Tirzepatide Improved Markers of Islet Cell Function (Fasting Glucagon and HOMA2-B) and Insulin Sensitivity (Fasting Insulin and HOMA2-IR) Compared to Semaglutide in People with Type 2 Diabetes

Scan or click the QR code for a list of all Lilly content presented at the congress. Other company and product names are trademarks of their respective owners.

Katelyn Brown[1], Laura Fernandez Landó[1], Brandon Bergman[1], Melissa K. Thomas[1], Bing Liu[1], Clare Lee[1], Amanda M. Giebel (Non-author Presenter)[1]

[1]Eli Lilly and Company, Indianapolis, IN, USA

Sponsored by Eli Lilly and Company

OBJECTIVE

- To assess changes in markers of islet cell function (fasting glucagon and HOMA2-B) and insulin sensitivity (fasting insulin and HOMA2-IR) with tirzepatide, compared with semaglutide in patients with T2D in the SURPASS-2 study

CONCLUSION

- GIP/GLP-1 receptor agonist tirzepatide significantly improved markers of islet cell function and insulin sensitivity compared with selective GLP-1 receptor agonist semaglutide in people with T2D on concomitant metformin.
- Both improvements in insulin sensitivity and in islet cell function may contribute to the differentiated efficacy profile seen with tirzepatide compared with semaglutide.

World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease - 21st; Los Angeles, CA, USA; 07 - 09 Dec 2023

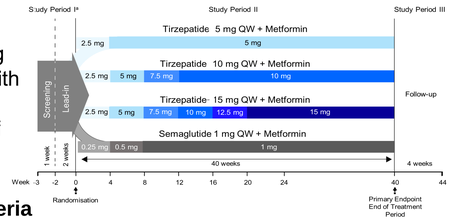
BACKGROUND

- Tirzepatide (TZP) is a once weekly GIP/GLP-1 receptor agonist approved in the US for treatment of type 2 diabetes (T2D) and obesity.
- Tirzepatide achieved significantly greater and clinically meaningful HbA1c and weight reductions with all doses (5,10, and15 mg) vs semaglutide 1 mg in a 40-week, randomized, open-label, active-controlled Phase 3 trial of 1879 people with T2D on background metformin (SURPASS-2)[1]
- In a 26-week, randomized, double-blind, Phase 2 trial in people with T2D that compared tirzepatide with placebo and dulaglutide[2], tirzepatide significantly:
  - increased marker of pancreatic beta cell function (HOMA2-B)
  - reduced fasting hyperglucagonemia
  - reduced marker of insulin resistance (HOMA2-IR)

SURPASS-2 STUDY DESIGN

Key Inclusion Criteria

- Type 2 diabetes
- HbA1c ≥7.0% to ≤10.5% screening
- BMI ≥25 kg/m2 with stable weight
- On stable dose of metformin ≥1500 mg/day



Key Exclusion Criteria

- Type 1 diabetes
- History of acute pancreatitis
- eGFR <45 mL/min/1.73 m^2
- Use of any antihyperglycemic treatment other than metformin in the 3 months prior to screening

Randomized, open-label, active-controlled, parallel group, multicenter, multinational trial. Participating Countries: US, Argentina, Australia, Brazil, Canada, Israel, Mexico, and UK. [a]Stable doses of metformin ≥1500 mg/day for at least 3 months prior to Visit 1 and during the screening/lead-in period.
Abbreviations:BMI = body mass index; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; QW = once weekly.

SURPASS-2 Baseline Demographics

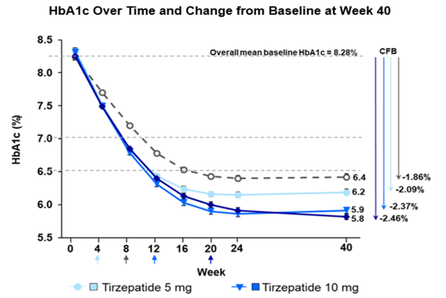
- Baseline demographics and clinical characteristics were well balanced across the treatment groups[1]

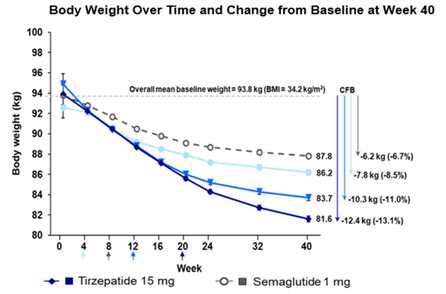
Parameter	Tirzepatide 5 mg N=470	Tirzepatide 10 mg N=469	Tirzepatide 15 mg N=470	Semaglutide 1 mg N=469	Total N=1878
Age (y)	56.3 ± 10.0	57.2 ± 10.5	55.9 ± 10.4	56.9 ± 10.8	56.6 ± 10.4
Female, n (%)	265 (56.4)	231 (49.3)	256 (54.5)	244 (52.0)	996 (53.0)
Duration of Diabetes (y)	9.1 ± 7.16	8.4 ± 5.90	8.7 ± 6.85	8.3 ± 5.80	8.6 ± 6.46
HbA1c	8.32 ± 1.08	8.30 ± 1.02	8.26 ± 1.00	8.25 ± 1.01	8.28 ± 1.03
FSG (mg/dL)	173.8 ± 51.87	174.2 ± 49.79	172.4 ± 54.37	171.4 ± 49.77	172.9 ± 51.46
Weight (kg)	92.5 ± 21.76	94.8 ± 22.71	93.8 ± 21.83	93.7 ± 21.12	93.7 ± 21.86
BMI (kg/m^2)	33.8 ± 6.85	34.3 ± 6.60	34.5 ± 7.11	34.2 ± 7.15	34.2 ± 6.93

Data are mean ± SD, unless otherwise indicated; mITT population. Abbreviations: BMI = body mass index; FSG = fasting serum glucose; HbA1c = glycated hemoglobin; mITT = modified intent-to-treat; N = population size, n = sample size; SD = standard deviations; y = years.

TIRZEPATIDE SIGNIFICANTLY REDUCED HbA1c AND BODY WEIGHT OVER TIME

- All tirzepatide doses were superior to semaglutide for change from baseline in HbA1c and body weight[1]

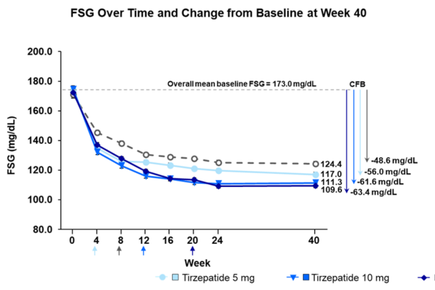


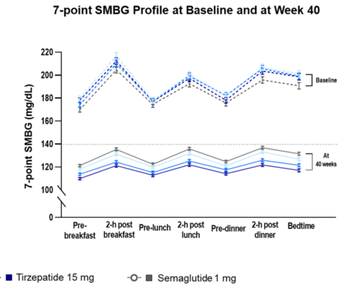


Data are LSM (SE); mITT (efficacy estimand) ANOVA analysis (Week 0) and MMRM analysis (Week 40). Arrows indicate when the maintenance dose of tirzepatide 5, 10 and 15 mg and semaglutide 1 mg is achieved. For HbA1c, estimated treatment difference (ETD) (95% CI) of tirzepatide vs semaglutide was: i) 5 mg -0.23** (-0.36, -0.10), ii) 10 mg -0.51** (-0.64, -0.38), and iii) 15 mg -0.60** (-0.73, -0.47). For body weight, ETD (95% CI) of tirzepatide vs semaglutide was: i) 5 mg -1.7** (-2.6, -0.7), ii) 10 mg -4.1** (-5.0, -3.2), and iii) 15 mg -6.2** (-7.1, -5.3). *p<0.05 and **p<0.001 vs. semaglutide 1 mg at 40 weeks. Abbreviations: ANOVA = analysis of variance; BMI = body mass index;
CFB = change from baseline; CI = confidence interval; ETD = estimated treatment difference; HbA1c = glycated hemoglobin; LSM = least squares mean; mITT = modified intent-to-treat; SE = standard error

Tirzepatide Significantly Reduced Fasting and Self-Monitored Glucose Profiles

- All tirzepatide doses improved fasting and self-monitored glucose profiles, compared with semaglutide[1]



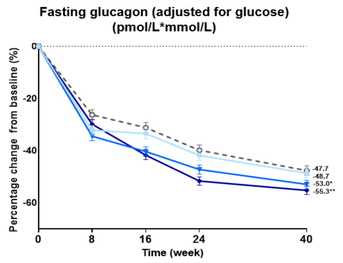


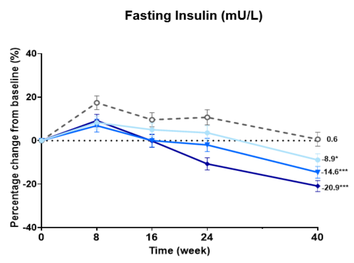
Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Semaglutide 1 mg

Data are LSM (SE); mITT (efficacy estimand) ANOVA analysis (Week 0) and MMRM analysis (Week 40). Arrows indicate when the maintenance dose of tirzepatide 5, 10 and 15 mg and semaglutide 1 mg is achieved. Abbreviations: ANOVA = analysis of variance; CFB = change from baseline; FSG = fasting serum glucose; LSM = least squares mean; mITT = modified int treat; SE = standard error; SMBG = self-monitoring blood glucose.

Tirzepatide Significantly Reduced Fasting Insulin and Fasting Glucagon Levels

- Tirzepatide 10 and 15 mg improved fasting insulin and fasting glucagon levels compared with semaglutide



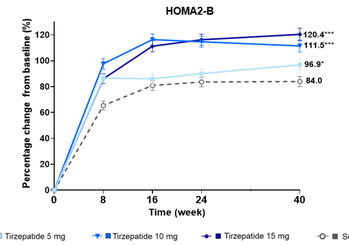


Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Semaglutide 1 mg

Data are percentage change from baseline (Estimated Mean ± SE) for fasting insulin and fasting glucagon adjusted for glucose (fasting glucagon x fasting serum glucose) from 0 to 40 weeks. Mixed model repeated measures analysis on log-transformed data then converted back to original scale. * p<0.05 vs semaglutide. ** p<0.01 vs semaglutide. *** p<0.001 vs semaglutide. Abbreviation: SE = standard error.

Tirzepatide Significantly and Rapidly Improved HOMA2-B

- All tirzepatide doses improved HOMA2-B (calculated with C-peptide) compared with semaglutide

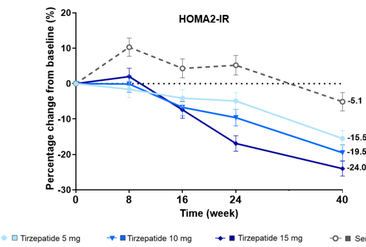


Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Semaglutide 1 mg

Data are percentage change from baseline (Estimated Mean ± SE) for HOMA2-B from 0 to 40 Weeks (on treatment without rescue). HOMA2-B was calculated with C-peptide. Mixed model repeated measures analysis on log-transformed data then converted back to original scale. * p<0.05 vs semaglutide. ** p<0.01 vs semaglutide. *** p<0.001 vs semaglutide. Abbreviation: SE = standard error.

Tirzepatide Significantly Improved HOMA2-IR, a Marker of Insulin Resistance

- All tirzepatide doses improved HOMA2-IR (calculated with insulin) compared with semaglutide



Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Semaglutide 1 mg

Data are percentage change from baseline (Estimated Mean ± SE) for HOMA2-IR from 0 to 40 weeks. Mixed model repeated measures analysis on log-transformed data then converted back to original scale. * p<0.05 vs semaglutide. HOMA-IR was calculated with insulin. ** p<0.01 vs semaglutide. *** p<0.001 vs semaglutide. Abbreviation: SE = standard error.

Summary

- GIP/GLP-1 receptor agonist tirzepatide significantly improved markers of islet cell function and insulin sensitivity compared with selective GLP-1 receptor agonist semaglutide in people with T2D on concomitant metformin.
- Both improvements in insulin sensitivity and in islet cell function may contribute to the differentiated efficacy profile seen with tirzepatide compared with semaglutide

References: 1. *Frias et al. N Eng J Med 2021;385(6):503-515* 2. *Frias et al. Lancet 2018 Nov 17;392(10160):2180-2193*

Disclosures:
- Katelyn Brown, Laura Fernández Landó, Brandon Bergman, Melissa K. Thomas, Bing Liu, and Clare Lee are employees and shareholders of Eli Lilly and Company.
- Previously presented at the American Diabetes Association - 82nd Annual Scientific Sessions; New Orleans, LA, USA; 3–7 June 2022

Acknowledgements
- This study was sponsored by Eli Lilly and Company.
- Medical writing and editorial assistance were provided by Ciara O' Neill, Eli Lilly and Company.