749-P

Tirzepatide as an Add-on for Participants With Inadequate Glycemic Control Using Basal Insulin: Pooled Subgroup Analysis of SURPASS-5 and -6

Harpreet S. Bajaj[1], Liana K. Billings[2], Joshua A. Levine[3], Angel Rodriguez[3], Hiren Patel[3]

[1]LMC, Diabetes and Endocrinology, Brampton, Canada, [2]Department of Medicine, NorthShore University Health System/Endeavor Health/University of Chicago Pritzker School of Medicine, Skokie, USA, [3]Eli Lilly and Company, Indianapolis, USA

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OBJECTIVE

- In a post hoc analysis, to investigate the use of tirzepatide in participants with T2D on basal insulin with inadequate glycemic control, by subgroups of baseline age, T2D duration (duration of type 2 diabetes [DoD]), baseline HbA1c, and insulin dose using pooled data from SURPASS-5 and -6 studies

CONCLUSIONS

- In this post hoc analysis of SURPASS -5 and -6 trials in participants with T2D and inadequate glycemic control with basal insulin:
  - Tirzepatide treatment was associated with significantly and consistently improved HbA1c and weight loss across different baseline subgroups
  - Risk of clinically significant hypoglycemia (levels 2 and 3) was higher in trial participants from certain subgroups across all tirzepatide doses (baseline HbA1c >8.5% vs. ≤8.5%, insulin dose ≥50 IU/day vs. <50 IU/day)

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BACKGROUND

- Tirzepatide is a long-acting glucose-dependent insulinotropic polypeptide receptor and glucagon-like peptide-1 receptor agonist and is approved for the treatment of people with type 2 diabetes (T2D)[1] and obesity[2]
- In the SURPASS-5 and -6 trials, tirzepatide added to basal insulin significantly improved glycemic control vs. comparators in participants with T2D with inadequate glycemic control:
  - In SURPASS-5, mean change from baseline for glycated hemoglobin (HbA1c) at Week 40 was -2.1% for tirzepatide 5 mg, -2.4% for tirzepatide 10 mg, and -2.3% for tirzepatide 15 mg vs. -0.9% for placebo (PBO) (all p<0.001 vs. PBO)[3]
  - In SURPASS-6, mean change from baseline for HbA1c at Week 52 was -2.1% vs. -1.1% with insulin lispro 3 times daily for pooled tirzepatide, -1.9% for tirzepatide 5 mg, -2.2% for tirzepatide 10 mg, and -2.3% for tirzepatide 15 mg (p<0.001)[4]

SURPASS-5 AND -6 STUDY DESIGN

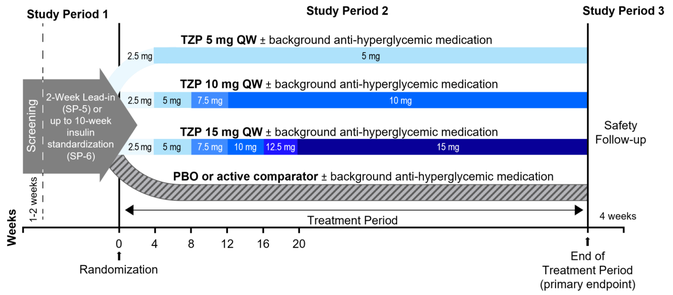
Key Eligibility Criteria

SURPASS-5

- Adults with T2D with baseline HbA1c 7.0-10.5% inclusive
- Body mass index (BMI) of ≥23 kg/m^2
- Receiving stable doses of once-daily insulin glargine (>20 IU/day or >0.25 IU/kg/day) with or without metformin (≥1500 mg/day)

SURPASS-6

- Adults with T2D with baseline HbA1c 7.5-11.0%
- BMI of 23-45 kg/m^2
- Receiving stable doses of basal insulin with or without any combination of up to 2 of the following: metformin ≥1500 mg/day, sulfonylurea, or dipeptidyl peptidase-4 inhibitors

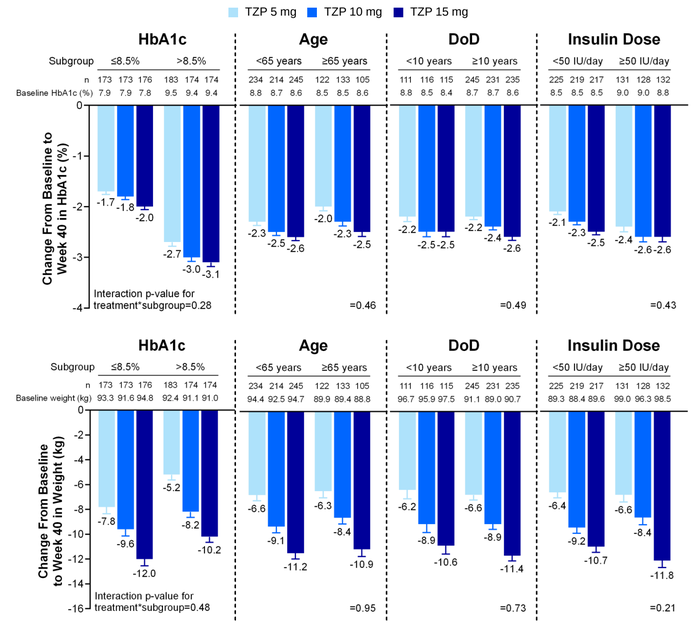


- Targets for basal insulin dose titration were ≤100 mg/dL (SURPASS-5) and 125 mg/dL (SURPASS-6)

Trial	(Sample Size); Randomization Ratio; Background Glucose-Lowering Therapy	Comparator	Primary Endpoint
SURPASS-5	(N=475); 1:1:1:1; Add-on to titrated iGlar ± metformin	PBO QW	Week 40
SURPASS-6	(N=1428); 1:1:1:3; Add-on to iGlar (100 IU/mL) ± metformin	iLispro TID	Week 52

KEY RESULTS

Tirzepatide Was Associated With Significant and Consistent Reduction of HbA1c and Weight at Week 40 Across All Baseline Subgroups



Notes: Includes all participants randomized to TZP and in the Efficacy Analysis Set (excluding data after rescue or discontinuation of study drug). Data are from an MMRM with model terms: baseline + study identifier + sex + age + treatment + time + treatment*time interaction.

Methods

Post Hoc Analysis

- A post hoc analysis of SURPASS-5 and -6 participants treated with tirzepatide using titrated insulin glargine with or without metformin, by subgroups defined by the following baseline characteristics:

HbA1c (≤8.5%, >8.5%) | **Age (<65 years, ≥65 years)** | **DoD (<10 years, ≥10 years)** | **Insulin dose (<50 IU/day, ≥50 IU/day)**

Data were pooled for SURPASS-5 and -6 up to Week 40

Statistical Analysis

- Mixed model for repeated measures was utilized with a modified intent-to-treat population,[a] adjusting for the baseline covariates of study, age, sex, treatment, time, and treatment*time interaction
- Incidence of clinically significant hypoglycemia (severe hypoglycemia or blood glucose <54 mg/dL) was summarized using descriptive statistics

[a]Includes all participants randomized to tirzepatide and in the Efficacy Analysis Set (excluding data after rescue or discontinuation of study drug).

Results

Baseline Demographics and Clinical Characteristics

Characteristic	Pooled TZP 5 mg, 10 mg, and 15 mg Groups							
	HbA1c ≤8.5% (n=530)	HbA1c >8.5% (n=541)	Age <65 Years (n=702)	Age ≥65 Years (n=370)	DoD <10 Years (n=350)	DoD ≥10 Years (n=722)	Insulin Dose <50 IU/day (n=677)	Insulin Dose ≥50 IU/day (n=394)
Age, years	60.2 (9.9)	58.5 (9.8)	53.9 (7.5)	69.6 (3.9)	55.8 (10.6)	61.1 (9.0)	60.2 (9.9)	57.8 (9.6)
Female, n (%)	273 (51.5)	309 (57.1)	383 (54.6)	200 (54.1)	171 (48.9)	412 (57.1)	377 (55.7)	206 (52.3)
Body weight, kg	93.2 (20.3)	91.4 (19.0)	93.9 (20.1)	89.2 (18.5)	96.6 (20.5)	90.2 (19.0)	89.0 (19.2)	98.0 (19.2)
BMI, kg/m^2	33.4 (5.7)	33.3 (5.5)	33.7 (5.7)	32.8 (5.3)	34.4 (5.7)	32.8 (5.5)	32.4 (5.6)	34.9 (5.2)
DoD, years	13.5 (7.3)	13.6 (7.2)	12.3 (6.7)	15.8 (7.6)	6.0 (2.4)	17.2 (5.9)	13.4 (7.5)	13.8 (6.9)
HbA1c, %	7.8 (0.5)	9.4 (0.7)	8.7 (1.0)	8.5 (1.0)	8.6 (1.0)	8.7 (1.0)	8.5 (0.9)	8.9 (1.0)
FSG, mg/dL	140.8 (43.6)	178.0 (59.5)	161.8 (56.3)	155.2 (53.4)	163.9 (51.9)	157.4 (56.9)	156.5 (52.2)	164.8 (60.4)
iGlar daily dose, IU/day, median (range)	40 (17-152)	45 (12-268)	44 (16-268)	40 (12-164)	40 (20-106)	43 (12-268)	34 (12-49)	63 (50-268)

Note: Data are shown as mean (SD) unless stated otherwise.

Clinically Significant Hypoglycemia Reported for Tirzepatide-Treated Participants by Baseline Subgroup

- Risk of clinically significant hypoglycemia (levels 2 and 3) was consistently higher in subgroups with baseline HbA1c >8.5% vs. ≤8.5% and insulin dose ≥50 IU/day vs. <50 IU/day across all tirzepatide doses

Proportion of Participants With Clinically Significant Hypoglycemia (Levels 2 and 3),[a] %	TZP 5 mg	TZP 10 mg	TZP 15 mg	TZP Pooled
HbA1c ≤8.5% (n=530)	11.0	11.4	9.9	10.8
HbA1c >8.5% (n=541)	14.5	12.8	12.6	13.3
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Insulin dose ≥50 IU/day (n=394)	17.4	16.3	14.3	16.0

[a]Severe hypoglycemia or blood glucose <54 mg/dL during Weeks 0-40 (excludes safety follow-up).
Note: Includes all participants randomized to TZP and in the Safety Analysis Set.

References

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Abbreviations

BMI=body mass index; DoD=duration of type 2 diabetes; FSG=fasting serum glucose; HbA1c=glycated hemoglobin; iGlar=insulin glargine; iLispro=insulin lispro; IU=international units; MMRM=mixed model for repeated measures; PBO=placebo; QW=once weekly; SD=standard deviation; SP=SURPASS; T2D=type 2 diabetes; TID=3 times daily; TZP=tirzepatide

Disclosures

H. S. Bajaj has received trial fees paid to his institution by: Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Ionis Pharmaceuticals, Kowa Pharmaceuticals Co. Ltd., Novartis, Novo Nordisk, and Pfizer; **L. K. Billings** has received consulting honoraria from: Bayer Pharmaceuticals, Eli Lilly and Company, Endogenex, Novo Nordisk, Pfizer, Sanofi, and Xeris Pharmaceuticals; **J. A. Levine**, **A. Rodriguez**, and **H. Patel** are employees and shareholders of: Eli Lilly and Company

The analysis for this poster was contributed by Minzhi Liu of Tigermed-BDM Consulting, Inc. and Palash Sharma of Eli Lilly and Company

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Background and Objective

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SURPASS-5 and -6 Study Design

Key Eligibility Criteria

SURPASS-5

- Adults with T2D with baseline HbA1c 7.0-10.5% inclusive
- Body mass index (BMI) of ≥23 kg/m^2
- Receiving stable doses of once-daily insulin glargine (>20 IU/day or >0.25 IU/kg/day) with or without metformin (≥1500 mg/day)

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- Adults with T2D with baseline HbA1c 7.5-11.0%
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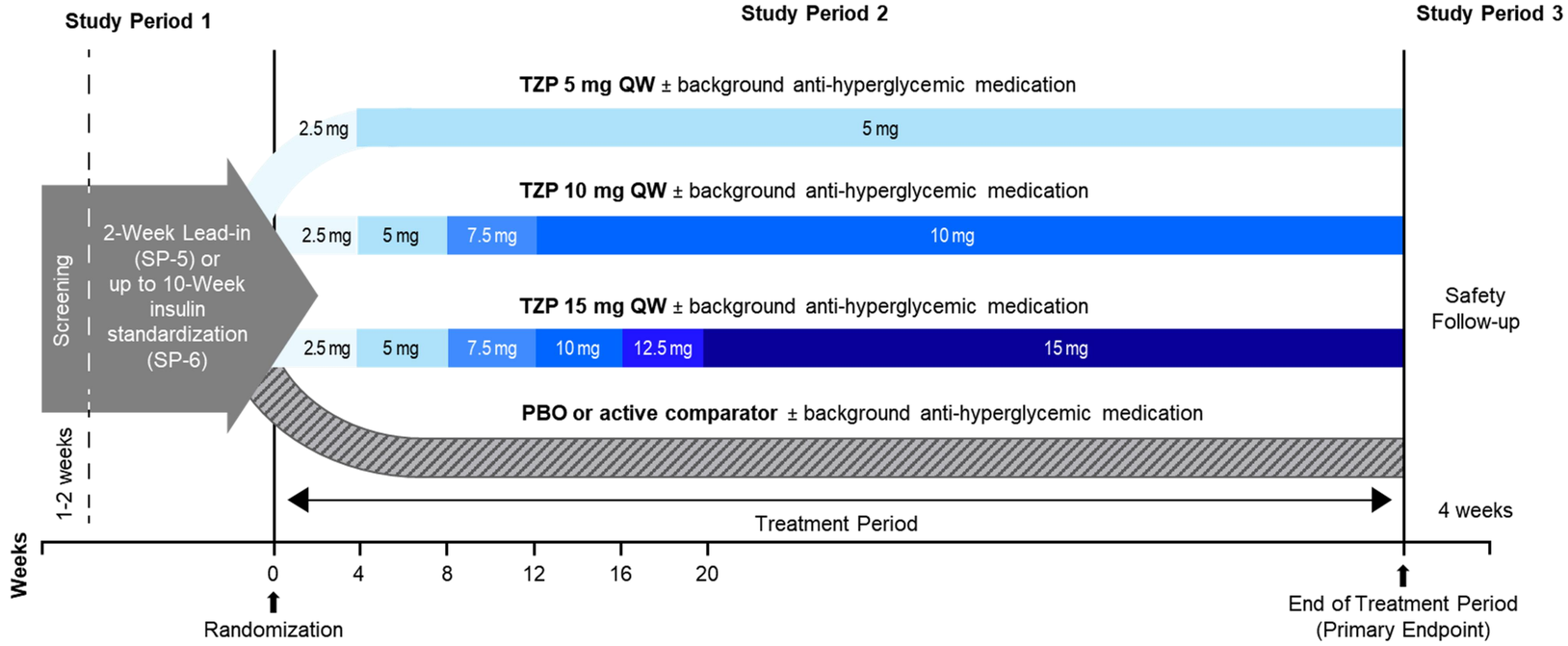

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Baseline Demographics and Clinical Characteristics

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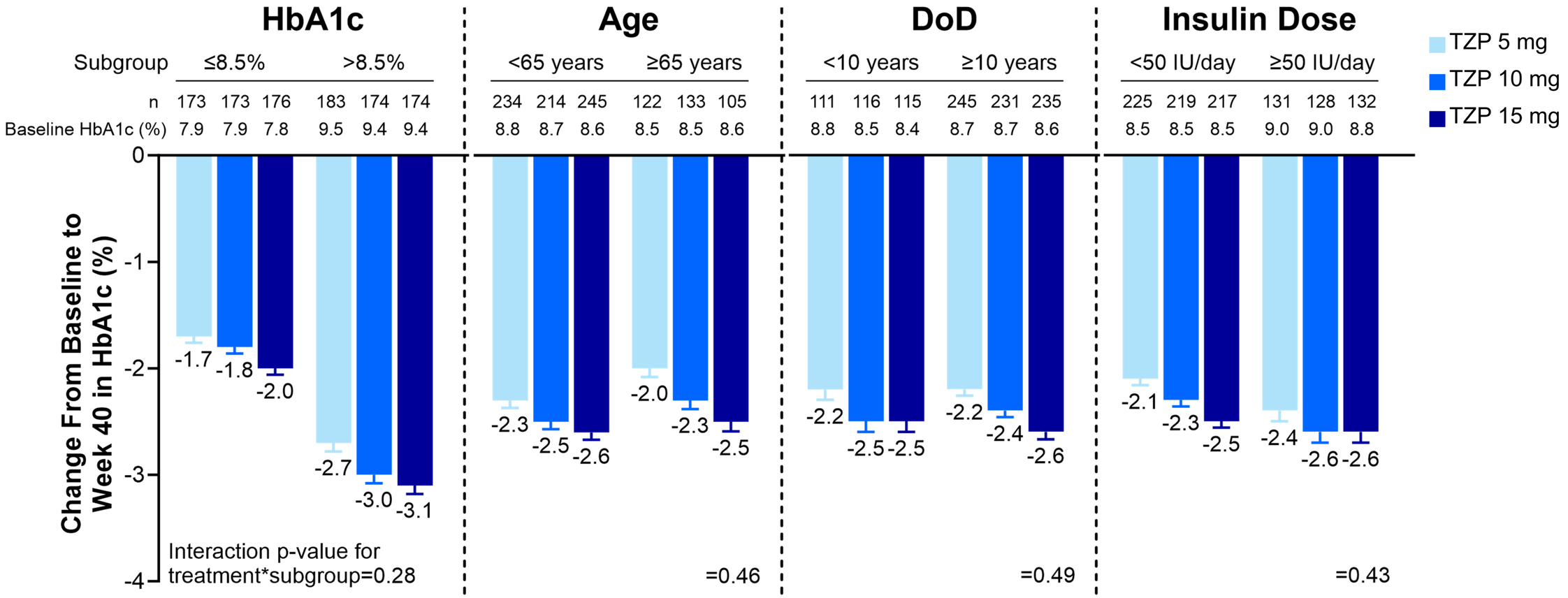
Key Results (1 of 2)
Tirzepatide Was Associated With Significant and Consistent Reduction in HbA1c at Week 40 Across All Baseline Subgroups



Notes: Includes all participants randomized to TZP and in the Efficacy Analysis Set (excluding data after rescue or discontinuation of study drug). Data are from an MMRM with model terms: baseline + study identifier + sex + age + treatment + time + treatment*time interaction.

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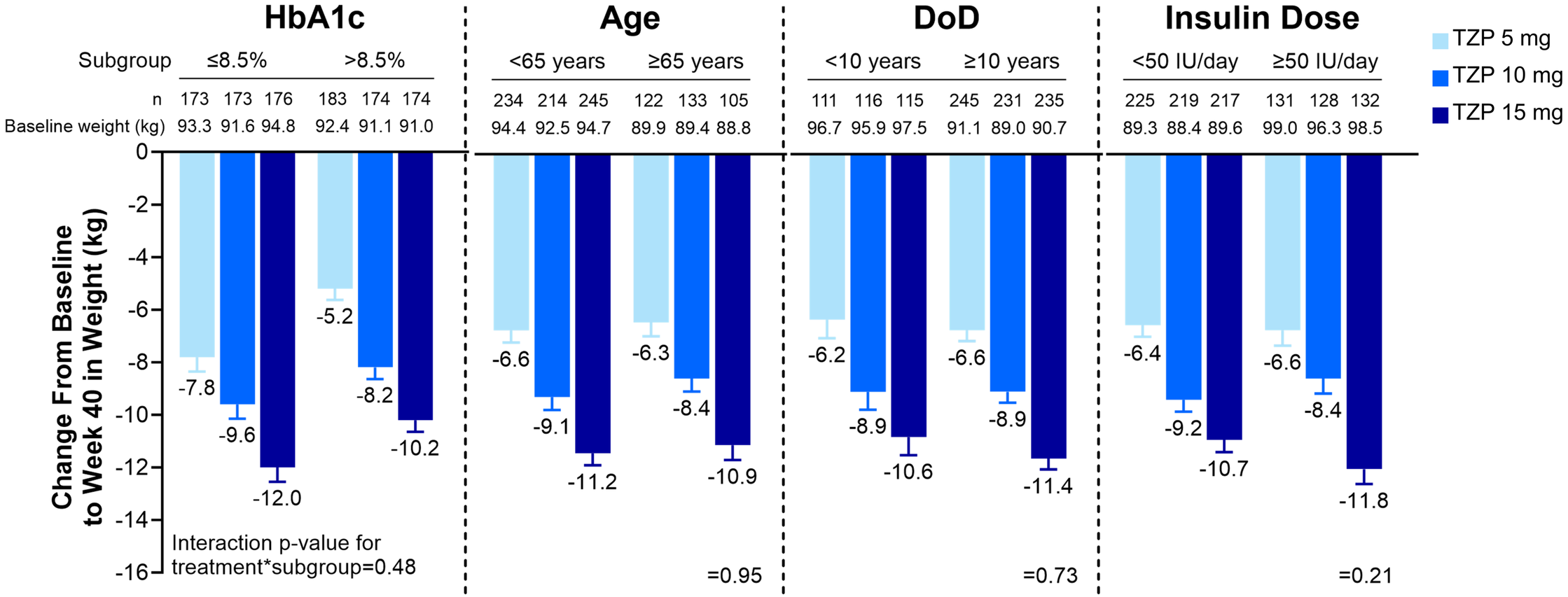
Key Results (2 of 2)
Tirzepatide Was Associated With Significant and Consistent Reduction in Weight at Week 40 Across all Baseline Subgroups



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- Risk of clinically significant hypoglycemia (levels 2 and 3) was consistently higher in subgroups with baseline HbA1c >8.5% vs. ≤8.5% and insulin dose ≥50 IU/day vs. <50 IU/day across all tirzepatide doses

[a]Severe hypoglycemia or blood glucose <54 mg/dL during Weeks 0-40 (excludes safety follow-up).
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DoD=duration of type 2 diabetes; HbA1c=glycated hemoglobin; IU=International units; TZP=tirzepatide.

Conclusions

- In this post hoc analysis of SURPASS -5 and -6 trials in participants with T2D and inadequate glycemic control with basal insulin:
  - Tirzepatide treatment was associated with significantly and consistently improved HbA1c and weight loss across different baseline subgroups
  - Risk of clinically significant hypoglycemia (levels 2 and 3) was higher in trial participants from certain subgroups across all tirzepatide doses (baseline HbA1c >8.5% vs. ≤8.5%, insulin dose ≥50 IU/day vs. <50 IU/day)

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HbA1c=glycated hemoglobin; IU=International units; T2D=type 2 diabetes.

References

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Abbreviations

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- The analysis for this poster was contributed by Minzhi Liu of Tigermed-BDM Consulting, Inc. and Palash Sharma of Eli Lilly and Company
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