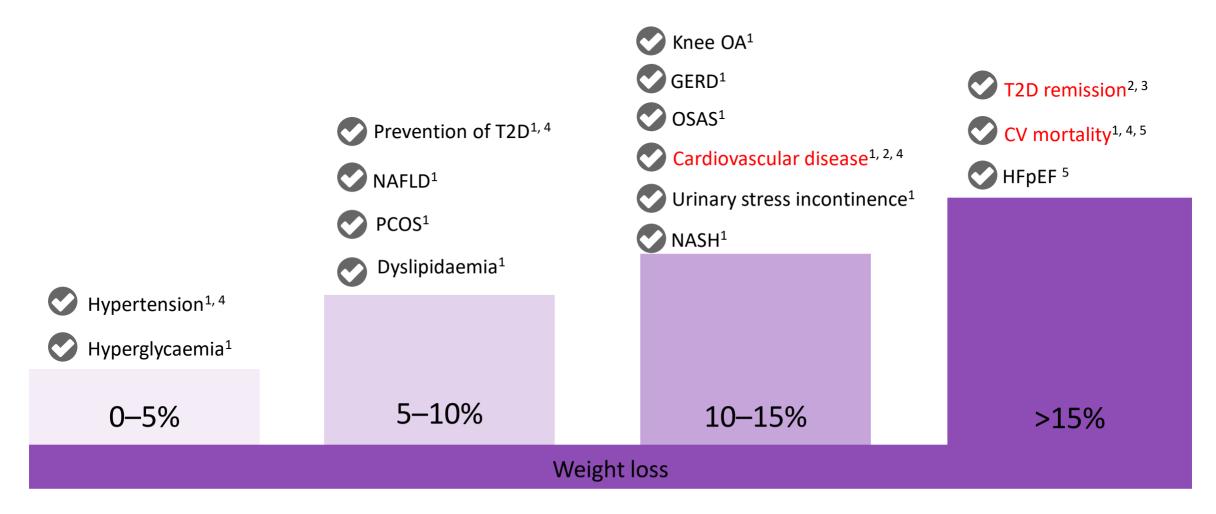
- 36% of patients in the weightmanagement intervention group achieved HbA1c <6.5% without use of antidiabetic medication
- 60% of patients in the intervention group were managing their T2D without use of antidiabetic medication at the 2 year follow up*
- There is a 25% increase in the odds of achieving HbA1c <6.5% per kilogram of weight loss



Odds ratio (per kilogram of weight loss): 1.25 (95% Cl, 1.16-1.35; *P*<0.0001)

[†]Participants from the weight management intervention and standard of care control group were pooled for this analysis by weight loss category *After withdrawal of antidiabetes drugs at baseline. 1, Lean MEJ, et al. *Lancet Diabetes Endocrinol*, 2019;7(5):344-355.

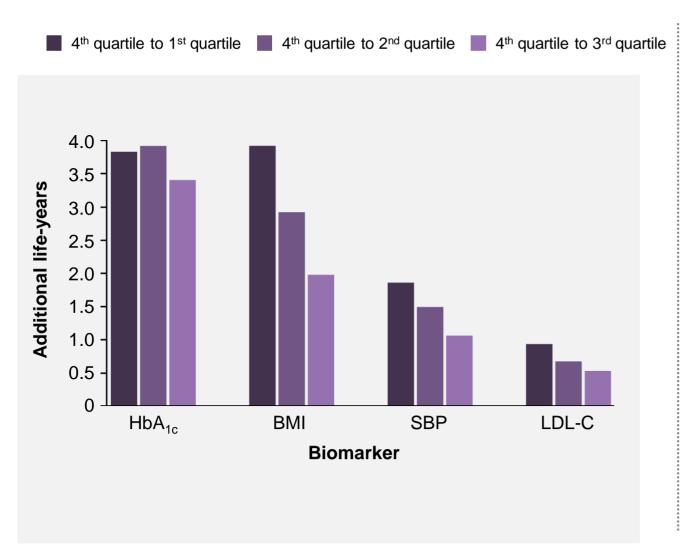
Benefits of weight loss



CV = cardiovascular; GERD = gastro-oesophageal reflux disease; HFpEF = heart failure with preserved ejection fraction; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis; OSAS = obstructive sleep apnoea syndrome; PCOS = polycystic ovary syndrome; TG = triglycerides.

¹Garvey WT, et al. Endocr Pract. 2016;22(Suppl. 3): 1–203; ²Look AHEAD Research Group. Lancet Diabetes Endocrinol. 2016;4(16): 913–921; ³Lean ME, et al. Lancet. 2018;391(17): 541–551; ⁴Benraoune F, Litwin SE. Curr Opin Cardiol. 2011;26(6): 555–561; ⁵Sundström J, et al. Circulation. 2017;135(6): 1577–1585.

Gains in Life-Years Associated With Different Levels of Biomarkers in Individuals With T2D



| Biomarker | 1 st | 2 nd | 3 rd | 4 th |
|----------------|-----------------|------------------|------------------|-----------------|
| | Quartile | Quartile | Quartile | Quartile |
| HbA1c* (%) | <6.4 (5.9) | 6.4-7.2 (6.8) | 7.3-8.2 (7.7) | >8.2 (9.9) |
| BMI* | <27 (24.3) | 27-31 (28.6) | 32-36 (33.0) | >36 (41.4) |
| SBP* (mm Hg) | <122 | 122-132 | 133-134 | >122 |
| | (114.1) | (128.1) | (139.1) | (160.4) |
| LDL-C* (mg/dL) | <73 | 73-96 | 97-122 | >122 |
| | (58.9) | (84.0) | (107.0) | (146.0) |

- Life expectancy gained through lower BMI was the largest among the 4 modifiable biomarkers examined:
 - For people with T2D and a high BMI (fourth quartile), reduction in BMI to the first quartile was associated with an estimated LE gain of 3.9 years

^{*}Values in () represent mean values.

Unsatisfied With her HbA1c and Weight, Concerned About Her Future Health





You know she's making the effort but not seeing results

- Recently diagnosed with type 2 diabetes
- Has not reached glycemic targets on metformin alone
- A1C >7% and BMI >25 kg/m²
- Continues to struggle with her weight despite her efforts with diet and exercise

Having excess weight contributes to her disease progression¹⁻³



A hypothetical patier

^{1.} National Heart, Lung, and Blood Institute. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.pdf. Accessed February 25, 2022. 2. Van Gaal L, et al. *Diabetes Care*. 2015;38(6):1161-1172.3. Wing RR, et al. *Obesity*. 2021;29(8):1246-1258.



The First in a New Class of Treatment for Adults With T2D

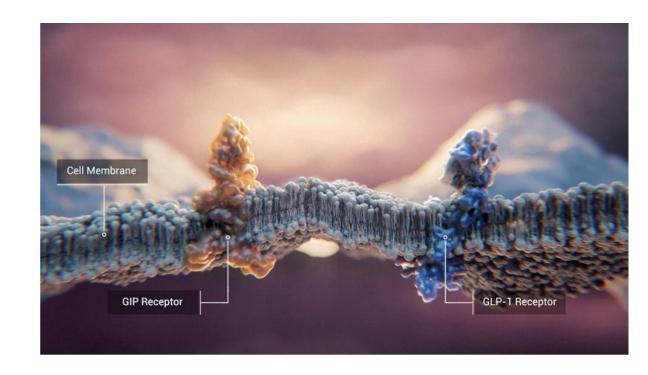


Mounjaro Is the First and Only Approved GIP and GLP-1 Receptor Agonist



Mounjaro is a single molecule that activates GIP and GLP-1 receptors in the body¹

| Structure | Based on the native GIP sequence , but modified to also bind to the GLP-1 receptor ^{1,2} | | | |
|---------------------|--|--|--|--|
| Mechanism of action | Selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1 ² | | | |
| Mean half-life | Approximately 5 days, enabling once-weekly dosing ^{1,2} | | | |
| Dose adjustment | No dose adjustment of Mounjaro is recommended for patients with renal or hepatic impairment ¹ | | | |



GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide-1.

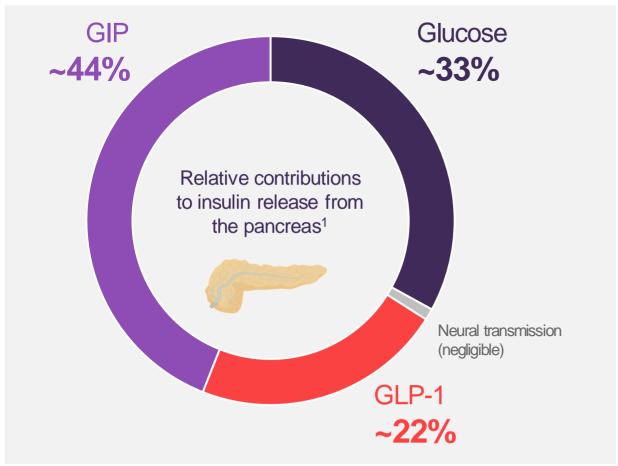
^{1.} Mouniaro SmPC. UAE

^{2.} Coskun T. et al. Mol Metab. 2018:18:3-14.

GIP and GLP-1 Are Incretin Hormones Released From the Gut in Response to Food Intake^{1,2}



GIP Has Greater Impact on Insulin Secretion

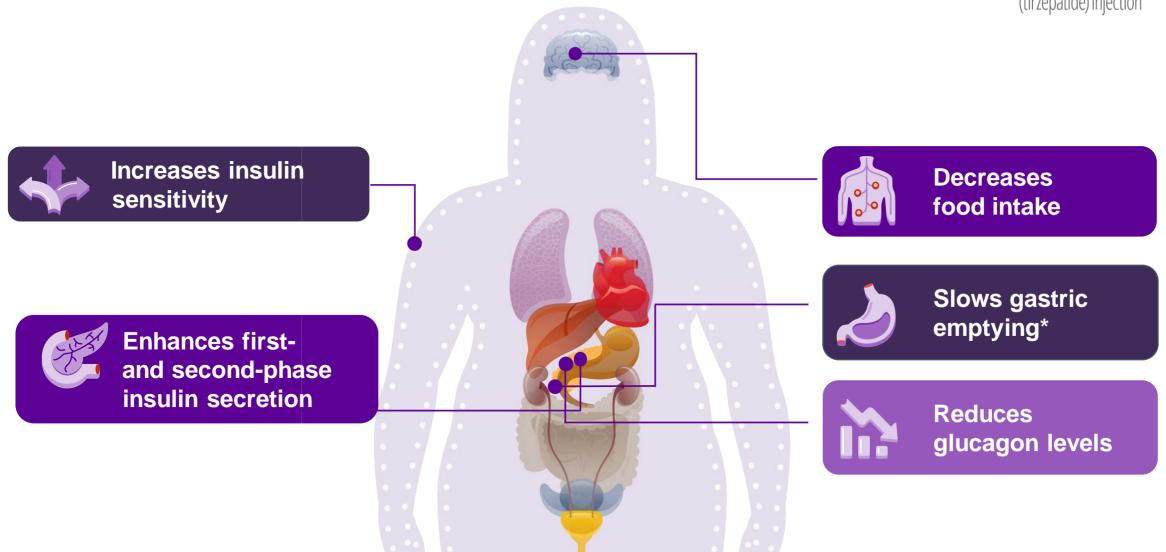


Incretin Effect

- of the incretin effect in healthy people, generating a more significant impact on insulin secretion than GLP-1^{1,2}
- In people with T2D, the total incretin effect is diminished¹

Mounjaro Works in the Following Ways



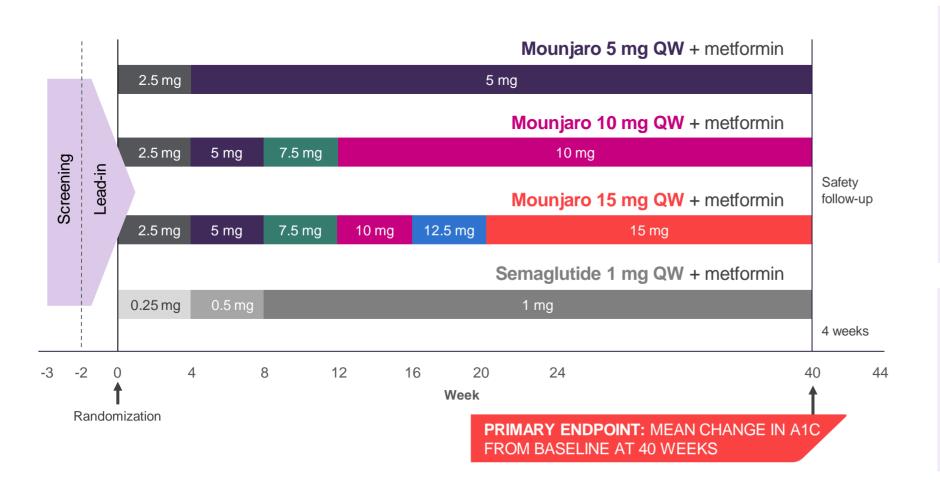


Superior A1C and Weight Reduction With Tirzepatide vs Semaglutide 1.0 mg in patients with T2D

(SURPASS-2)

SURPASS-2 Study Design Mounjaro 5 mg, 10 mg, and 15 mg vs Semaglutide 1 mg as the Only Add-on to Metformin in patients with T2D 12





Study Objectives^{1,2}

- ➤ The primary objective was to demonstrate noninferiority of Mounjaro 10 mg and/or 15 mg to Semaglutide in mean change from baseline in A1C at 40 weeks
- ➤ The key secondary objectives were assessed at 40 weeks: noninferiority of Mounjaro 5 mg to Semaglutide in mean change from baseline in A1C; superiority of Mounjaro to Semaglutide in mean change from baseline in A1C; superiority of proportion of patients with A1C <7%; superiority in mean change from baseline in weight; superiority of Mounjaro 10 mg and/or 15 mg to Semaglutide in proportion of patients with A1C <5.7%

Select overall baseline demographics^{1,2}

- ► Mean A1C: 8.3%
- ► Mean BMI: 34.2 kg/m²
- ▶ Mean duration of T2D: 8.6 years

Number of Patients

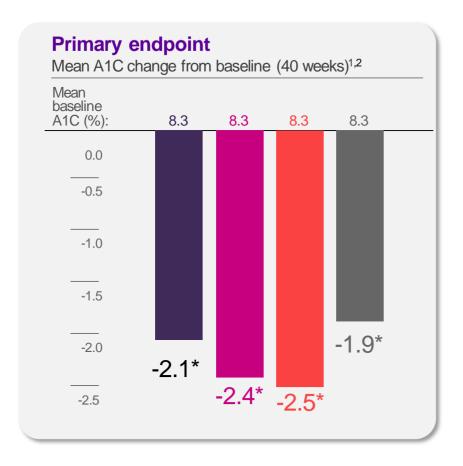
- Mounjaro 5 mg SC QW (n=470)
- Mounjaro 10 mg SC QW (n=469)
- Mounjaro 15 mg SC QW (n=469)
- Semaglutide 1 mg SC QW (n=468)

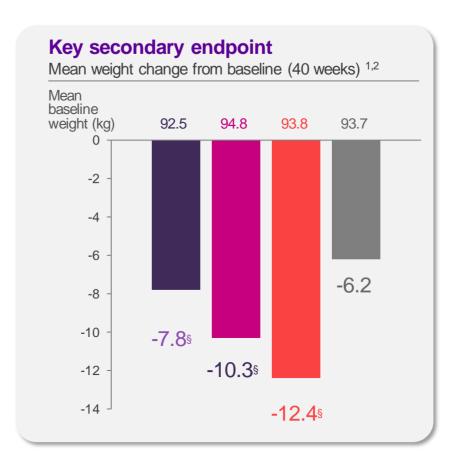
- 1. Mounjaro SmPC, UAE
- 2. Frías JP, et al. *N Engl J Med*. 2021;385(6):503-515

SURPASS-2

Mounjaro Demonstrated Superior A1C & Weight Reductions Compared with Semaglutide 1mg in patients with T2D 12*1





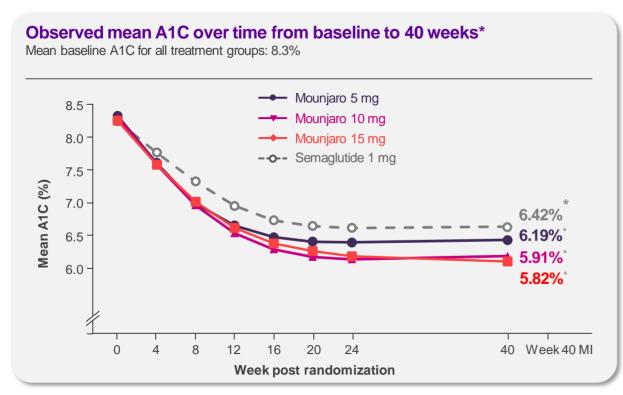




^{*}P<0.001 vs baseline, not adjusted for multiplicity.1, \$P<0.001 vs semaglutide 1 mg for superiority, adjusted for multiplicity.12

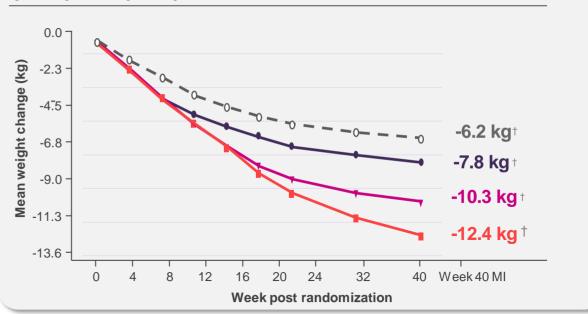
SURPASS-2 Mounjaro demonstrated sustained A1C¹ and Weight¹ Reductions in Patients with T2D 14







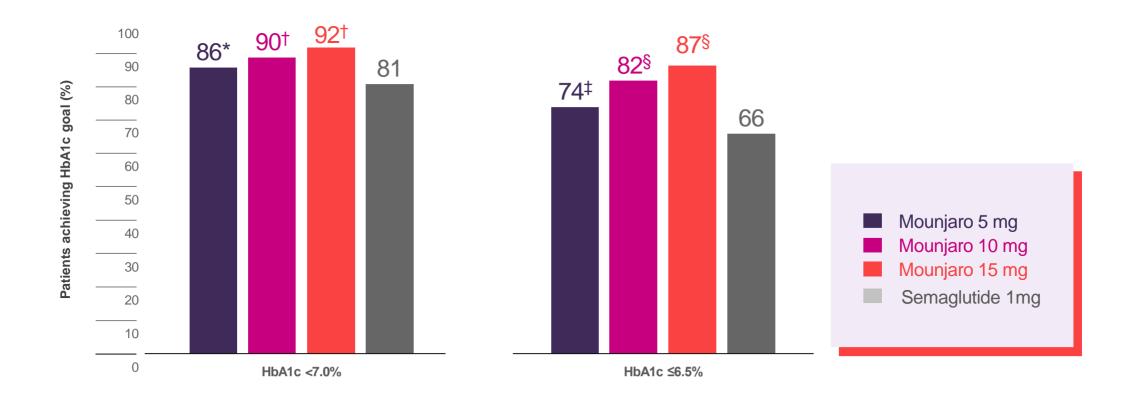
Observed mean weight change over time from baseline to 40 weeks[†] Mean baseline weight: Mounjaro 5 mg, 92.5 kg; Mounjaro 10 mg, 94.8 kg, Mounjaro 15 mg, 93.8 kg, Semaglutide 1 mg, 93.7 kg



†Data represent observed mean changes from week 0 to week 40, and least-squares mean at week 40 MI. mITT

SURPASS-2 More Patients with T2D Achieved Glycemic Control vs Semaglutide 1mg¹





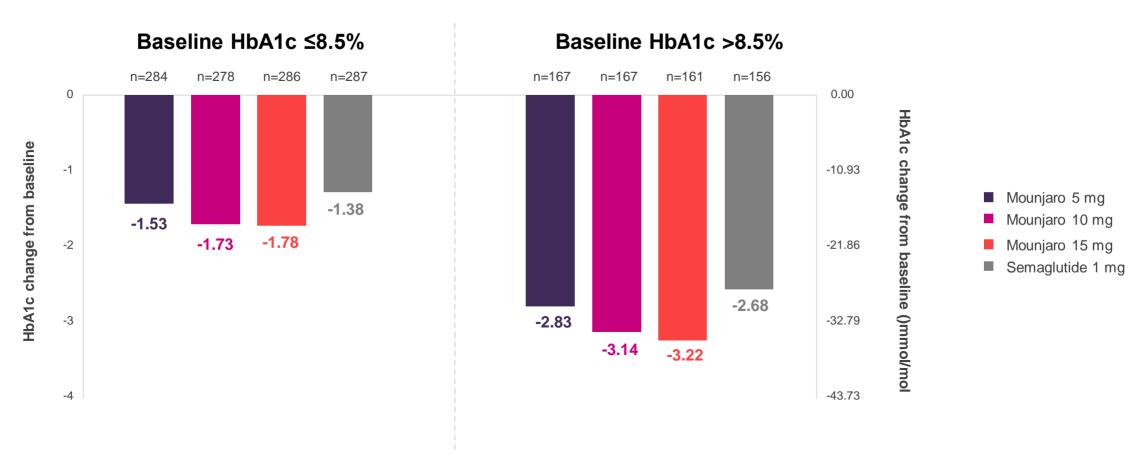
^{*}P<0.05 for superiority, adjusted for multiplicity. †P<0.001 for superiority, adjusted for multiplicity. †P<0.05 vs semaglutide 1 mg, not adjusted for multiplicity, \$P<0.001 vs semaglutide 1 mg, not adjusted for multiplicity. 1 l/Normoglycemia is defined by an HbA1c <5.7%.^{2.3}

Efficacy estimand: estimated means, logistic regression, mITT population (efficacy analysis set). Mounjaro vs semaglutide 1 mg at 40 weeks.2

SURPASS-2

Mounjaro in T2D Patients with baseline HbA1c ≤8.5% and >8.5%





Note: Data are LSM at 40 weeks by baseline HbA1c (\leq 8.5%, >8.5%). Estimated treatment difference are LSM (95% confidence interval) at 40 weeks. ANCOVA with imputation method: retrieved dropout imputation, mITT population (treatment-regimen estimand). The widths of confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

ANCOVA=Analysis of Covariance; ETD=Estimated Treatment Difference; HbA1c=Glycated Haemoglobin; LSM=Least Squares Mean; mITT=Modified Intent-to-Treat.

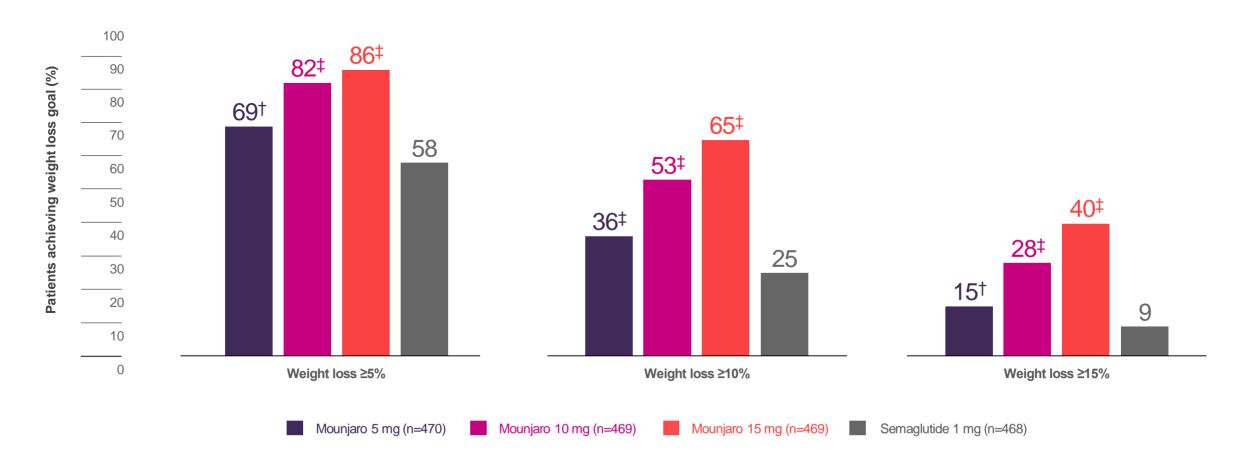
Frias JP, et al. N Engl J Med. 2021;385(6):503-515.

Mounjaro SmPC, UAE

SURPASS-2

More Patients Achieved Weight Loss of ≥5%, ≥10%, and ≥15% vs Semaglutide 1 mg^{1,2,*}





In SURPASS clinical trials, weight change was a secondary endpoint.1

†P<0.05 vs semaglutide 1 mg, not adjusted for multiplicity, ‡P<0.001 vs semaglutide 1 mg, not adjusted for multiplicity.1

Efficacy estimand: estimated means, logistic regression, mITT population (efficacy analysis set). Mounjaro vs semaglutide 1 mg at 40 weeks.²

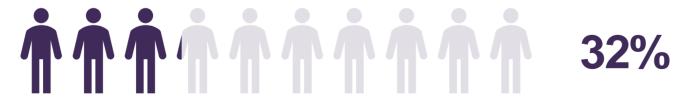
1. Mounjaro SmPC, UAE.

^{2.} Data from Frías JP, et al. N Engl J Med. 2021;385(6):503-515.

SURPASS-2 Composite Endpoint: Tirzepatide Vs Semaglutide 1 mg







Mounjaro 10 mg (n=469)



Mounjaro 15 mg (n=469)



Semaglutide 1 mg (n=468)



Mounjaro 15 mg
Helped about 3 times
as Many Patients as
Semaglutide 1 mg
Achieve
a Composite Endpoint

- ≤6.5% HbA1c
- Weight Reduction ≥10%*
- No clinically significant[†] or severe hypoglycemia[‡]

^{1.} Frías JP, et al. N Engl J Med. 2021;385(6):503-515.

^{*†}In SURPASS clinical trials, weight change was a secondary endpoint. † Hypoglycemia defined as plasma glucose <54 mg/dL (3.0 mmol/L). The incidence of hypoglycemia is uncommon when Mounjaro is used with metformin. ‡Severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia.

Changes in Other
Metabolic Parameters
Observed in SURPASS
Trials





Blood Pressure and Triglycerides and Triglycerides

Pooled Analysis of 5, 10, and 15 mg¹⁻⁵

Observed reduction in blood pressure from phase 3 pooled placebo-controlled studies*

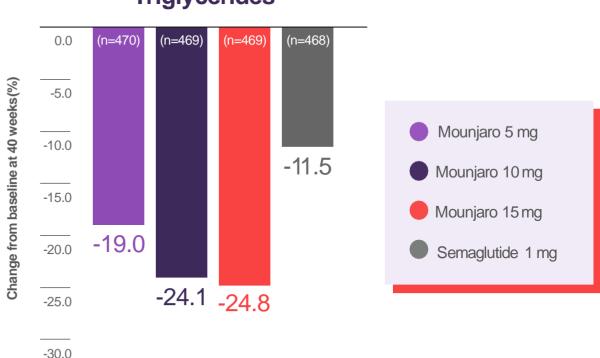
Blood Pressure



SURPASS-2²

Observed reductions in triglycerides †

Triglycerides



^{*}Mounjaro is not indicated for the management of hypertension. † Mounjaro is not indicated for the management of hyperlipidemia.

Mounjaro is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus, and weight management in adults with BMI>30kg/m2 and BMI>27kg/m2 with weight-related comorbidities.

In SURPASS clinical trials, weight change was a secondary endpoint.

^{1.} Rosenstock J, Wysham C, Frías JP, Lancet. 2021;398(10295):143-155. **2.** Frías JP, Davies MJ, Rosenstock J, N Engl J Med. 2021;385(6):503-515. **3.** Ludvik B, Giorgino F, Jódar Lancet. 2021;398(10300):583-598. **4.** Del Prato S, Kahn SE, Pavo . Lancet. 2021;398(10313):1811-1824. **5.** Dahl D, Onishi Y, Norwood P, JAMA. 2022;327 (6): 534 – 545

Mounjaro Safety Profile

(SURPASS-2)

SURPASS-2

The Most Common AEs for Mounjaro and Semaglutide Were Gl-Related and Were Mostly **Mild to Moderate** in Severity^{1,2}



| | Mounjaro 5 mg (n=470) | Mounjaro 10 mg (n=469) | Mounjaro 15 mg (n=469) | Semaglutide 1 mg (n=468) | | |
|---|-----------------------------|------------------------------|------------------------------|--------------------------------|--|--|
| AEs occurring in ≥5% of patients in the Mounjaro treatment groups, n (%)¹ | | | | | | |
| Nausea | 82 (17.4) | 90 (19.2) | 104 (22.1) | 84 (17.9) | | |
| Diarrhea | 62 (13.2) | 77 (16.4) | 65 (13.8) | 54 (11.5) | | |
| Vomiting | 27 (5.7) | 40 (8.5) | 46 (9.8) | 39 (8.3) | | |
| Dyspepsia | 34 (7.2) | 29 (6.2) | 43 (9.1) | 31 (6.6) | | |
| Decreased appetite | 35 (7.4) | 34 (7.2) | 42 (8.9) | 25 (5.3) | | |
| Abdominal pain | 14 (3.0) | 21 (4.5) | 24 (5.1) | 24 (5.1) | | |
| Constipation | 32 (6.8) | 21 (4.5) | 21 (4.5) | 27 (5.8) | | |
| All GI-related AEs, n (%) ¹ | 188 (40.0) | 216 (46.1) | 211 (44.9) | 193 (41.2) | | |
| Discontinuation due to AEs, n (%) ¹ | 28 (6.0) | 40 (8.5) | 40 (8.5) | 19 (4.1) | | |
| Discontinuation due to GI-related AEs, n (%) | 13 (2.8) | 20 (4.3) | 20 (4.3) | 15 (3.2) | | |

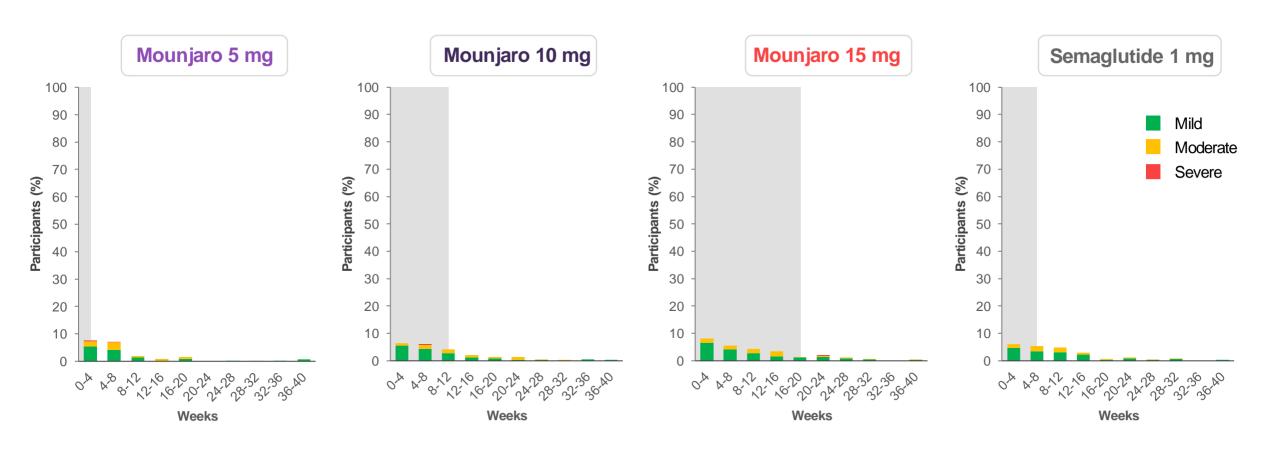
Most cases of AEs occurred during the dose-escalation period in all groups.

^{1.} Frías JP, et al. *N Engl J Med*. 2021;385(6):503-515.

^{2.} Mounjaro SmPC, November 2023

SURPASS-2 Incidence of Nausea Over Time Through 40 Weeks 12*





^{*}Shaded areas indicate the period of time before reaching the maintenance dose of the study treatments.1

^{1.} Frías JP, et al. *N Engl J Med*. 2021;385(6):503-515.

^{2.} Mounjaro SmPC, UĂE

SURPASS-2 Mounjaro Demonstrated a Low Risk of Hypoglycemia¹²



| Mounjaro vs Semaglutide 1 mg (add-on to MET) ¹ | Mounjaro 5 mg (n=470) | Mounjaro 10 mg (n=469) | Mounjaro 15 mg (n=470) | Semaglutide 1 mg (n=469) |
|---|--------------------------|---------------------------|---------------------------|-----------------------------|
| Hypoglycemia (BG <54 mg/dL), % | 0.6 | 0.2 | 1.7 | 0.4 |
| Severe hypoglycemia, % | 0.2 | 0 | 0.2* | 0 |

^{*}This patient had a hypoglycemic event that was not considered by the investigator to be severe, but it was reported as a serious adverse event.

Hypoglycemia was more frequent when Mounjaro was used in combination with a sulfonylurea. In a clinical trial up to 104 weeks of treatment, when administered with a sulfonylurea, severe hypoglycemia occurred in 0.5%, 0%, and 0.6%, and hypoglycemia (glucose level <54 mg/dL) occurred in 13.8%, 9.9%, and 12.8% of patients treated with Mounjaro 5 mg, 10 mg, and 15 mg, respectively.²

BG=blood glucose.

^{1.} Frías JP, et al. N Engl J Med. 2021;385(6):503-515.

^{2.} Mounjaro SmPC, UAE

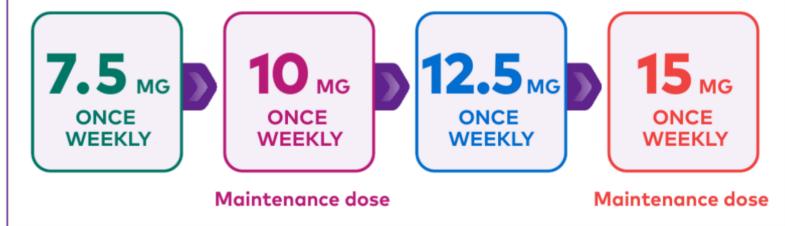
Start and Continue with Confidence With Mounjaro Once Weekly







INDIVIDUALIZE



Start Mounjaro with 2 steps

- 1 Initiate with the 2.5-mg starting dose
- After 4 weeks on the 2.5-mg dose, increase to the 5-mg dose

- If needed to achieve individual treatment goals, you can continue to increase the dose by 2.5 mg after at least 4 weeks at the current dose
- Recommended maintenance doses are 5 mg, 10 mg, and 15 mg (maximum dose)

Mounjaro:

A new class - with UNSURPASSED results!





First and only single-peptide GIP/GLP-1 RA²



Superior HbA1c reduction of up to -2.6%^{1,3,†}



Unmatched
Weight
reduction of up
to -12.9 kg^{1,4,‡}



Well-tolerated with low risk of hypoglycemia^{1,5}



From This Day Forward The T2D Diabetes Treatment Landscape Has a New Look!

*Mounjaro vs active comparators or placebo in 5 phase 3 studies (N=6271) ranging from 40 to 104 weeks in duration. Treatment was studied vs an active comparator or placebo and was added to diet and exercise or 1 to 3 background therapies, including metformin, SGLT2i, sulfonylureas, or basal insulin, depending on the study.¹ The primary endpoint was HbA1c change from baseline to Week 40 or 52 (study dependent).¹ †Mean reductions in HbA1c from baseline were -2.2% for the 5-mg dose, -2.6% for the 10-mg dose, and -0.9% for placebo.¹¹³ ‡Mean reductions in body weight were -7.5 kg for the 5-mg dose, -10.7 kg for the 10-mg dose, and +2.3 kg for insulin degludec. Percentage of weight loss was an approximate calculation of the LS mean for change from baseline divided by the mean baseline value.¹⁴ GIP=glucose-dependent insulinotropic polypeptide; GLP-1=glucagon-like peptide-1; HbA1c=glycated hemoglobin; LS=least squares; SGLT2i=sodium-glucose cotransporter 2 inhibitor.

1. Mounjaro SmPC, UAE

^{2.} Willard FS, et al. JCI Insight. 2020;5(17): e140532.

^{3.} Dahl D, et al. JAMA. 2022;327(6): 534–545.

Ludvik B, et al. Lancet. 2021;398(10300): 583–598.
 Frías JP, et al. N Engl J Med. 2021;385(6): 503–515

Thank you





