Efficacy and Safety of Tirzepatide in Type 2 Diabetes: The SURPASS Clinical Trial Program

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ABSTRACT

Tirzepatide is a novel, once-weekly, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that is approved for the treatment of type 2 diabetes (T2D). The efficacy and safety of tirzepatide has been assessed in five Phase 3 trials from the SURPASS program in a broad T2D population across the treatment continuum. The objective of this review is to summarize the results from the completed trials.

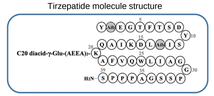
At primary endpoints of 40 and 52 weeks, tirzepatide 5, 10, and 15 mg demonstrated superiority in reductions from baseline in glycated hemoglobin (HbA1c) and body weight versus placebo (SURPASS-1 monotherapy and SURPASS-5 add-on to basal insulin), versus semaglutide 1 mg (SURPASS-2 add-on to metformin), versus insulin degludec (SURPASS-3 add on to metformin ± sodium glucose cotransporter 2 inhibitor [SGLT2i]), and versus insulin glargine (SURPASS-4 add-on to metformin ± sulfonylurea ± SGLT2i]). A greater proportion of tirzepatide-treated participants reached HbA1c targets of <7.0%, ≤6.5% and <5.7% (i.e., normoglycemia) without increased risk in clinically significant hypoglycemia (blood glucose <54 mg/dL). Adding tirzepatide to basal insulin decreased the total daily insulin dosage. The overall safety profile of tirzepatide was similar to that of the GLP-1 receptor agonist class. The most common adverse events were gastrointestinal, mostly mild to moderate in severity, transient, and decreased over time.

Given the unprecedented reduction in HbA1c and body weight without increased risk of hypoglycemia in various populations along the spectrum of diabetes care, tirzepatide demonstrated potential as first-line therapy for T2D treatment.

BACKGROUND

- Tirzepatide, a once weekly, GIP and GLP-1 receptor agonist, was recently approved in the US for the treatment of type 2 diabetes (T2D)

Tirzepatide molecule structure



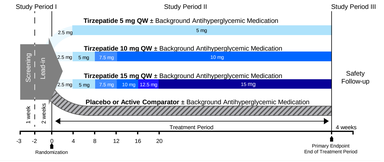
Shading indicates non-coded amino acids.

- In Phase 3 clinical trials, tirzepatide produced substantial reductions in HbA1c and body weight, enabling many people with T2D to achieve normalization of glucose control[1-5]

OBJECTIVE

This review summarizes the primary results from completed SURPASS trials.

SURPASS STUDY DESIGN



	Sample Size, Randomization ratio, Background glucose lowering therapy	Comparator	Primary endpoint
SURPASS-1	(N=478) 1:1:1:1 None	Placebo QW	Week 40
SURPASS-2	(N= 1879) 1:1:1:1 + Metformin	Semaglutide 1 mg QW	Week 40
SURPASS-3	(N=1444) 1:1:1:1 + Metformin ± SGLT2i	Titrated Insulin Degludec QD	Week 52
SURPASS-4	(N=2002) 1:1:1:3 ± Metformin ± SGLT2i ± SU	Titrated Insulin Glargine QD	Week 52
SURPASS-5	(N=475) 1:1:1:1 + Titrated Insulin Glargine ± Metformin	Placebo QW	Week 40

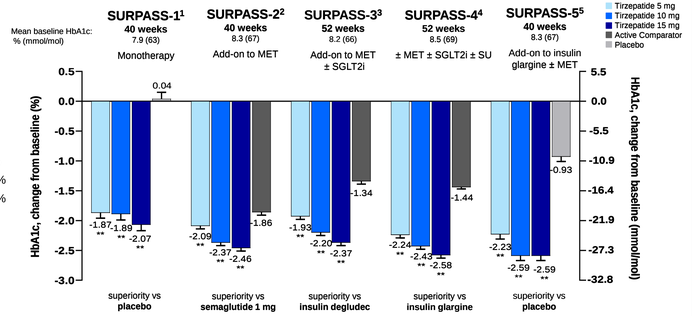
Abbreviations: QD = once-daily; QW = once-weekly; SGLT-2i = sodium-glucose co-transporter 2 inhibitors; SU = sulfonylurea

KEY RESULTS

Across the SURPASS trials,

- HbA1c reductions from baseline ranged from:
  - Tirzepatide 5 mg: -1.87 to -2.24%
  - Tirzepatide 10 mg: -1.89 to -2.59%
  - Tirzepatide 15 mg: -2.07 to -2.59%
  - Comparator: +0.04 to -1.86%

At the primary endpoints of 40 and 52 weeks, all tirzepatide doses demonstrated superior reductions from baseline in HbA1c vs placebo and active comparators



Data are LSM (SE). mITT population (efficacy analysis set). MMRM analysis. Data labels are % HbA1c. **p<0.001 vs comparator. Abbreviations: HbA1c = glycosylated hemoglobin; LSM = least squares mean; MET = metformin; mITT = modified intent-to-treat; MMRM = mixed-model repeated measures; SE = standard error; vs = versus

CONCLUSION

Across the diabetes treatment continuum, tirzepatide has demonstrated significant and clinically meaningful improvements in glycemic control and body weight reductions against all comparators.

- The overall safety profile of tirzepatide was similar to that of the GLP-1 receptor agonist class:
  - The most common adverse events were gastrointestinal (nausea, vomiting and diarrhea), mostly mild to moderate in severity, occurred during dose-escalation and decreased over time
  - In general, clinically relevant decreases in systolic blood pressure and diastolic blood pressure

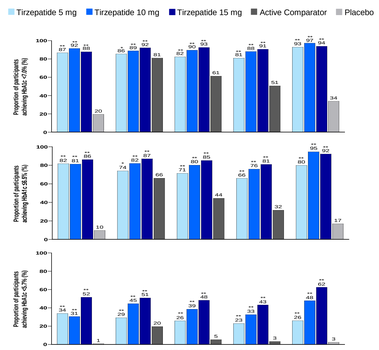
Baseline Demographics and Clinical Characteristics from the Overall Population

Parameter	SURPASS-1 N=478	SURPASS-2 N=1878	SURPASS-3 N=1437	SURPASS-4 N=1995	SURPASS-5 N=475
Age, years	54.1 ± 11.9	56.6 ± 10.4	57.4 ± 10.0	63.6 ± 8.6	60.6 ± 9.9
Sex, female, n (%)	231 (48.3)	996 (53.0)	635 (44.2)	749 (37.5)	211 (44.4)
Ethnicity, n (%)					
Not Hispanic or Latino	184 (38.5)	561 (29.9)	1009 (70.2)	1030 (51.6)	380 (80.0)
Hispanic or Latino	207 (43.3)	1317 (70.1)	421 (29.3)	950 (47.6)	22 (4.6)
Race, n (%)					
American Indian or Alaska Native	118 (24.7)	208 (11.1)	4 (0.3)	173 (8.7)	2 (0.4)
Asian	168 (35.1)	25 (1.3)	76 (5.3)	70 (3.5)	85 (17.9)
Black or African American	22 (4.6)	79 (4.2)	44 (3.1)	73 (3.7)	6 (1.3)
Multiple	0	12 (0.6)	2 (0.1)	43 (2.2)	2 (0.4)
Native Hawaiian or Other Pacific Islander	0	3 (0.2)	4 (0.3)	3 (0.2)	0
White	170 (35.6)	1551 (82.6)	1307 (91.0)	1629 (81.8)	380 (80.0)
T2D duration, years	4.7 ± 5.38	8.6 ± 6.46	8.4 ± 6.24	11.8 ± 7.51	13.3 ± 7.31
HbA1c, %	7.9 ± 0.87	8.3 ± 1.03	8.2 ± 0.91	8.5 ± 0.88	8.3 ± 0.85
FSG, mg/dL	153.6 ± 39.83	172.9 ± 51.46	169.3 ± 45.89	171.2 ± 50.75	162.4 ± 51.27
Weight, kg	85.9 ± 19.77	93.7 ± 21.86	94.3 ± 20.06	90.3 ± 18.66	95.2 ± 21.64
BMI, kg/m²	31.9 ± 6.59	34.2 ± 6.93	33.5 ± 6.06	32.6 ± 5.54	33.4 ± 6.06

Data are mean (SD), unless otherwise indicated. Abbreviations: BMI = body mass index; FSG = fasting serum glucose; SD = standard deviation; T2D = type 2 diabetes

Proportion of Participants Achieving HbA1c Targets

A greater proportion of participants achieved the ADA/EASD-recommended HbA1c target <7.0%, AACE-recommended HbA1c target ≤6.5%, and achieved normoglycemia (HbA1c <5.7%) with tirzepatide vs comparators

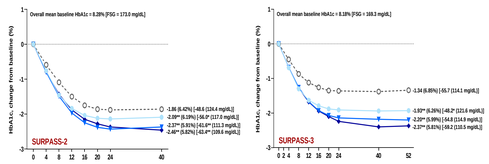


Logistic Regression, mITT population (efficacy analysis set). *p<0.05 and **p<0.001 vs comparator

Change from Baseline in HbA1c Over Time

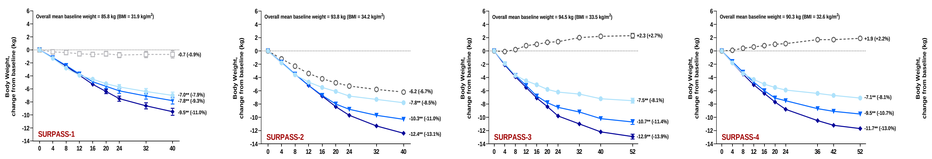
Tirzepatide (all doses) demonstrated superior reductions in HbA1c vs comparators. Tirzepatide also demonstrated greater reductions in FSG vs placebo and semaglutide 1 mg (all doses), and vs insulin glargine (tirzepatide 15 mg). Greater FSG reductions were observed with insulin degludec vs tirzepatide 5 mg but did not differ with tirzepatide 10 mg or 15 mg.

Example: Change from baseline in HbA1c in SURPASS-2 and SURPASS-3. FSG data are in brackets



Change from Baseline in Body Weight Over Time

Tirzepatide (all doses) demonstrated superior reductions in body weight vs comparators, which were dose-dependent, progressive and did not reach plateau at the end of the treatment periods.

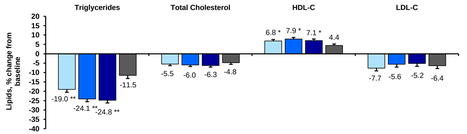


Data are LSM (SE) (HbA1c and body weight over time) and estimated mean (SD) (lipid profile). MMRM analysis, mITT population (efficacy analysis set). Abbreviations: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol. *p<0.05 and **p<0.001 vs comparator

Lipid Profile at the Primary Endpoints

- Triglycerides significantly decreased from baseline with tirzepatide (all doses) vs comparators, except with tirzepatide 5 mg which did not differ with insulin degludec
- Total cholesterol significant decreased from baseline tirzepatide (all doses) vs placebo and insulin glargine but did not differ from semaglutide or insulin degludec
- HDL-C significantly increased from baseline with tirzepatide (all doses) vs comparators, except in SURPASS-5 which did not differ from placebo
- LDL-C significant decreased from baseline with tirzepatide (all doses) vs placebo (15 mg dose only in SURPASS-1) and vs insulin glargine but did not differ from semaglutide or insulin degludec

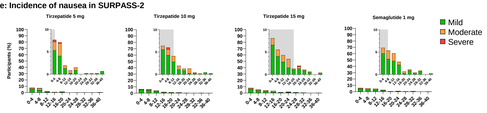
Example: Percent change from baseline in lipid profile in SURPASS-2



Additional Safety Results

- The safety profile of tirzepatide was consistent with GLP-1 receptor agonists
- The most common adverse events were mostly mild to moderate, transient gastrointestinal events, including:
  - Nausea: 12-24% with tirzepatide vs 2-18% with comparator
  - Diarrhea: 12-22% with tirzepatide vs 4-12% with comparator
  - Vomiting: 2-13% with tirzepatide 1-8% with comparator
- Decreased appetite was also more frequently reported with tirzepatide (6-14%) vs comparator (≤2%) in SURPASS-3, SURPASS-4 and SURPASS-5
- Small transient increases in pulse rate were observed with tirzepatide
- In general, clinically relevant decreases in systolic blood pressure and diastolic blood pressure were observed with tirzepatide

Example: Incidence of nausea in SURPASS-2



Data are percent of participants who reported a new event relative to participants at risk during a time interval; mITT population (safety analysis set). Shaded areas indicate the period of time before reaching the maintenance dose of the study treatments. Note: incidence refers to the proportion of participants who have a new event during a time interval.

Treatment Arm	Incidence of Hypoglycemia (Blood Glucose <54 mg/dL) or Severe Hypoglycemia, n (%)				
	SURPASS-1[1]	SURPASS-2[2]	SURPASS-3[3]	SURPASS-4[4]	SURPASS-5[5]
Tirzepatide 5 mg	0	4 (0.9)	29 (8.8)	18 (1.5)	18 (15.5)
Tirzepatide 10 mg	0	1 (0.2)	4 (1.1)	20 (6.1)	23 (19.3)
Tirzepatide 15 mg	0	8 (1.7)	8 (2.2)	27 (8.0)	17 (14.2)
Semaglutide 1 mg	---	2 (0.4)	---	---	---
Insulin Degludec	---	---	26 (7.2)	---	---
Insulin Glargine	---	---	---	191 (19.1)	---
Placebo	1 (0.8)	---	---	---	15 (12.5)

Safety evaluation included all available data from the entire study periods, i.e., 40-week treatment + 4-week safety follow-up period for SURPASS-1, -2 and -5, 52-week treatment + 4-week safety follow-up period for SURPASS-3, and 52-week treatment (primary) + variable treatment period (to 104 weeks) + 4-week safety follow-up for SURPASS-4

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