742-P

Anti-drug Antibodies do not Impact Pharmacokinetics, Efficacy, and Safety of Tirzepatide: Analysis of Data from Seven Phase 3 Studies

Boris Calderon[1], Garrett Mullins[1], Michael E. Hodsdon[1], Ying Grace Li[1], Greg Anglin[2], Shweta Urva[1], Karen Schneck[1], Jennifer N. Bardos[1], Ricardo Fonseca Martins[1], Katelyn Brown[1]

[1]Eli Lilly and Company, Indianapolis, IN, USA; [2]Eli Lilly Canada Inc, Toronto, ON, Canada

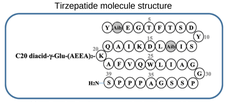
OBJECTIVE

To evaluate treatment-emergent (TE) anti-drug antibodies (ADA) in tirzepatide-treated participants across seven Phase 3 trials and its potential effect on pharmacokinetics (PK), efficacy, and safety.

BACKGROUND

- Tirzepatide, a once weekly GIP/GLP-1 receptor agonist, was recently approved in the US for treatment of people with type 2 diabetes (T2D).
- In multiple Phase 3 clinical trials, tirzepatide improved glycemic control and resulted in significant reductions in body weight.[1-5]
- Since tirzepatide is a 39 amino acid synthetic peptide, it could generate an immune response.

Tirzepatide molecule structure



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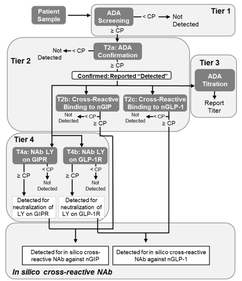
MULTI-TIERED TESTING STRATEGY

- Multi-tiered immunogenicity testing strategy with 1 ligand-binding method used for several assays:
  - Tier 1. ADA screening
  - Tier 2a. ADA confirmation
  - Tier 2b. Cross-reactive binding to nGIP
  - Tier 2c. Cross-reactive binding to nGLP-1
  - Tier 3. ADA titration
- Cell-based method used for 2 NAb assays:
  - Tier 4a. NAb on GIPR
  - Tier 4b. NAb on GLP-1R
- In silico classifications to detect cross-reactive NAb against nGIP and nGLP-1.



KEY RESULTS

INCIDENCE OF IMMUNOGENICITY

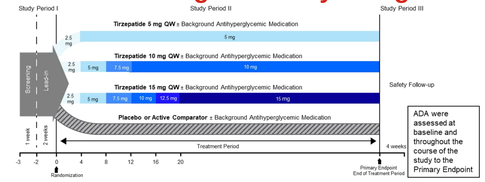
	Baseline N=5025	Postbaseline N=5025
Pre-existing ADA	353 (7.0)	--
TE ADA+	--	2570 (51.1)
Median ADA titer	1:20	1:160
ADA titer range	1:10 to 1:10240	--
TE ADA+ titer range	--	1:20 to 1:81920
NAb against TZP activity on GIPR	2 (<0.1)	94 (1.9)
NAb against TZP activity on GLP-1 R	2 (<0.1)	107 (2.1)
Cross-reactive binding ADA to nGIP	97 (1.9)	1705 (33.9)
Cross-reactive binding ADA to nGLP-1	34 (0.7)	716 (14.2)
Cross-reactive NAb against nGIP	0	43 (0.9)
Cross-reactive NAb against nGLP-1	0	18 (0.4)

Data presented as n (%), median, or range. N = total ADA-evaluable patients. n = number of patients with characteristic. Postbaseline defined as during the planned treatment period until primary endpoint at Week 40 (SURPASS-1, -2, and -5) or Week 52 (SURPASS -3, -4, -Japan-mono, and -Japan-combo).

CONCLUSIONS

- Across seven Phase 3 clinical studies, approximately 50% of tirzepatide-treated patients developed TE ADA.
- Tirzepatide pharmacokinetic profile was not affected by ADA status or ADA titer.
- TE ADA status or titer had no discernible impact on HbA1c change from baseline at endpoint.
- More tirzepatide-treated patients who developed ADA experienced hypersensitivity or injection site reactions than those who did not develop ADA.
- No pattern was detected between the time of the hypersensitivity or injection site reaction event reporting and ADA status, and the events resolved irrespective of ADA status.
- NAb status assessment on the low sample size showed no visual clinical impact on PK, efficacy, or safety profile.
- **Overall, immunogenicity was not associated with any impact on tirzepatide PK, efficacy, or safety.**

The SURPASS Program Study Design



	(Sample Size). Randomization ratio, Background glucose lowering therapy	Comparator	Primary end point
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 ± SU ± SGLT-2i	Titrated Insulin Glargine QD	Week 52
SURPASS-5	(N=475) 1:1:1:1 + Titrated Insulin Glargine ± Metformin	Placebo QW	Week 40
SURPASS-Japan Mono	(N=636) 1:1:1:1 None	Dulaglutide 0.75 mg QW	Week 52
SURPASS-Japan Combo	(N=443) 1:1:1 ± SU ± biguanides ± TZD ± α-Gis ± glinides ± SGLT-2i	None	Week 52

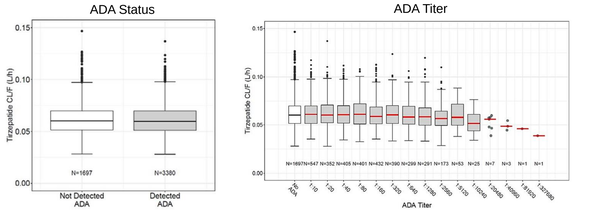
Baseline Characteristics

	TZP 5 mg (N=1701)	TZP 10 mg (N=1702)	TZP 15 mg (N=1716)	TZP All (N=5119)
Age, years	58.1 (10.4)	58.5 (10.4)	58.0 (10.7)	58.2 (10.5)
Sex, female	749 (44.0)	684 (40.2)	741 (43.2)	2174 (42.5)
Race, white	1098 (64.6)	1100 (64.6)	1141 (66.5)	3339 (65.3)
HbA1c, %	8.31 (0.97)	8.32 (0.95)	8.29 (0.99)	8.31 (0.97)
Body weight, kg	89.7 (20.5)	90.1 (20.6)	90.1 (20.5)	90.0 (20.5)
BMI, kg/m^2	32.4 (6.5)	32.4 (6.4)	32.5 (6.4)	32.4 (6.4)
Duration of diabetes, years	9.1 (6.9)	9.0 (6.7)	9.2 (7.0)	9.1 (6.9)

Data presented as mean (SD) for continuous data or *n* (%) for categorical data. N=total number of patients in each group. n=number of patients with specified characteristic.
Data from SURPASS-1 to -5, SURPASS-Japan mono, and SURPASS-Japan combo trials.

Pharmacokinetic Results: Tirzepatide clearance was not affected by ADA status or titer

Tirzepatide clearance by ADA status and titer



The top and bottom margins of the boxplot represent the 75th and 25th percentiles; the whiskers extend to ±1.5x interquartile range from median; solid circles denote individual values outside the whiskers. There were low numbers of samples with high ADA titer and clearance at the highest titers was consistent with the range seen in lower titer and TE ADA- groups.

Abbreviations:
A-Gis = alpha-glucosidase inhibitors; ADA = anti-drug antibodies; BMI = body mass index; CL/F = apparent clearance; CP = cut point; GIP = glucose-dependent insulinotropic polypeptide; GLP = glucagon-like peptide; HbA1c = glycated hemoglobin; MET = metformin; N= number of patients; NAb = neutralizing antibodies; nGIP = native GIP; nGLP = native GLP; OAM = oral antihyperglycemic medication; PK = pharmacokinetics; QD = once-daily; QW = once-weekly; R = receptor; SD = standard deviation; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; TE = treatment emergent; TZD = thiazolidinedione; TZP = tirzepatide.

References
[1]Rosenstock et al. Lancet 2021;398(10295):143-155.
[2]Frias et al. N Engl J Med 2021;385(6):503-515.
[3]Ludvik et al. Lancet 2021;398(10300):583-589.
[4]Del Prato et al. Lancet 2021; 398(10313): 1811–1824.
[5]Dahl et al. JAMA 2022;327(6):534-545.

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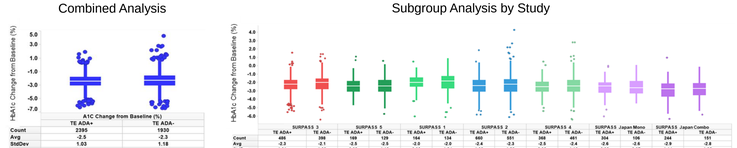
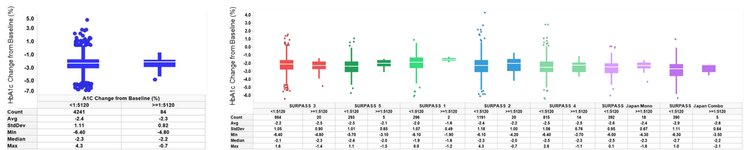
Disclosures:
BC, GM, MEH, YGL, GA, SU, KS, JNB, RFM, and KB are employees and stockholders of Eli Lilly and Company.

Efficacy Results: HbA1c change from baseline was not affected by ADA status or titer

HbA1c change from baseline (%) by ADA status



HbA1c change from baseline for tirzepatide-treated patients with ADA titer <1:5120 vs ≥1:5120



Boxplot. The median is indicated by horizontal line in the central box.

Safety Results

HYPERSENSITIVITY REACTIONS

	Hypersensitivity reactions - n (%)			
TE ADA Status	TZP 5 mg (N=1701)	TZP 10 mg (N=1702)	TZP 15 mg (N=1716)	TZP All (N=5119)
TE ADA+	32 (1.88)	31 (1.82)	43 (2.51)	106 (2.07)
TE ADA-	26 (1.53)	26 (1.53)	21 (1.22)	73 (1.43)

- The events in TE ADA+ patients were mostly mild to moderate in severity.
- The majority of reactions first occurred within 16 weeks of receiving tirzepatide and resolved independent of TE ADA status or titer.
- No anaphylactic reactions were observed in tirzepatide-treated patients.

INJECTION SITE REACTIONS

	Injection site reactions - n (%)			
TE ADA Status	TZP 5 mg (N=1701)	TZP 10 mg (N=1702)	TZP 15 mg (N=1716)	TZP All (N=5119)
TE ADA+	25 (1.47)	38 (2.23)	56 (3.26)	119 (2.32)
TE ADA-	7 (0.41)	7 (0.41)	4 (0.23)	18 (0.35)
Not evaluable	1 (0.06)	1 (0.06)	0	2 (0.04)

- All events were nonserious and nonsevere.
- The majority of reactions first occurred within 16 weeks of receiving tirzepatide and resolved irrespective of TE ADA status or titer level.

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ADA 2022

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American Diabetes Association - 82nd Annual Scientific Sessions; New Orleans, LA, USA; 3 – 7 June 2022

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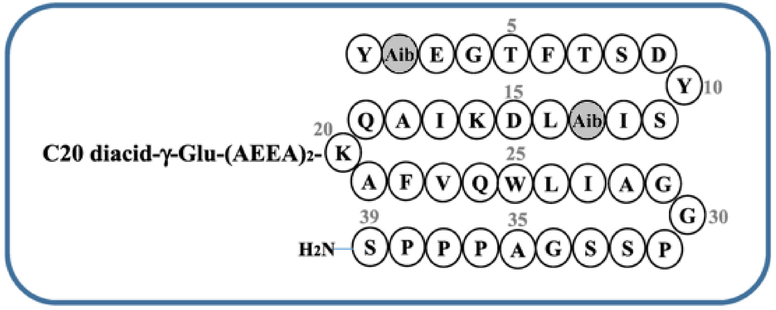

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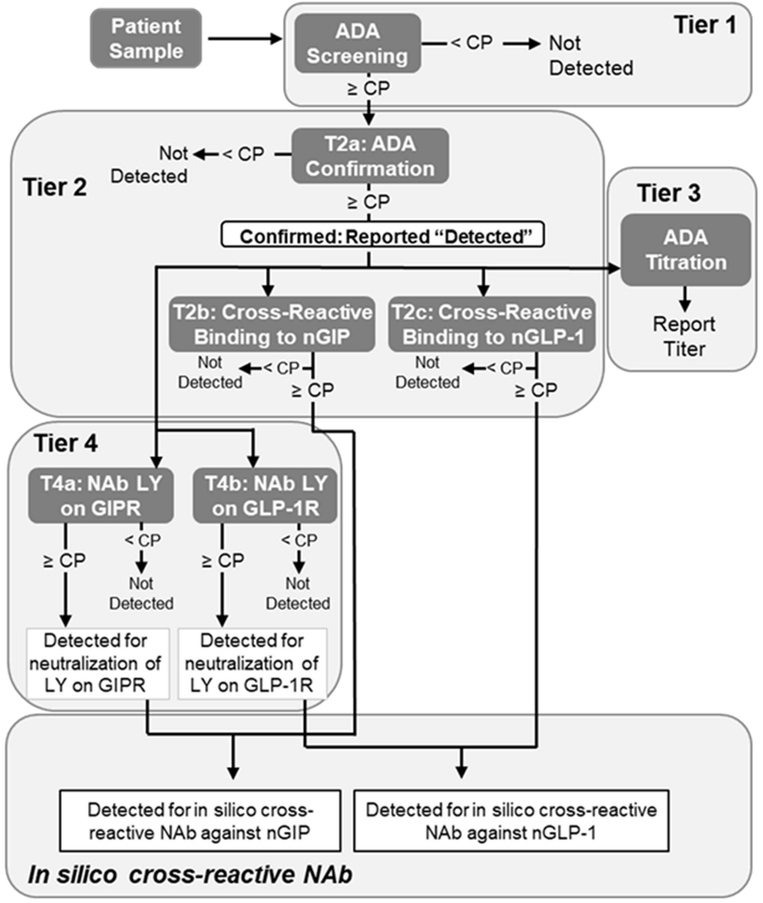

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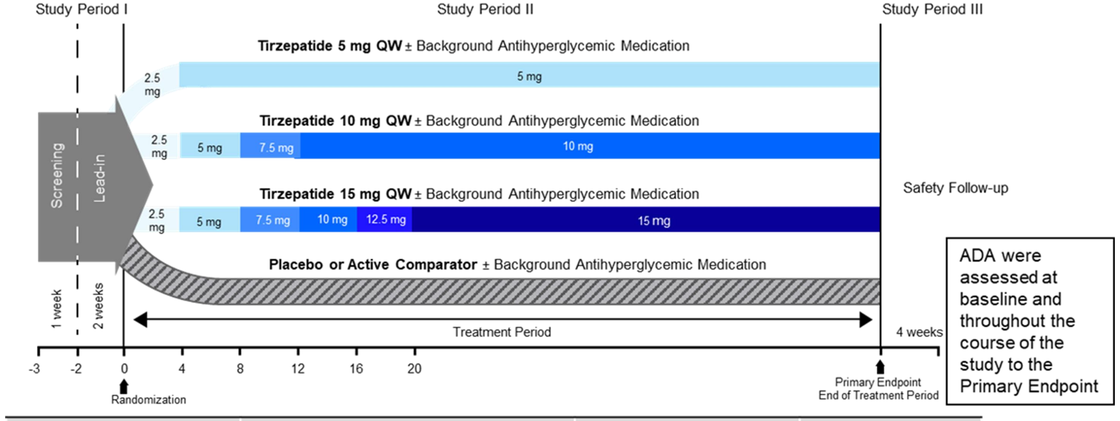

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KEY RESULT

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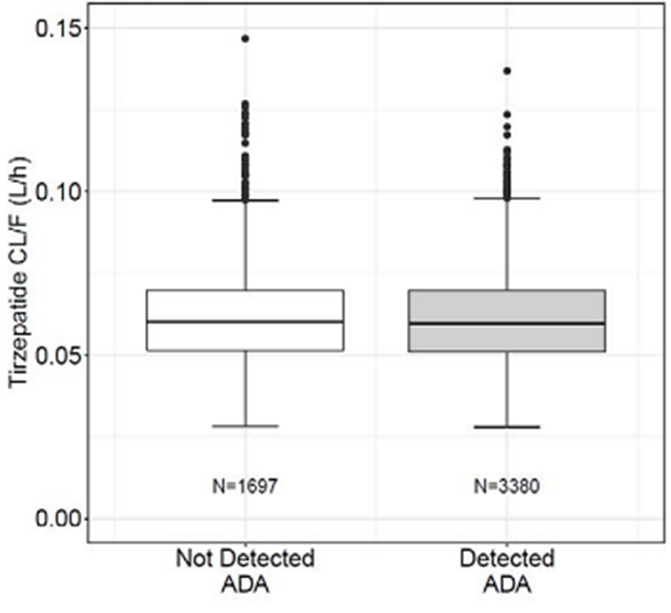
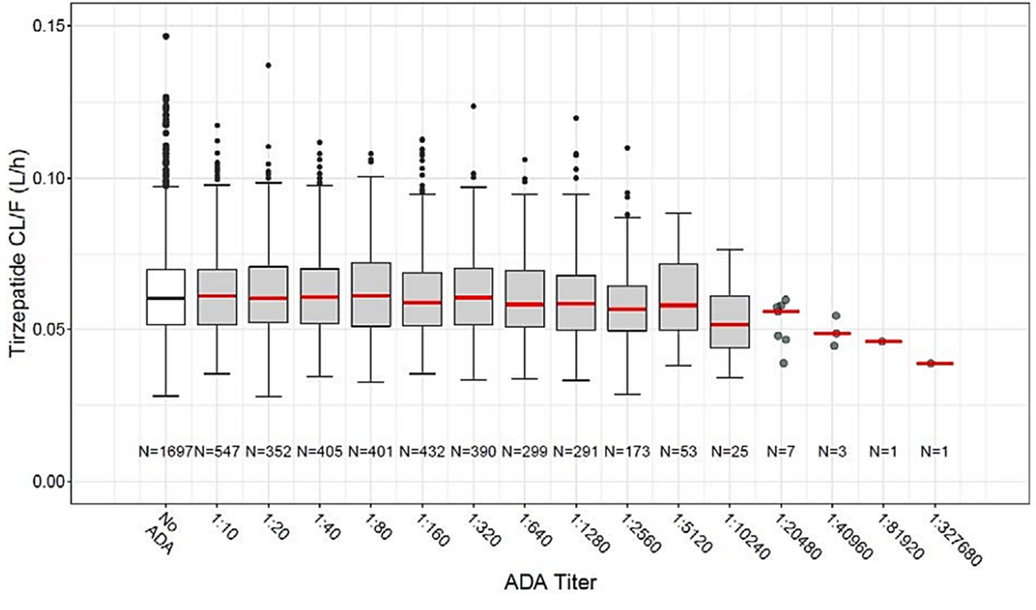
Pharmacokinetic Results: Tirzepatide clearance was not affected by ADA status or titer

Tirzepatide clearance by ADA status and titer

ADA Status



ADA Titer



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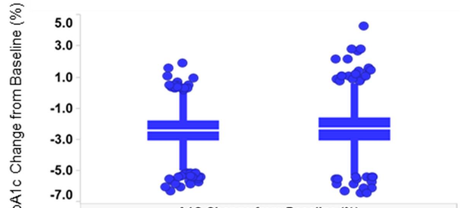
Efficacy Results: HbA1c change from baseline was not affected by ADA status or titer

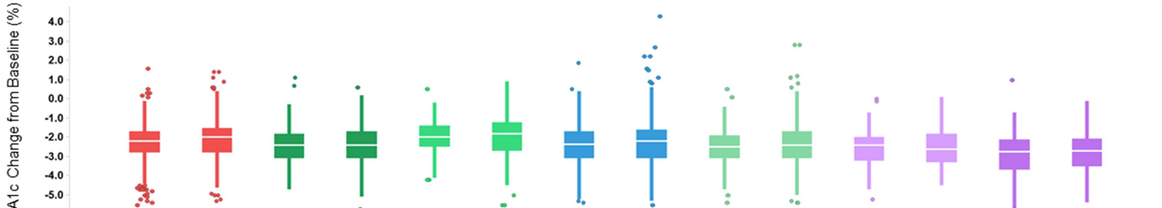
HbA1c change from baseline (%) by ADA status

Combined Analysis



A1C Change from Baseline (%)	TE ADA+	TE ADA-
Count	2395	1930
Avg	-2.5	-2.3
StdDev	1.03	1.18
Min	-6.30	-6.40
Median	-2.4	-2.3
Max	1.9	4.3

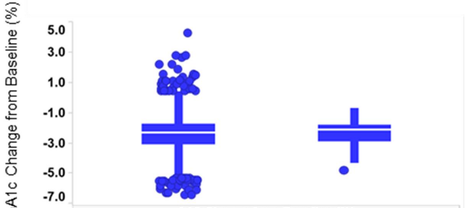
Subgroup Analysis by Study



	SURPASS 3		SURPASS 5		SURPASS 1		SURPASS 2		SURPASS 4		SURPASS Japan Mono		SURPASS Japan Combo	
	TE ADA+	TE ADA-	TE ADA+	TE ADA-	TE ADA+	TE ADA-	TE ADA+	TE ADA-	TE ADA+	TE ADA-	TE ADA+	TE ADA-	TE ADA+	TE ADA-
Count	486	398	169	129	164	134	660	551	368	461	304	106	244	151
Avg	-2.3	-2.1	-2.5	-2.5	-2.0	-2.0	-2.4	-2.3	-2.5	-2.4	-2.6	-2.6	-2.9	-2.8
StdDev	1.01	1.08	0.93	1.10	0.90	1.24	1.08	1.28	0.90	1.16	0.93	0.97	1.14	1.05
Min	-5.50	-6.40	-4.70	-5.70	-6.00	-6.10	-5.80	-6.10	-5.40	-6.40	-6.00	-4.50	-6.30	-5.80
Median	-2.2	-2.0	-2.4	-2.4	-2.0	-1.8	-2.4	-2.2	-2.5	-2.4	-2.4	-2.6	-2.8	-2.7
Max	1.6	1.4	1.1	0.6	0.5	0.9	1.9	4.3	0.5	2.8	0.0	0.1	1.0	-0.1

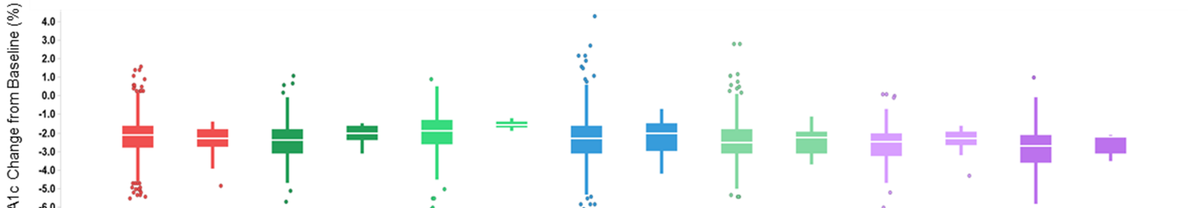
HbA1c change from baseline for tirzepatide-treated patients with ADA titer <1:5120 vs ≥1:5120

Combined Analysis



A1C Change from Baseline (%)	<1:5120	>=1:5120
Count	4241	84
Avg	-2.4	-2.3
StdDev	1.11	0.82
Min	-6.40	-4.80
Median	-2.3	-2.2
Max	4.3	-0.7

Subgroup Analysis by Study



	SURPASS 3		SURPASS 5		SURPASS 1		SURPASS 2		SURPASS 4		SURPASS Japan Mono		SURPASS Japan Combo	
	<1:5120	>=1:5120	<1:5120	>=1:5120	<1:5120	>=1:5120	<1:5120	>=1:5120	<1:5120	>=1:5120	<1:5120	>=1:5120	<1:5120	>=1:5120
Count	864	20	293	5	296	2	1191	20	815	14	392	18	390	5
Avg	-2.2	-2.5	-2.5	-2.1	-2.0	-1.6	-2.4	-2.2	-2.5	-2.5	-2.6	-2.4	-2.9	-2.6
StdDev	1.05	0.90	1.01	0.65	1.07	0.49	1.18	1.00	1.06	0.76	0.95	0.67	1.11	0.64
Min	-6.40	-4.80	-5.70	-3.10	-6.10	-1.90	-6.10	-4.20	-6.40	-3.70	-6.00	-4.30	-6.30	-3.50
Median	-2.1	-2.3	-2.4	-2.0	-1.9	-1.6	-2.3	-2.0	-2.5	-2.3	-2.5	-2.3	-2.7	-2.2
Max	1.6	-1.4	1.1	-1.5	0.9	-1.2	4.3	-0.7	2.8	-1.1	0.1	+1.6	1.0	-2.1

Boxplot. The median is indicated by horizontal line in the central box. Abbreviations: ADA = anti-drug antibodies; HbA1c = glycated hemoglobin; N= number of patients.

Safety Results

HYPERSENSITIVITY REACTIONS

	Hypersensitivity reactions - n (%)			
TE ADA Status	**TZP 5 mg (N=1701)**	**TZP 10 mg (N=1702)**	**TZP 15 mg (N=1716)**	**TZP All (N=5119)**
TE ADA+	32 (1.88)	31 (1.82)	43 (2.51)	106 (2.07)
TE ADA-	26 (1.53)	26 (1.53)	21 (1.22)	73 (1.43)

- The events in TE ADA+ patients were mostly mild to moderate in severity.
- The majority of reactions first occurred within 16 weeks of receiving tirzepatide and resolved independent of TE ADA status or titer.
- No anaphylactic reactions were observed in tirzepatide-treated patients.

INJECTION SITE REACTIONS

	Injection site reactions - n (%)			
TE ADA Status	**TZP 5 mg (N=1701)**	**TZP 10 mg (N=1702)**	**TZP 15 mg (N=1716)**	**TZP All (N=5119)**
TE ADA+	25 (1.47)	38 (2.23)	56 (3.26)	119 (2.32)
TE ADA-	7 (0.41)	7 (0.41)	4 (0.23)	18 (0.35)
Not evaluable	1 (0.06)	1 (0.06)	0	2 (0.04)

- All events were nonserious and nonsevere.
- The majority of reactions first occurred within 16 weeks of receiving tirzepatide and resolved irrespective of TE ADA status or titer level.

Abbreviations: ADA = anti-drug antibodies; N= number of patients; TE = treatment emergent; TZP = tirzepatide.

CONCLUSIONS

- Across seven Phase 3 clinical studies, approximately 50% of tirzepatide-treated patients developed TE ADA.
- Tirzepatide pharmacokinetic profile was not affected by ADA status or ADA titer.
- TE ADA status or titer had no discernible impact on HbA1c change from baseline at endpoint.
- More tirzepatide-treated patients who developed ADA experienced hypersensitivity or injection site reactions than those who did not develop ADA.
- No pattern was detected between the time of the hypersensitivity or injection site reaction event reporting and ADA status, and the events resolved irrespective of ADA status.
- NAb status assessment on the low sample size showed no visual clinical impact on PK, efficacy, or safety profile.
- **Overall, immunogenicity was not associated with any impact on tirzepatide PK, efficacy, or safety.**

Disclosures

BC, **GM**, **MEH**, **YGL**, **GA**, **SU**, **KS**, **JNB**, **RFM**, and **KB** are employees and stockholders of Eli Lilly and Company.

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