Tirzepatide-induced Weight Loss in Type 2 Diabetes is Independent of Nausea, Vomiting, or Diarrhea

Hiren Patel[1], Kamlesh Khunti[2], Helena W. Rodbard[3], Harpreet S. Bajaj[4], Ross Bray[1], Zbigniew Kindracki[1], Ángel Rodríguez[1], Adriana Sobel (Non-author Presenter)[1]

[1]Eli Lilly and Company, Indianapolis, IN, USA; [2]Diabetes Research Centre, University of Leicester, Leicester, UK; [3]Endocrine and Metabolic Consultants, Rockville, MD, USA; [4]LMC Diabetes and Endocrinology, Brampton; Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Toronto, ON, Canada

BACKGROUND

- Tirzepatide, a once-weekly glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor agonist, demonstrated superior reduction in HbA_{1c} and body weight vs comparators in participants with type 2 diabetes across the SURPASS 1-5 randomised clinical trials.[1-5]
- The most common adverse events in tirzepatide-treated participants were gastrointestinal in nature and mainly occurred during the dose-escalation period.

OBJECTIVE

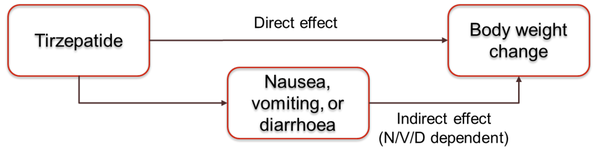
This *post hoc* analysis evaluated the impact of nausea, vomiting, or diarrhea adverse events on weight loss with tirzepatide across the SURPASS 1-5 trials.

[1]Rosenstock et al. Lancet 2021;398(10295):143-155.
[2]Frias et al. N Eng J Med 2021;385(6):503-515.
[3]Ludvik et al. Lancet 2021;398(10300):583-598.
[4]Del Prato et al. Lancet 2021;398(10313):1811-1824.
[5]Dahl et al. JAMA 2022;327(6):534-545.

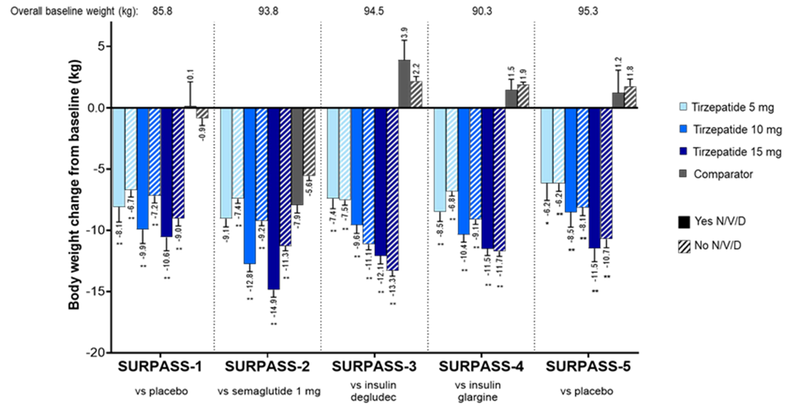
METHODS

***Post Hoc* Analysis**

- Participants within trials were subdivided into subgroups by self-reporting (yes/no) of any nausea, vomiting, or diarrhea.
- Change from baseline in body weight at the time of the primary endpoint was assessed within each trial and subgroup.
- Mediation analyses evaluated the contribution of direct and indirect (mediated by nausea, vomiting, or diarrhea) effects of tirzepatide on weight change vs comparators at the time of the primary endpoint.



Change From Baseline In Body Weight By Subgroups Reporting (Yes/No) Nausea, Vomiting, Or Diarrhea



Data are LSM (SE). mITT (efficacy analysis set). *p<0.01 and **p<0.001 vs comparator.
Abbreviations: LSM = least-squares mean; mITT = modified Intent-to-Treat; SE = standard error.

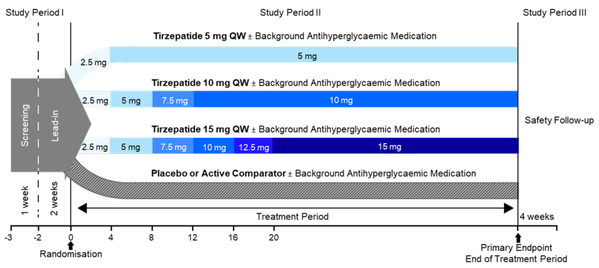
SUMMARY

- Mean weight loss with tirzepatide was consistent in participants reporting nausea, vomiting, or diarrhea vs those who did not report these GI AEs.
- Mediation analyses suggested minimal contribution of nausea, vomiting, or diarrhea in overall difference in weight change between tirzepatide and comparators across SURPASS 1-5 studies.

CONCLUSION

Superior weight loss with tirzepatide vs comparators appears to be independent of reported nausea, vomiting, or diarrhea adverse events across the SURPASS 1-5 clinical trials

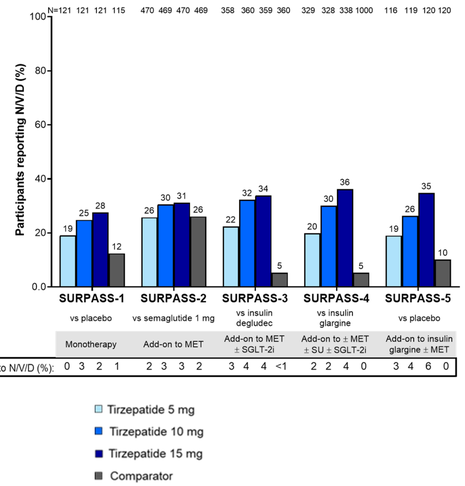
Description of SURPASS Study Designs



Trial	(Sample Size) Randomisation Ratio, Background Glucose-Lowering Therapy	Comparator	Primary Endpoint
SURPASS-1	(N=478) 1:1:1:1, None	Placebo QW	Week 40
SURPASS-2	(N=1878) 1:1:1:1, + Metformin	Semaglutide 1 mg QW	Week 40
SURPASS-3	(N=1437) 1:1:1:1, + Metformin ± SGLT-2i	Titrated Insulin Degludec QD	Week 52
SURPASS-4	(N=1995) 1:1:1:3, ± Metformin ± Sulfonylurea ± SGLT-2i	Titrated Insulin Glargine QD	Week 52
SURPASS-5	(N=475) 1:1:1:1, + Titrated Insulin Glargine ± Metformin	Placebo QW	Week 40

Abbreviations: QD = once daily; QW = once weekly; SGLT-2i = sodium-glucose cotransporter-2 inhibitor.

Patients Reporting Nausea, Vomiting or Diarrhea



mITT population.
Abbreviations: MET = metformin; mITT = modified Intent-to-Treat; N/V/D = nausea, vomiting, or diarrhoea; SGLT-2i = sodium-glucose cotransporter-2 inhibitor; SU = sulfonylurea.

Baseline Demographics and Clinical Characteristics by Subgroups Reporting (Yes/No) N/V/D

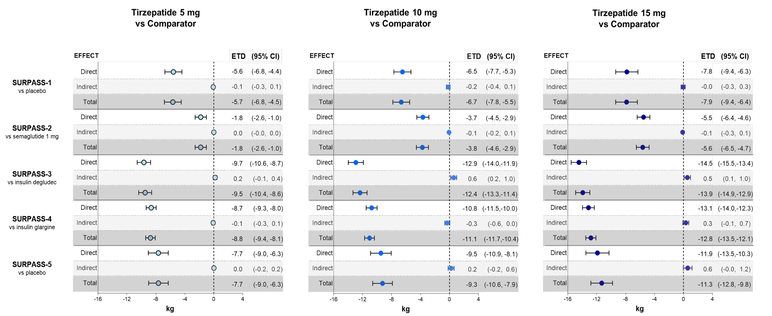
Pooled Tirzepatide Data From the SURPASS 1-5 Trials

	N/V/D (Yes) (N=924)	N/V/D (No) (N=2693)
Age, years	57.6 (10.5)	58.3 (10.2)
Female, n (%)	500 (54%)	1174 (44%)
HbA_{1c}, mmol/mol	67.1 (10.0)	67.4 (10.7)
HbA_{1c}, %	8.29 (0.91)	8.32 (0.98)
Duration of type 2 diabetes, years	9.1 (6.8)	9.5 (7.1)
Body weight, kg	92.0 (20.7)	93.7 (20.4)
BMI, kg/m^2	33.6 (6.4)	33.6 (6.3)
Waist circumference, cm	108.8 (14.6)	109.8 (14.8)
eGFR, mL/min/1.73m^2	92.1 (19.7)	91.5 (19.1)

Baseline demographics and clinical characteristics were similar between subgroups (reporting/not reporting any nausea, vomiting, or diarrhea)

Data are mean (SD) or n (%) from tirzepatide-treated participants on treatment without rescue therapy at the time of the primary endpoint.
Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; HbA_{1c} = haemoglobin A_{1c}; N/V/D = nausea, vomiting, or diarrhoea; SD = standard deviation.

Impact Of N/V/D On Weight Change Of Tirzepatide Vs Comparators



mITT (efficacy analysis set). Effects were estimated with model including the interaction between treatment and participants experiencing N/V/D during the treatment period or not, together with the baseline variables of body weight and stratification factors as covariates. **Indirect effects are mediated by N/V/D.**
Abbreviations: CI = confidence interval; ETD = estimated treatment difference; mITT = modified Intent-to-Treat; N/V/D = nausea, vomiting, or diarrhea.

Disclosures:

- KK is supported by the National Institute for Health and Care Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC); KK's institution has received research grants from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Merck Sharp & Dohme, Novartis, Novo Nordisk, and Sanofi; and he is a consultant to Abbott, Amgen, AstraZeneca, Bayer, Berlin Chemie AG/Menarini Group, Boehringer Ingelheim, Eli Lilly and Company, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, Sanofi, and Servier.
- HWR is a consultant to Abbott, Bayer, Boehringer Ingelheim, Eli Lilly and Company, Merck, and Regeneron; has received payment for lectures including service on speaker bureaus from Bayer, Vivus, and Zealand Pharma; and is involved in clinical trials for Eli Lilly and Company and Novo Nordisk.
- HSB reports trial fees paid to his institution by Amgen, AstraZeneca, Boehringer Ingelheim, Ceapro, Eli Lilly and Company, Gilead Sciences, Janssen, Kowa Pharmaceuticals Co. Ltd, Madrigal Pharmaceuticals, Merck, Novartis, Novo Nordisk, Pfizer, Sanofi, and Tricida.
- HP, RB, ZK, and AR are employees and shareholders of Eli Lilly and Company.
- Previously presented at the European Association for the Study of Diabetes - 58th Annual Meeting.

Scan the QR code to access this presentation or use this URL,

for a list of all Lilly content presented at the congress.

Association of Diabetes Care & Education Specialists - 2023 Annual Conference; Houston, TX, United States; 04 - 07 Aug 2023