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The Cardiovascular Outcomes in Participants on Tirzepatide Versus Dulaglutide of the SURPASS-CVOT

Stephen Nicholls

Monash University, Melbourne, Australia

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Presenter Disclosure

Consultant: Abcentra, Akcea Therapeutics, Amarin, Anthera Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, CSL Behring, CSL Seqirus, Daiichi Sankyo, Eli Lilly & Company, Esperion, Merck, Omthera Pharmaceuticals, Resverlogix, Sanofi-Regeneron, Scribe Therapeutics, Silence Therapeutics, Takeda and Vaxxinity

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Trial Academic Leadership

Academic Executive Committee: Stephen J. Nicholls (Co-Chair; Monash University, Australia), David D'Alessio (Co-Chair; Duke University, USA), Deepak L. Bhatt (Mount Sinai, USA), John B. Buse (UNC School of Medicine, USA), Stefano Del Prato (University of Pisa School of Medicine, Italy), Steven E. Kahn (UW Medicine Diabetes Institute, USA), A. Michael Lincoff (Cleveland Clinic, USA), Darren K. McGuire (UT Southwestern Medical Center, USA), Michael A. Nauck (Katholisches Klinkum Bochum, Germany), Steven E. Nissen (Cleveland Clinic, USA), Naveed Sattar (University of Glasgow, UK), Bernard Zinman (Lunenfeld-Tanenbaum Research Institute, Canada), Sophia Zoungas (Monash University, Australia)

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Background

- Tirzepatide, a dual GLP-1 and GIP receptor agonist,¹ has been shown to improve glycaemic control and promote weight loss when compared with selective GLP-1 receptor agonists^{2,3}
- Benefits of tirzepatide have also been observed for atherogenic lipoproteins, blood pressure, high sensitivity C-reactive protein and kidney function in comparison with selective GLP-1 receptor agonists or basal insulins³⁻⁷
- The SURPASS-CVOT trial used an active comparator known to reduce cardiovascular events to determine the CV outcome benefits for tirzepatide compared with dulaglutide in a high-risk population with type 2 diabetes

1. Nauck MA, D'Alessio DA. *Cardiovasc Diabetol*. 2022;21:169. 2. Frias JP, et al. *Lancet*. 2018;392:2180–2193. 3. Frias JP, et al. *N Engl J Med*. 2021;385:503–515. 4. Ludvik B, et al. *Lancet*. 2021;398:583–598. 5. Del Prato S, et al. *Lancet*. 2021;398:1811–1824. 6. Heerspink HJL, et al. *Lancet Diab Endocrinol*. 2022;10:774–785. 7. Bhatt DL, et al. *Circulation*. 2023;148:Suppl_1 (Abstract 16779).

Abbreviations: *GIP=glucose-dependent insulinotropic polypeptide; GLP-1 RA=glucagon-like peptide-1 receptor agonist.*

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Source:

References:

1. Nauck MA, D'Alessio DA. Tirzepatide, a dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regarding glycaemic control and body weight reduction. *Cardiovasc Diabetol* 2022;21(1):169.
2. Frias JP , Nauck MA , Van J , et al . Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet* 2018;392:2180–93.
3. Frias JP , Davies MJ , Rosenstock J , et al . Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 2021;385:503–15.

4. Ludvik B , Giorgino F , Jódar E , et al . Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without sodium-glucose co-transporter-2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet* 2021;398:583–98.
5. Del Prato S , Kahn SE , Pavo I , et al . Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. *Lancet* 2021;398:1811–24.
6. Heerspink HJL , Sattar N , Pavo I , et al . Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial. *Lancet Diab Endocrinol* 2022;10:774–85.
7. Bhatt DL, et al. *Circulation*. 2023;148:Suppl_1 (Abstract 16779).

Primary Objective

- To assess the efficacy of tirzepatide compared with dulaglutide on time to first occurrence of the composite endpoint of death from cardiovascular causes, myocardial infarction or stroke when added to standard of care in participants with type 2 diabetes and established atherosclerotic cardiovascular disease
- The primary objective was to initially determine non-inferiority of tirzepatide compared with dulaglutide on the primary end point and then to determine potential superiority of tirzepatide compared with dulaglutide

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Key Secondary Objectives

- To assess the superiority of tirzepatide compared with dulaglutide for:
 - Time to first occurrence of the expanded composite outcome of cardiovascular death, myocardial infarction, stroke, or coronary revascularisation
 - Time to first occurrence of cardiovascular death or heart failure event requiring hospitalisation and/or urgent heart failure visit
 - Time to cardiovascular death
 - Time to all-cause death
 - Change from baseline to 36 months in estimated glomerular filtration rate (eGFR) (CKD-EPI Creatinine-Cystatin Equation 2021) in participants with high-risk chronic kidney disease^a

^aDefined by Kidney Disease Improving Global Outcomes (KDIGO) Guideline 2025 as having at baseline: (1) eGFR ≥ 60 mL/min/1.73 m² and UACR >300 mg/g; (2) eGFR ≥ 45 to <60 mL/min/1.73 m² and UACR >30 mg/g; or (3) eGFR <45 mL/min/1.73 m².

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Eligibility Criteria

Key Inclusion Criteria

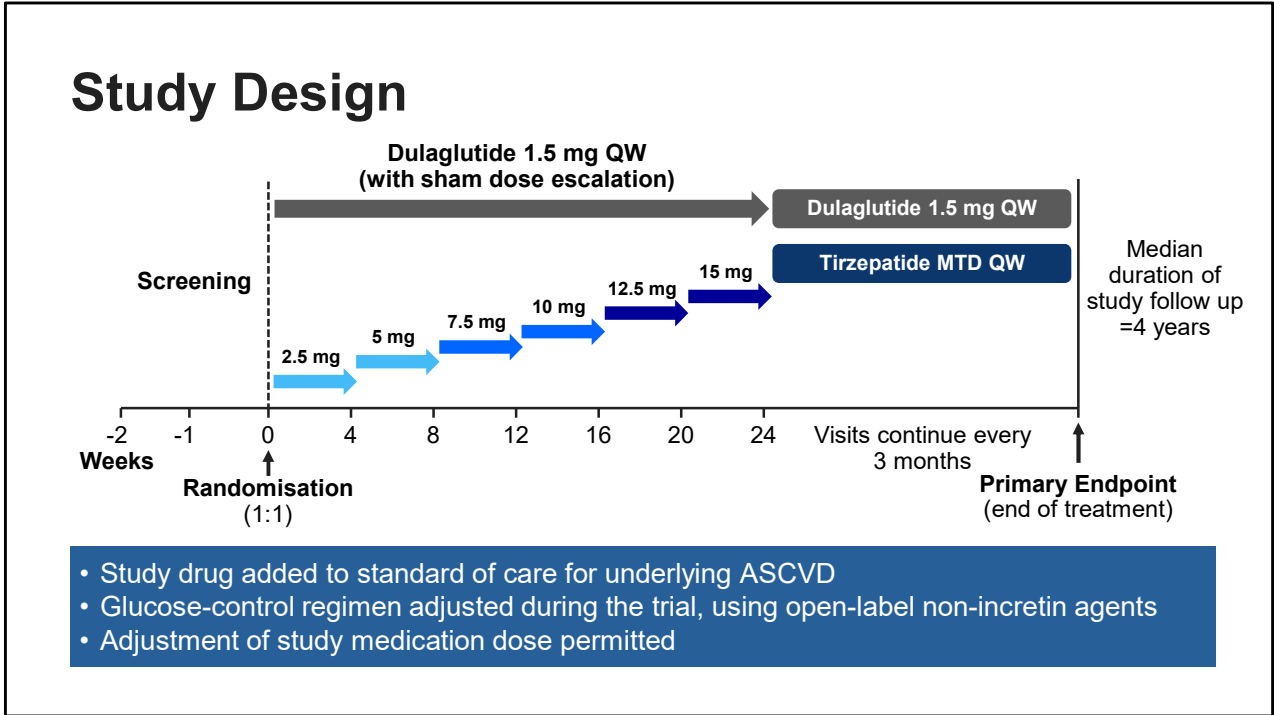
- ≥40 years with diagnosis of type 2 diabetes
- Established atherosclerotic cardiovascular disease, including ≥1 of the following: coronary artery disease, cerebrovascular disease, peripheral artery disease (each as defined per protocol)
- Glycated haemoglobin (HbA1c) ≥7% and ≤10.5% at screening
- Body mass index ≥25 kg/m²

Key Exclusion Criteria

- Type 1 diabetes or uncontrolled diabetes requiring immediate therapy
- ≥1 episode of severe hypoglycaemia and/or hypoglycaemia unawareness within 6 months prior to screening
- Hospitalised for congestive heart failure within the prior 2 months
- Chronic New York Heart Association Functional Classification IV congestive heart failure
- Family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma (MTC) or personal history of nonfamilial MTC
- Treatment with GLP-1 receptor agonist or pramlintide within 3 months prior to Visit 1

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Abbreviations: ASCVD=atherosclerotic cardiovascular disease;
MTD=maximum tolerated dose; QW=once weekly.

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Statistical Analysis

- Non-inferiority to dulaglutide: Upper bound of $<1.05^a$ for the 95.3% confidence interval (CI) for the hazard ratio (HR) of tirzepatide vs. dulaglutide
 - This 1.05 margin ensured tirzepatide superiority to a putative placebo
- Superiority to dulaglutide: Upper bound of <1.00 for the 95.3% CI for the HR of tirzepatide vs. dulaglutide
- Study power was calculated based on the following assumptions:
 - 10.5% relative risk reduction in primary endpoint for non-inferiority
 - 15% relative risk reduction in primary endpoint for superiority
 - Projected dulaglutide group primary endpoint event rate 3.5% per year
- 1616 participants with positively adjudicated primary endpoint (90% power)
- Enrolment of 12,500 participants with ~4 years of follow-up
- Key secondary endpoints tested via graphical approach¹ with separate alpha-spending function, after primary endpoint superiority met

*Chosen to be consistent with guidance requiring that the margin ensures tirzepatide superiority to a putative placebo while preserving $\geq 50\%$ of dulaglutide vs. placebo efficacy.²
1. Maurer W, Bretz F. *Stats Biopharm Res.* 2013;5:11-320. 2. McGuire DK, et al. *Cardiovasc Diabetol.* 2022;21:163.

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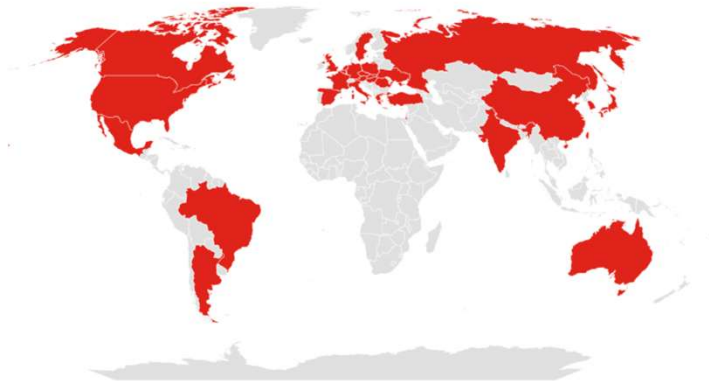
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Source:

1. Maurer W, Bretz F. *Stats Biopharm Res.* 2013;5:11-320.
2. McGuire DK, et al. *Cardiovasc Diabetol.* 2022;21(1):163.

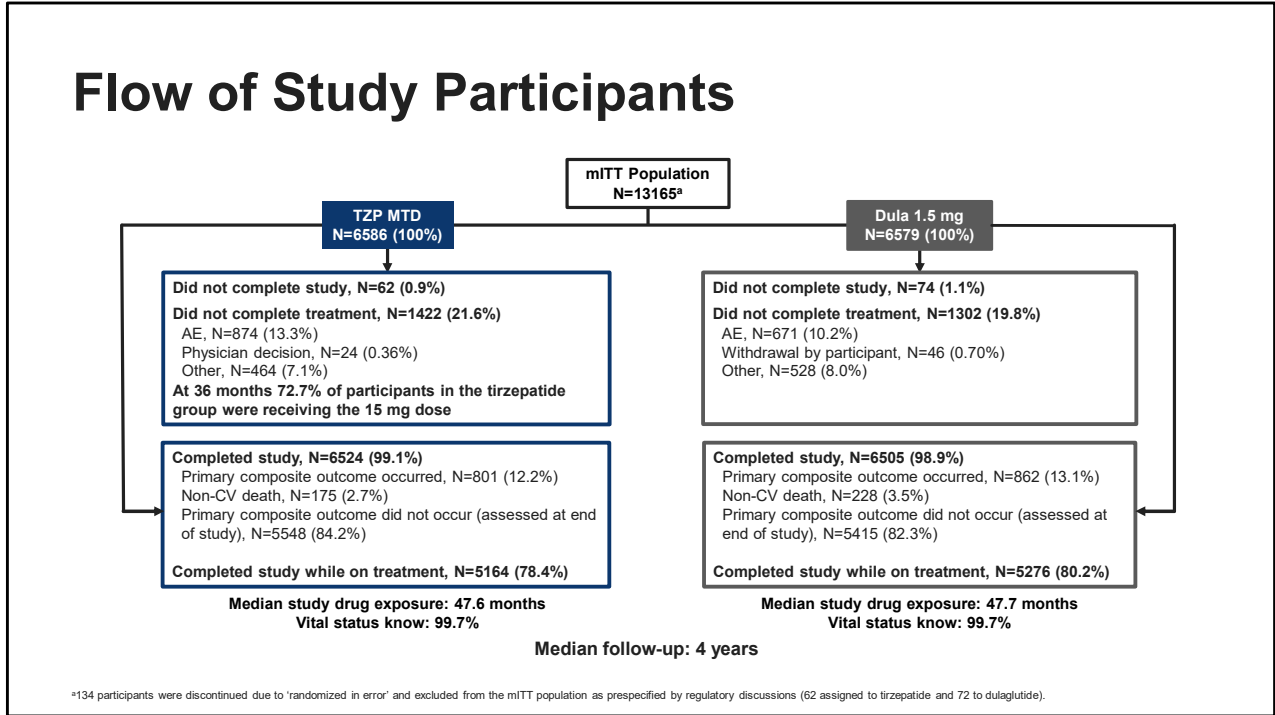
Enrolment

- Enrolment occurred at 640 sites in 30 countries between May 29, 2020 and June 27, 2022



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Abbreviations: AE=adverse event; CV=cardiovascular; Dula=dulaglutide; mITT=modified intention to treat; MTD=maximum tolerated dose; TZP=tirzepatide.

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Baseline Characteristics

Parameter	TZP MTD (N=6586)	Dula 1.5 mg (N=6579)
Age, mean, years	64.0	64.1
Female, %	28.7	29.3
Race, %		
White	81.5	81.4
Asian	8.8	9.1
Native Hawaiian or Other Pacific Islander	0.1	0.1
Ethnicity, %		
Hispanic or Latino	30.2	30.1

Note: Data are from the mITT population.

Abbreviations: *Dula=dulaglutide; mITT=modified intent-to-treat; MTD=maximum tolerated dose; TZP=tirzepatide.*

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Baseline Medication Use

Parameter, %	TZP MTD (N=6586)	Dula 1.5 mg (N=6579)
Statin	86.0	85.6
Antihypertensive medications		
ACE inhibitor	40.3	39.4
ARB	40.0	40.9
Mineralocorticoid receptor antagonist	9.7	9.3
Antihyperglycaemic medications		
Metformin	81.1	81.7
SGLT-2 inhibitor	30.4	30.8
Sulfonylurea	21.3	22.0
DPP-4 inhibitor	5.8	5.7
Thiazolidinedione	2.4	2.7
Alpha-glucosidase inhibitor	1.7	1.6
Insulin	49.4	48.3

Note: Data are from the mITT population.

Abbreviations: : ACE=angiotensin-converting enzyme; ARB=angiotensin II receptor blocker; DPP-4=dipeptidyl peptidase-4; Dula=dulaglutide; mITT=modified intent-to-treat; MTD=maximum tolerated dose; SGLT-2=sodium-glucose co-transporter-2; TZP=tirzepatide.

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Baseline Characteristics and CV Risk Factors

Parameter	TZP MTD (N=6586)	Dula 1.5 mg (N=6579)
ASCVD history, %		
Coronary artery disease	65.1	64.9
Coronary revascularisation	57.0	57.3
Myocardial infarction	47.0	47.4
Peripheral artery disease	25.2	25.4
Prior heart failure	19.9	20.8
Stroke	19.0	19.3
Cardiovascular risk factors		
Weight, mean, kg	92.6	92.5
BMI, mean, kg/m ²	32.6	32.6
Systolic blood pressure, mean, mmHg	135.1	135.5
HbA1c, mean, % (mmol/mol)	8.4 (68.4)	8.4 (68.1)
LDL cholesterol, mean, mg/dL (mmol/L)	80.5 (2.1)	80.7 (2.1)
Triglycerides, median, mg/dL (mmol/L)	160.3 (1.81)	159.4 (1.80)
eGFR, mean, mL/min/1.73 m ²	78.5	79.2
UACR, median, mg/g	22.0	22.0

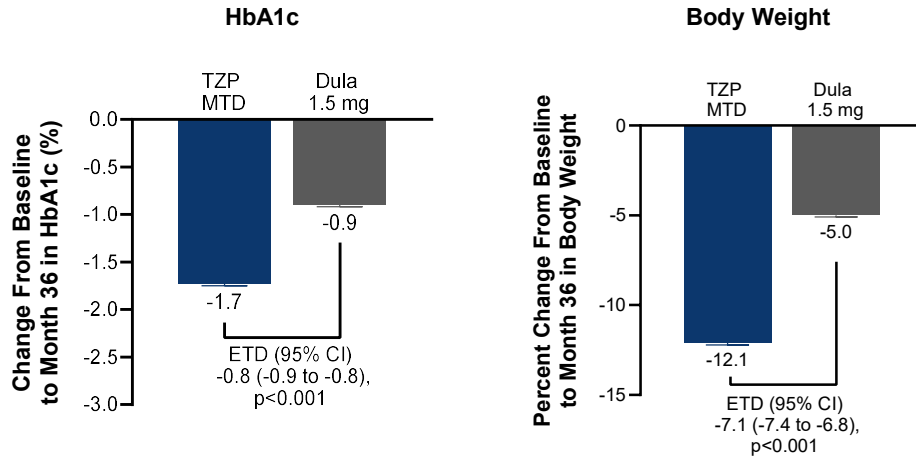
Note: Data are from the mITT population.

Abbreviations: ASCVD=atherosclerotic cardiovascular disease; BMI=body mass index; Dula=dulaglutide; eGFR=estimated glomerular filtration rate; HbA1c=glycated haemoglobin; LDL=low-density lipoprotein; mITT=modified intent-to-treat; MTD=maximum tolerated dose; TZP=tirzepatide; UACR=urinary albumin creatinine ratio.

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Change From Baseline in HbA1c and Weight



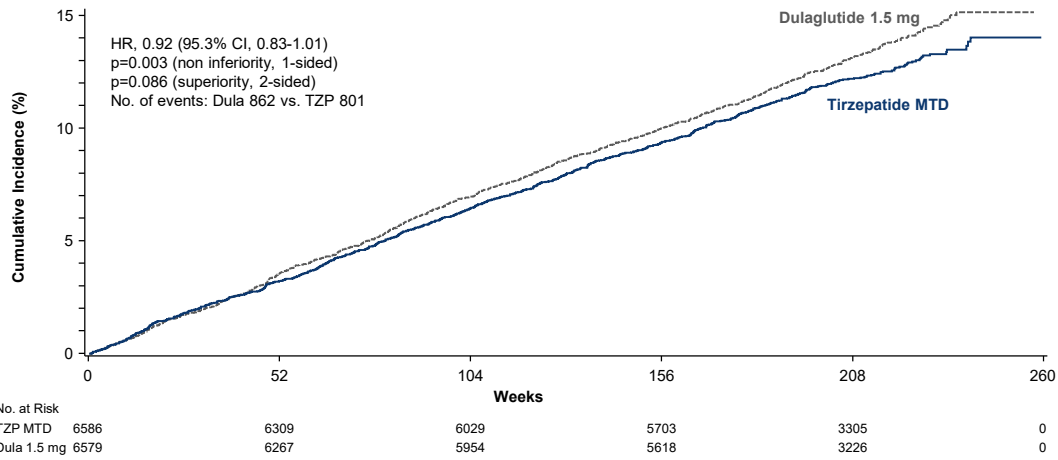
Notes: Data are mean estimates (SE). Change from baseline to Month 36 were analysed using an ANCOVA model with treatment, SGLT-2 inhibitor use at baseline and country as fixed factors and baseline value as a covariate, with multiple imputation of missing values.

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; Dula=dulaglutide; ETD=estimated treatment difference; HbA1c=glycated haemoglobin; MTD=maximum tolerated dose; SE=standard error; SGLT2=sodium-glucose co-transport protein-2; TZP=tirzepatide.

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Primary Endpoint: CV Death, MI or Stroke



Note: HR and 95.3% CI were derived from a Cox proportional hazards model with treatment as a fixed effect, stratified by SGLT-2 inhibitor use at baseline.

Abbreviations: *CI=confidence interval; Dula=dulaglutide; HR=hazard ratio; MI=myocardial infarction; MTD=maximum tolerated dose; SGLT-2=sodium-glucose co-transporter-2; TZP=tirzepatide.*

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Key Secondary Efficacy Endpoints

Outcome	TZP MTD (N=6586)	Dula 1.5 mg (N=6579)	HR (95% CI)
Key Secondary Efficacy Endpoints, % of Participants With Event			
MI	4.7	5.4	0.86 (0.74-1.00)
Stroke	3.5	3.8	0.91 (0.76-1.09)
CV death	5.6	6.2	0.89 (0.77-1.02)
CV death, MI, stroke, coronary revascularisation	16.5	18.5	0.88 (0.81-0.96)
CV death or hospitalisation or urgent visits for HF	7.8	8.5	0.91 (0.81-1.03)
All-cause death	8.6	10.2	0.84 (0.75-0.94)
Outcome	TZP MTD (N=1520)	Dula 1.5 mg (N=1403)	Difference (95% CI)
Key Secondary Endpoint: Change in eGFR in high-risk CKD group^a			
Change from baseline to 36 months in eGFR, mL/min/1.73 m ² , estimate	-5.0	-8.5	3.5 (2.6-4.5)

^aIn participants with high or very high-risk CKD as defined by KDIGO guidelines 2025 definition, identified as having eGFR ≥ 60 mL/min/1.73 m² and UACR >300 mg/g, eGFR 45- <60 mL/min/1.73 m² and UACR >30 mg/g, or eGFR <45 mL/min/1.73 m² at baseline.

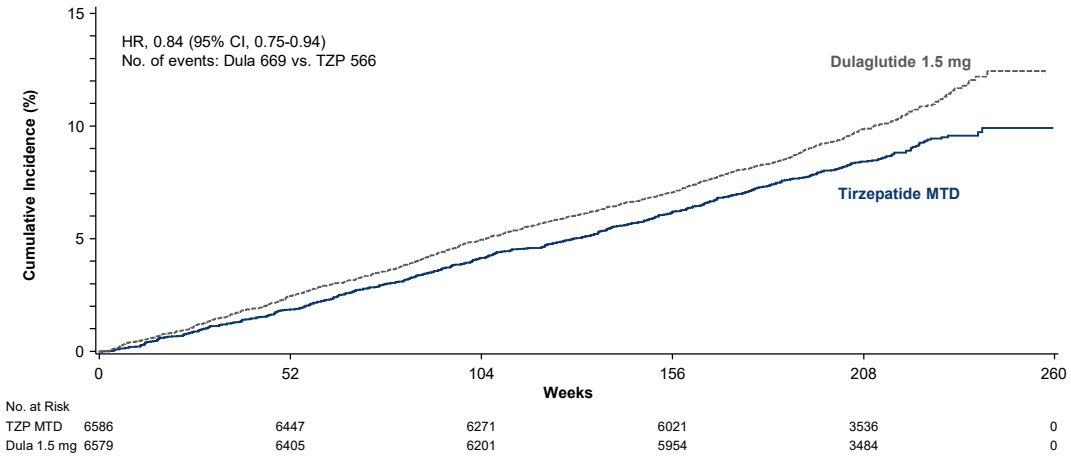
Notes: Data are percentage of participants with event unless stated otherwise. HR and 95% CI were derived from a Cox proportional hazards model with treatment as a fixed effect, stratified by SGLT-2 inhibitor use at baseline. Change from baseline to Month 36 was analysed using an ANCOVA model with treatment, SGLT-2 inhibitor use at baseline, and country as fixed factors and baseline value as a covariate, with multiple imputation of missing values.

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; CKD=chronic kidney disease; CV=cardiovascular; Dula=dulaglutide; eGFR=estimated glomerular filtration rate; HF=heart failure; HR=hazard ratio; MI=myocardial infarction; MTD=maximum tolerated dose; SGLT-2=sodium-glucose co-transporter-2; TZP=tirzepatide; UACR=urinary albumin-to-creatinine ratio.

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All-Cause Mortality



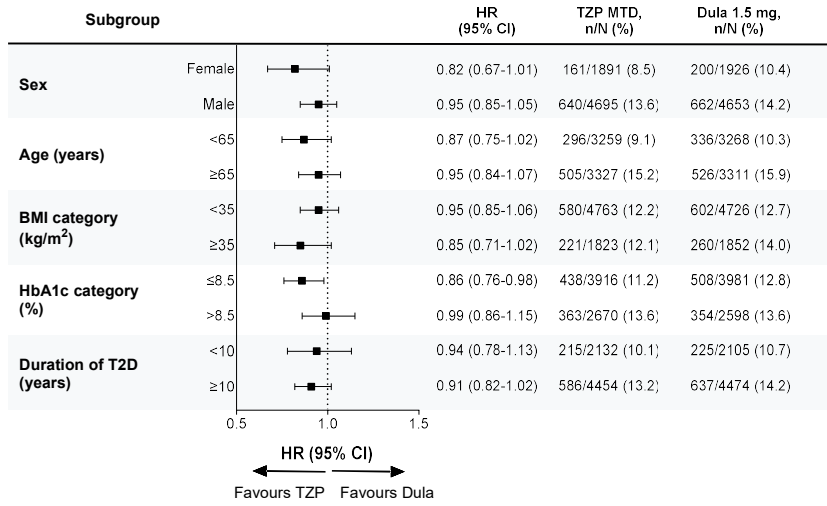
Note: HR and 95% CI were derived from a Cox proportional hazards model with treatment as a fixed effect, stratified by SGLT-2 inhibitor use at baseline.

Abbreviations: *CI=confidence interval; Dula=dulaglutide; HR=hazard ratio; MTD=maximum tolerated dose; SGLT-2=sodium-glucose co-transporter-2; TZP=tirzepatide.*

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Primary Endpoint Subgroup Analysis



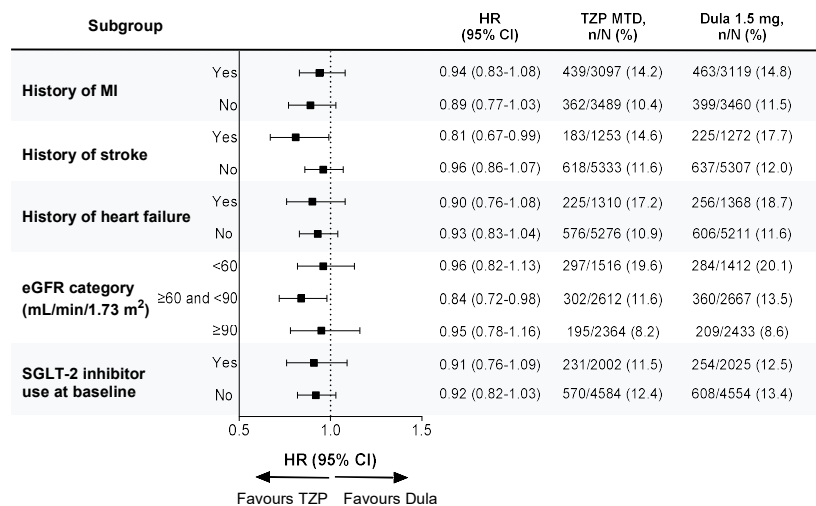
Note: HR and 95% CI were derived from a Cox proportional hazards model with treatment as a fixed effect, stratified by SGLT2 inhibitor use at baseline within each subgroup.

Abbreviations: BMI=body mass index; CI=confidence interval; Dula=dulaglutide; HbA1c=glycated haemoglobin; HR=hazard ratio; MTD=maximum tolerated dose; SGLT2=sodium-glucose co-transporter 2; T2D=type 2 diabetes; TZP=tirzepatide.

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Primary Endpoint Subgroup Analysis (Cont'd)



Notes: HR and 95% CI were derived from a Cox proportional hazards model with treatment as a fixed effect, stratified by SGLT2 inhibitor use at baseline within each subgroup. When analysing SGLT2 inhibitor use as a subgroup, the model was not stratified by SGLT2 inhibitor use.

Abbreviations: CI=confidence interval; Dula=dulaglutide; eGFR=estimated glomerular filtration rate; HR=hazard ratio; MI=myocardial infarction; MTD=maximum tolerated dose; SGLT2=sodium-glucose co-transporter 2; TZP=tirzepatide.

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Safety Overview

Participants, %	TZP MTD (N=6647)	Dula 1.5 mg (N=6647)
Any TEAE	89.6	88.7
SAE ^a	31.8	31.9
AEs leading to study drug discontinuation	18.7	16.7
TEAEs occurring in ≥5% of participants ^b		
Nausea	25.1	22.4
Diarrhoea	24.8	19.1
COVID-19	16.4	16.2
Decreased appetite	17.1	9.7
Constipation	12.7	11.6
Vomiting	11.6	9.7
Dyspepsia	9.9	8.2
Urinary tract infection	7.1	7.5
Dizziness	7.0	6.2
Arthralgia	6.2	6.4
Cataract	5.8	6.1
Back pain	5.7	5.8
Nasopharyngitis	5.7	5.7
Hypertension	4.9	5.9

^aExcluding CV endpoints confirmed by clinical endpoint committee; ^bIn the total group from the safety population.

Abbreviations: *AE=adverse event; Dula=dulaglutide; MTD=maximum tolerated dose; SAE=serious AE; TEAE=treatment-emergent AE; TZP=tirzepatide.*

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Indirect Estimate of Tirzepatide Effect vs. a Putative Placebo Matched Population of REWIND

REWIND (Dula: 1011, PBO: 1044) ^a SURPASS-CVOT (TZP: 6586, Dula: 6579)		Event Rate (n/100pys) ^b	Adjusted HR (95% CI), ^b p-Value	Adjusted Indirect Estimate of TZP MTD vs. PBO HR (95% CI), ^b p-Value
CV death, MI or stroke				
REWIND	PBO	4.47	0.78 (0.61-1.01), 0.06	0.72 (0.55-0.94), 0.02
	Dula 1.5 mg	3.52		
SURPASS-CVOT	Dula 1.5 mg	3.47	0.92 (0.83-1.01), 0.09	
	TZP MTD	3.19		
CV death, MI, stroke, or coronary revascularization				
REWIND	PBO	5.77	0.91 (0.73-1.12), 0.37	0.80 (0.64-1.01), 0.06
	Dula 1.5 mg	5.23		
SURPASS-CVOT	Dula 1.5 mg	5.07	0.88 (0.81-0.96), 0.003	
	TZP MTD	4.47		
CV death				
REWIND	PBO	2.25	0.85 (0.60-1.20), 0.35	0.75 (0.52-1.09), 0.13
	Dula 1.5 mg	1.92		
SURPASS-CVOT	Dula 1.5 mg	1.58	0.88 (0.77-1.02), 0.09	
	TZP MTD	1.40		
All-cause death				
REWIND	PBO	3.87	0.73 (0.55-0.96), 0.03	0.61 (0.45-0.82), 0.001
	Dula 1.5 mg	2.82		
SURPASS-CVOT	Dula 1.5 mg	2.60	0.84 (0.75-0.94), 0.002	
	TZP MTD	2.18		
CV death or HF events				
REWIND	PBO	3.19	0.77 (0.58-1.03), 0.08	0.70 (0.51-0.96), 0.03
	Dula 1.5 mg	2.46		
SURPASS-CVOT	Dula 1.5 mg	2.16	0.91 (0.80-1.02), 0.12	
	TZP MTD	1.96		

See Notes section for all footnotes.

Notes: ^aParticipants who would have been eligible to enrol in SURPASS-CVOT were identified if they had a baseline HbA1c $\geq 7.0\%$ and a history of ≥ 1 of the following: MI, $>50\%$ stenosis, coronary revascularisation, ischaemic stroke, carotid artery revascularisation, ankle-brachial index < 0.9 , (peripheral revascularisation [iliac or femoral artery] or amputation); ^bAdjusted based on stabilised inverse-probability weight, calculated based on the estimated propensity score, defined as the probability of belonging to SURPASS-CVOT, estimated based on covariates including age, sex, baseline BMI, history of coronary revascularisation, history of heart failure, history of MI, history of stroke, T2D duration, baseline HbA1c, baseline SBP, baseline eGFR, logarithm of baseline UACR, baseline non-HDL and smoking habit (current or non-current). Missing covariates were handled with multiple imputation.

Abbreviations: BMI=body mass index; CI=confidence interval; CV=cardiovascular; Dula=dulaglutide; eGFR=estimate glomerular filtration rate; HbA1c=glycated haemoglobin; HDL=high-density lipoprotein; HF=heart failure; HR=hazard ratio; MI=myocardial infarction; MTD=maximum tolerated dose; PBO=placebo; pys=person-years of follow-up; SBP=systolic blood pressure; TZP=tirzepatide; T2D=type 2 diabetes; UACR=urine albumin-to-creatinine ratio.

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Summary

- Treatment with tirzepatide met the pre-specified criteria for non-inferiority compared with dulaglutide on the rate of the primary composite endpoint of cardiovascular death, myocardial infarction or stroke
- Tirzepatide met the criteria for superiority compared with a putative placebo on the rate of the primary composite endpoint of cardiovascular death, myocardial infarction or stroke
- The trial did not meet superiority for the comparison of tirzepatide with dulaglutide for the primary endpoint
- Tirzepatide also had favourable effects on HbA1c, body weight, change in eGFR, all-cause death and the composite outcome of cardiovascular death, myocardial infarction, stroke or coronary revascularisation compared with dulaglutide
- Safety outcomes were similar for participants who received tirzepatide compared with dulaglutide; however, an increase in gastrointestinal adverse events was observed in the tirzepatide group compared with dulaglutide
- Overall, SURPASS-CVOT demonstrated that tirzepatide is cardioprotective in participants with established atherosclerotic cardiovascular disease and type 2 diabetes

Abbreviations: *AE=adverse event; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HbA1c=glycated haemoglobin; MI=myocardial infarction; T2D=type 2 diabetes.*

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Final Comment

- This active comparator study established that tirzepatide had favourable clinical effects for high-risk participants with type 2 diabetes and atherosclerotic cardiovascular disease, and could provide an additional incretin-targeted therapy for cardiovascular prevention in the setting of type 2 diabetes

Abbreviations: ASCVD=*atherosclerotic cardiovascular disease*;
CV=*cardiovascular*; T2D=*type 2 diabetes*.

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The Glycaemic Control and Metabolic Changes in Participants on Tirzepatide Versus Dulaglutide of the SURPASS-CVOT

David D'Alessio

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Clinicaltrials.gov identifier: -NCT04255433

Presenter Disclosure

Consultant: Arrowhead, Eli Lilly and Company, Eccogene, Fractyl, MBX, Structure Therapeutics, Sun Pharma



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Background

- Tirzepatide, a dual GLP-1 and GIP receptor agonist,¹ has been shown to have greater effects than the GLP-1 receptor agonists, semaglutide or dulaglutide, for reducing glycosylated haemoglobin (HbA1c) and weight loss in people with type 2 diabetes treated for 6-12 months²⁻⁴
- SURPASS-CVOT provides the opportunity to assess the long-term efficacy of tirzepatide compared with dulaglutide on glycaemic control, body weight, serum lipids and blood pressure in people with type 2 diabetes and established atherosclerotic cardiovascular disease

1. Nauck MA, D'Alessio DA. *Cardiovasc Diabetol*. 2022;21(1):169. 2. Frias JP, et al. *Lancet*. 2018;392:2180–2193. 3. Frias JP, et al. *N Engl J Med*. 2021;385:503–515. 4. Ludvik B, et al. *Lancet*. 2021;583-598.

Abbreviations: *GIP=glucose-dependent insulinotropic polypeptide; GLP-1 RA=glucagon-like peptide-1 receptor agonist.*

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Source:

References:

1. Nauck MA, D'Alessio DA. Tirzepatide, a dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regarding glycaemic control and body weight reduction. *Cardiovasc Diabetol* 2022;21(1):169.
2. Frias JP , Nauck MA , Van J , et al . Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-

- controlled and active comparator-controlled phase 2 trial. *Lancet* 2018;392:2180–93.
3. Frias JP , Davies MJ , Rosenstock J , et al . Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. *N Engl J Med* 2021;385:503–15.
 4. Ludvik B , Giorgino F , Jódar E , et al . Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without sodium-glucose co-transporter-2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet* 2021;398:583–98.

Objective

- To assess the long-term efficacy of tirzepatide compared with dulaglutide on glycaemic control, body weight, serum lipids and blood pressure in participants with type 2 diabetes and established atherosclerotic cardiovascular disease as evaluated in SURPASS-CVOT

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

SURPASS-CVOT Cardiometabolic Endpoints

Secondary endpoints included:

- Change in HbA1c from baseline to Week 156, and proportion of participants sustaining HbA1c targets (<7%, ≤6.5%, <5.7%) from Week 24 to Week 156
- Percent body weight change from baseline to Week 156, and proportion of participants sustaining weight-loss targets (≥5%, ≥10% and ≥15%) from Week 52 to Week 156
- Changes in serum lipids over 260 weeks
- Changes in blood pressure over 234 weeks

Abbreviations: *HbA1c=glycated haemoglobin.*

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Statistical Analysis

- Analyses were conducted with data from all randomly assigned participants excluding those who were randomised in error (modified intent-to-treat)
- Change from baseline in HbA1c and percent change from baseline in body weight were analysed using data from the on-treatment observation period^a

^aOn-treatment observation period defined as the date of last study drug administration plus 7 days, with data of last study drug administration defined as the earlier of the participant permanently discontinuing study drug or interrupting study drug for ≥3 consecutive months.

Abbreviations: *HbA1c=glycated haemoglobin.*

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Baseline Characteristics

Parameter	TZP MTD (N=6586)	Dula 1.5 mg (N=6579)
Age, years	64.0	64.1
Female, %	28.7	29.3
HbA1c, % (mmol/mol)	8.4 (68.4)	8.4 (68.1)
HbA1c category, %		
≤8.5%	59.5	60.5
>8.5%	40.5	39.5
Weight, kg	92.6	92.5
BMI, kg/m ²	32.6	32.6
BMI category, %		
<27 kg/m ²	14.2	13.8
≥27-30 kg/m ²	22.7	23.4
>30 kg/m ²	63.1	62.8
Waist circumference, cm	110.4	110.3
Type 2 diabetes duration, years	14.8	14.7
SGLT-2 inhibitor use, %	30.4	30.8
Triglycerides, median, mg/dL (mmol/L)	160.3 (1.8)	159.4 (1.8)
Total cholesterol, mg/dL (mmol/L)	159.3 (4.1)	159.1 (4.1)
LDL cholesterol, mg/dL (mmol/L)	80.5 (2.1)	80.7 (2.1)
HDL cholesterol, mg/dL (mmol/L)	41.2 (1.1)	41.2 (1.1)
Non-HDL cholesterol, mg/dL (mmol/L)	118.1 (3.1)	117.8 (3.1)

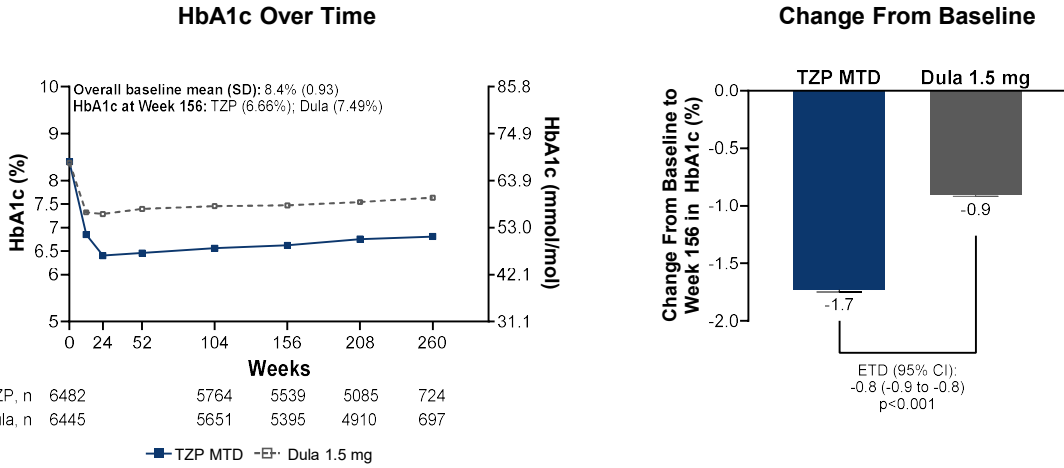
Note: Data are mean unless stated otherwise.

Abbreviations: BMI=body mass index; Dula=dulaglutide; HbA1c=glycated haemoglobin; HDL=high-density lipoprotein; LDL=low-density lipoprotein; MTD=maximum tolerated dose; SGLT-2=sodium-glucose co-transporter-2; TZP=tirzepatide

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Change in HbA1c



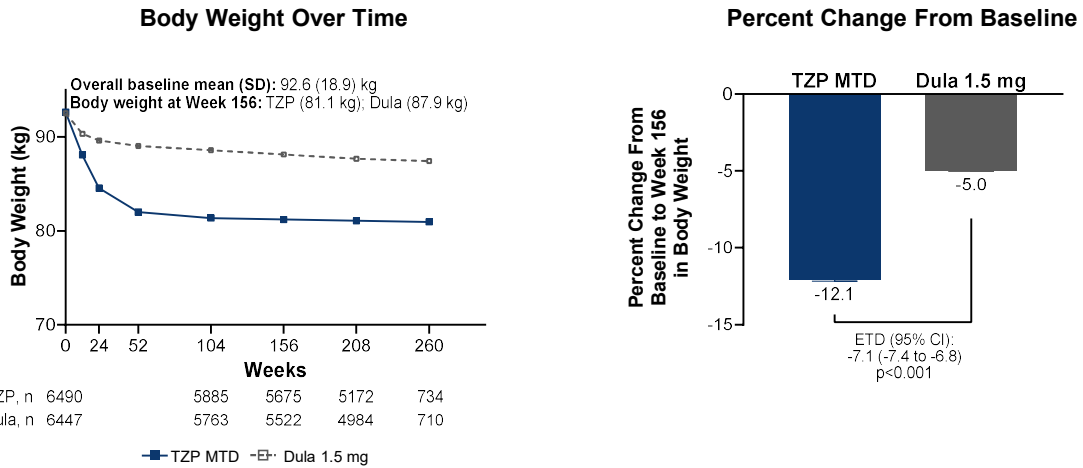
Notes: Data are estimate (SE) unless stated otherwise. Change over time was based on MMRM. Actual value at Week 156 and change from baseline to Week 156 were analysed using an ANCOVA model with multiple imputation of missing values.

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; Dula=dulaglutide; ETD=estimated treatment difference; HbA1c=glycated haemoglobin; MMRM=mixed model for repeated measures; MTD=maximum tolerated dose; SD=standard deviation; SE=standard error; TZP=tirzepatide.

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Change in Body Weight



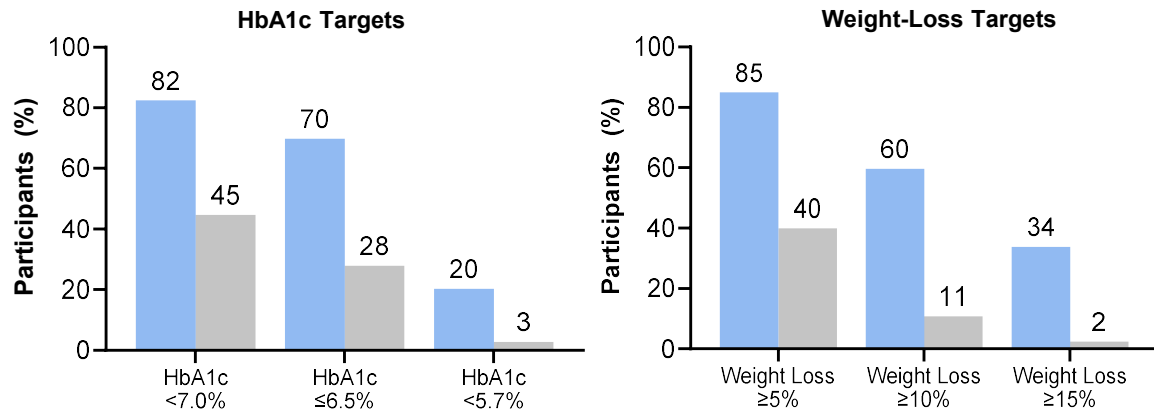
Notes: Data are estimate (SE) unless stated otherwise. Change over time was based on MMRM. Actual values at Week 156 and change from baseline to Week 156 were analysed using an ANCOVA model with multiple imputation of missing values.

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; Dula=dulaglutide; ETD=estimated treatment difference; MMRM=mixed model for repeated measures; MTD=maximum tolerated dose; SD=standard deviation; SE=standard error; TZP=tirzepatide.

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Percent of Participants Achieving HbA1c and Weight Loss Targets



Target achieved at W24 (HbA1c) and W52 (body weight) : ■ TZP MTD ■ Dula 1.5 mg

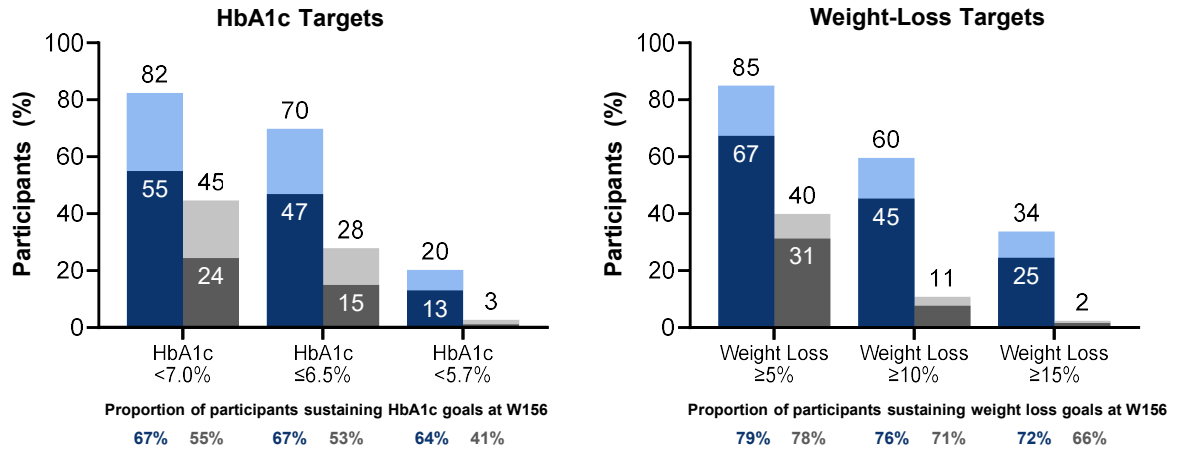
Notes: Participants who achieved HbA1c or weight-loss targets were analysed with a logistic regression model with treatment, SGLT-2 inhibitor use at baseline and country as fixed factors and baseline value as a covariate, with multiple imputation of missing values.

Abbreviations: *Dula=dulaglutide; HbA1c=glycated haemoglobin; MTD=maximum tolerated dose; SGLT2=sodium-glucose co-transporter-2; TZP=tirzepatide; W=Week.*

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Proportion of Participants Who Achieved HbA1c (<0.3% Increase) and Weight-Loss (<3 kg Increase) Targets to Week 156



Target achieved at W24 (HbA1c) and W52 (body weight) : ■ TZP MTD ■ Dula 1.5 mg
 Achieved value sustained from W24-W156: ■ TZP MTD ■ Dula 1.5 mg

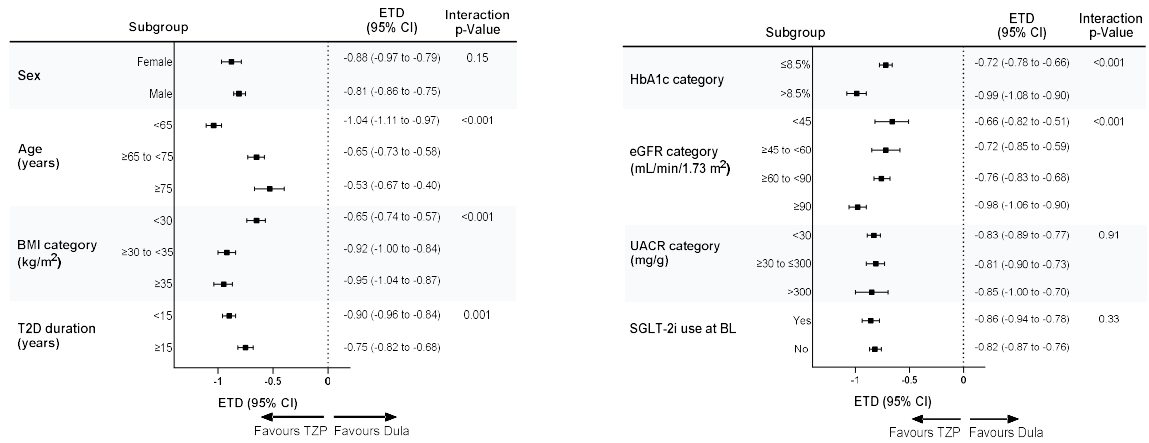
Notes: Participants who achieved and sustained HbA1c or weight-loss targets were analysed with a logistic regression model with treatment, SGLT-2 inhibitor use at baseline and country as fixed factors and baseline value as a covariate, with multiple imputation of missing values. For HbA1c, sustained response defined as a HbA1c of at/below target at Week 24 and a gain of ≤0.3% from Week 24 to Week 156. For weight loss, sustained response defined as weight loss of at/below target at Week 52 and a gain of ≤3 kg or less from Weeks 52 to 156.

Abbreviations: Dula=dulaglutide; HbA1c=glycated haemoglobin; MTD=maximum tolerated dose; SGLT2=sodium-glucose co-transporter-2; TZP=tirzepatide; W=Week.

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Subgroup Analysis: HbA1c at Week 156



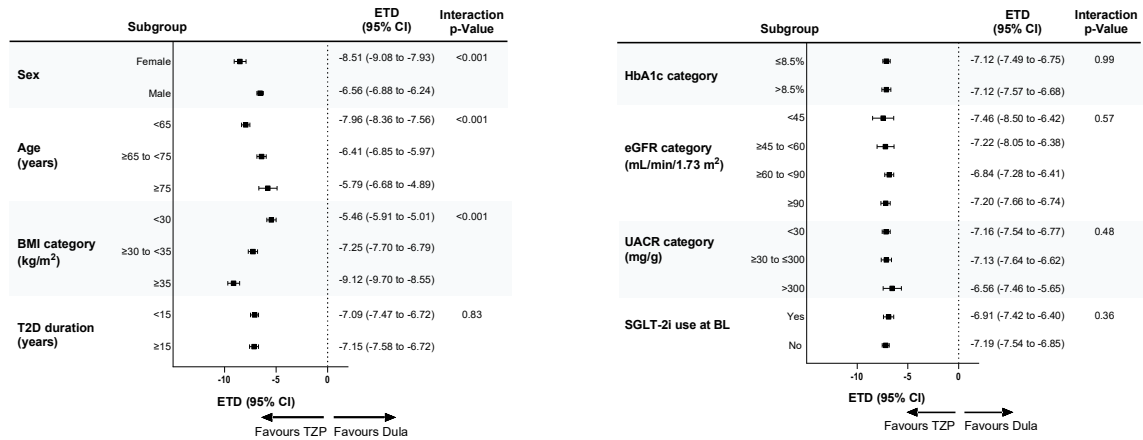
Note: ETD was analysed using an ANCOVA model with treatment, SGLT-2 inhibitor use at baseline and country as fixed factors and baseline value as a covariate, with multiple imputation of missing values. p-value for treatment*subgroup interaction was calculated based on Chi-square statistics. The Chi-square statistics was calculated based on ETD within each subgroup using Rubin's rule.

Abbreviations: ANCOVA=analysis of covariance; BL=baseline; BMI=body mass index; CI=confidence interval; Dula=dulaglutide; eGFR=estimated glomerular filtration rate; ETD=estimated treatment difference; HbA1c=glycated haemoglobin; SGLT-2i=sodium-glucose co-transporter-2 inhibitor; T2D=type 2 diabetes; TZP=tirzepatide; UACR=urinary albumin-to-creatinine ratio.

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Subgroup Analysis: Body Weight at Week 156



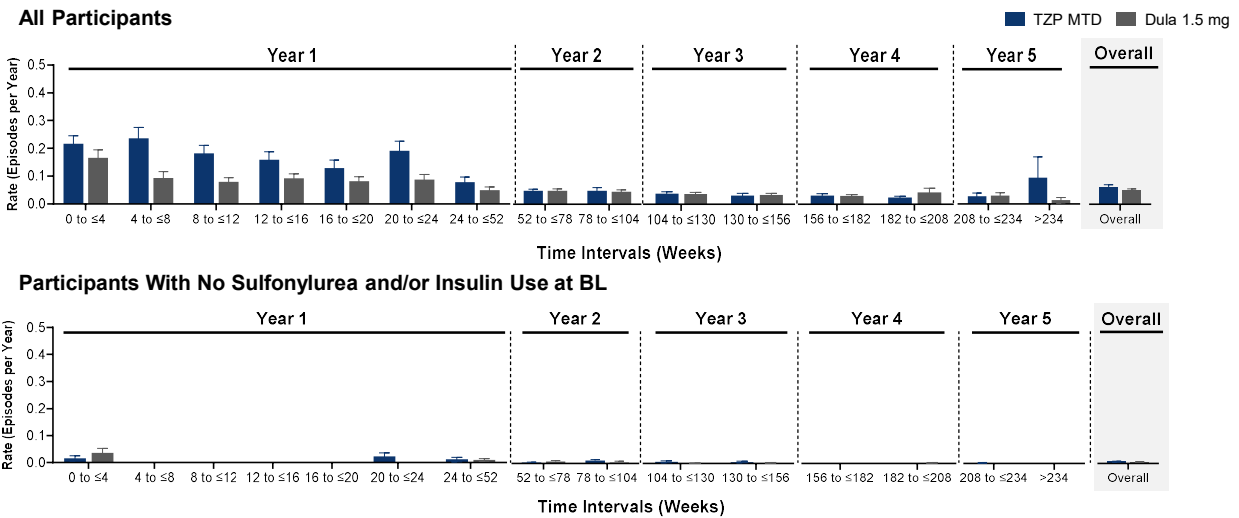
Note: ETD was analysed using an ANCOVA model with treatment, SGLT-2 inhibitor use at baseline and country as fixed factors and baseline value as a covariate, with multiple imputation of missing values. p-value for treatment*subgroup interaction was calculated based on Chi-square statistics. The Chi-square statistics was calculated based on ETD within each subgroup using Rubin's rule.

Abbreviations: ANCOVA=analysis of covariance; BL=baseline; BMI=body mass index; CI=confidence interval; Dula=dulaglutide; eGFR=estimated glomerular filtration rate; ETD=estimated treatment difference; HbA1c=glycated haemoglobin; SGLT-2i=sodium-glucose co-transporter-2 inhibitor; T2D=type 2 diabetes; TZP=tirzepatide; UACR=urinary albumin-to-creatinine ratio.

Study code: I8F-MC-GPGN

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Rate of Level 2 Hypoglycaemia or Severe Hypoglycaemia



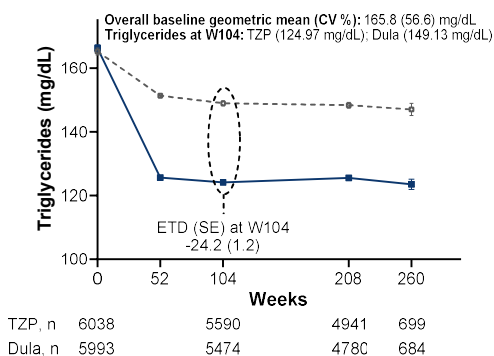
Abbreviations: *BL*=baseline; *Dula*=dulaglutide; *MTD*=maximum tolerated dose; *TZP*=tirzepatide.

Study code: I8F-MC-GPGN

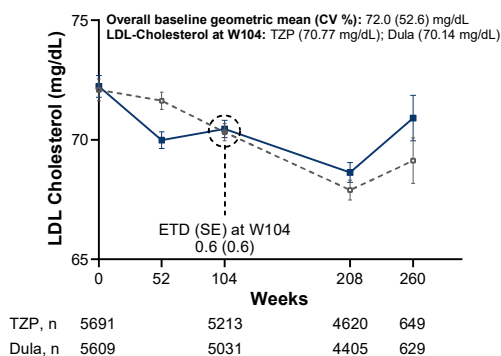
Clinicaltrials.gov identifier: -NCT04255433

Change in Lipids

Triglycerides Over Time



LDL-Cholesterol Over Time



■ TZP MTD -□- Dula 1.5 mg

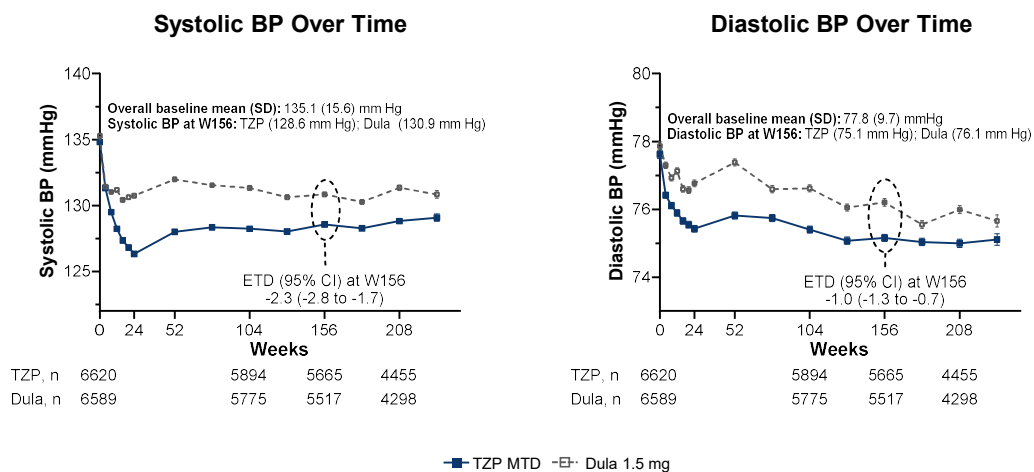
Notes: Data are estimate (SE) unless stated otherwise. Change over time was based on MMRM. Actual values at W104 were analysed using an ANCOVA model with multiple imputation of missing values.

Abbreviations: ANCOVA=analysis of covariance; CV=coefficient of variation; Dula=dulaglutide; ETD=estimated treatment difference; LDL=low-density lipoprotein; MMRM=mixed model for repeated measure; MTD=maximum tolerated dose; SE=standard error; TZP=tirzepatide.

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Change in Blood Pressure



Note: Data are estimate (SE) unless stated otherwise. Change over time was based on MMRM. Actual values at W156 were analysed using an ANCOVA model with multiple imputation of missing values.

Abbreviations: ANCOVA=analysis of covariance; BP=blood pressure; CI=confidence interval; Dula=dulaglutide; ETD=estimated treatment difference; MMRM=mixed model for repeated measure; MTD=maximum tolerated dose; SD=standard deviation; SE=standard error; TZP=tirzepatide.

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Summary

- In SURPASS-CVOT, a greater decrease in HbA1c was observed in participants on tirzepatide compared with dulaglutide over a median 210 weeks follow up
- Participants treated with tirzepatide experienced greater reduction in body weight than those on dulaglutide
- Tirzepatide had a greater effect on HbA1c and body weight than dulaglutide across a range of subgroups
 - Reported rates of hypoglycaemia did not differ between tirzepatide and dulaglutide
- Tirzepatide treatment had greater improvements on triglycerides and blood pressure compared with dulaglutide

Abbreviations: *HbA1c=glycated haemoglobin.*

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433



MONASH
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MEDICINE

The Evolution of Renal Status in Participants on Tirzepatide Versus Dulaglutide of the SURPASS-CVOT

Sophia Zoungas

Monash University, Melbourne, Australia

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Presenter Disclosure

Participant in advisory boards, steering committees and educational meetings (payments to institution [Monash University]): AstraZeneca, Boehringer Ingelheim, CSL Seqirus, Eli Lilly Australia, GSK, Moderna, Novo Nordisk and Sanofi

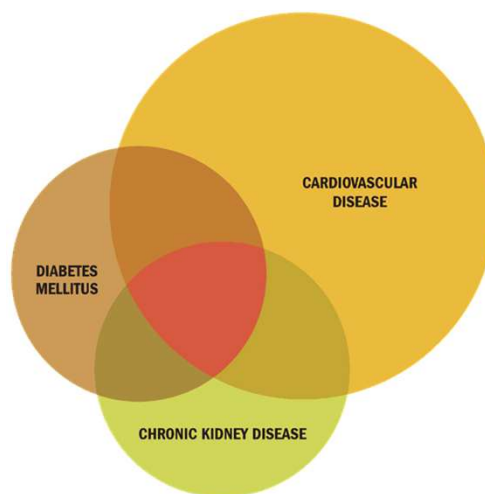


Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Diabetes and Chronic Kidney Disease

- Diabetes is the leading cause of chronic kidney disease globally and estimated to develop in approximately 40% of people living with diabetes
- While lifestyle interventions, glycaemic control, blood pressure management, and lipid regulation remain foundational in the prevention and management of chronic kidney disease, these are now complemented by therapies with established kidney protective effects



References:

1. Alicic RZ et al. Clin J Am So Nephrol 2017;12:2032-2045
2. IDF Atlas
3. KDIGO guideline

Background

- Tirzepatide in comparison with insulin glargine in people with type 2 diabetes and high cardiovascular risk has been observed to slow the rate of decline in estimated glomerular filtration, reduce albuminuria, and lower the risk of a composite kidney endpoint¹
- Dulaglutide, a selective GLP-1 receptor agonist, has also been shown to have kidney protective effects²
- The SURPASS-CVOT trial offered the opportunity to directly compare the effect of tirzepatide and a selective GLP-1 receptor agonist on clinically meaningful kidney outcomes

1. Heerspink HJL, et al. *Lancet Diab Endocrinol.* 2022;10:774-785. 2. Kim S, et al. *PLoS One.* 2022;17:e0273004.

Abbreviations: *GLP-1RA=glucagon-like peptide-1 receptor agonist.*

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

References:

1. Heerspink HJL , Sattar N , Pavo I , et al . Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes in the SURPASS-4 trial: post-hoc analysis of an open-label, randomised, phase 3 trial. *Lancet Diab Endocrinol* 2022;10:774–85.
2. Kim S, Nam An J, Rim Song Y, Gyun Kim S, Seok Lee H, Cho A, Kim J-K. Effect of once-weekly dulaglutide on renal function in patients with chronic kidney disease. *PLoS One.* 2022;17(8):e0273004.

Objective

- To assess the efficacy of tirzepatide compared with dulaglutide on kidney outcomes and safety in participants with type 2 diabetes and established cardiovascular disease and in participants with high-risk chronic kidney disease (CKD)^a in the SURPASS-CVOT

^aDefined as eGFR \geq 60 mL/min/1.73 m² and UACR >300 mg/g, eGFR 45 to <60 mL/min/1.73 m² and UACR >30 mg/g, or eGFR <45 mL/min/1.73 m² at baseline.

Abbreviations: *CKD=chronic kidney disease*

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Definition of High-Risk CKD

- Defined according to KDIGO guideline
- eGFR was calculated using the CKD-EPI serum creatinine-cystatin C equation

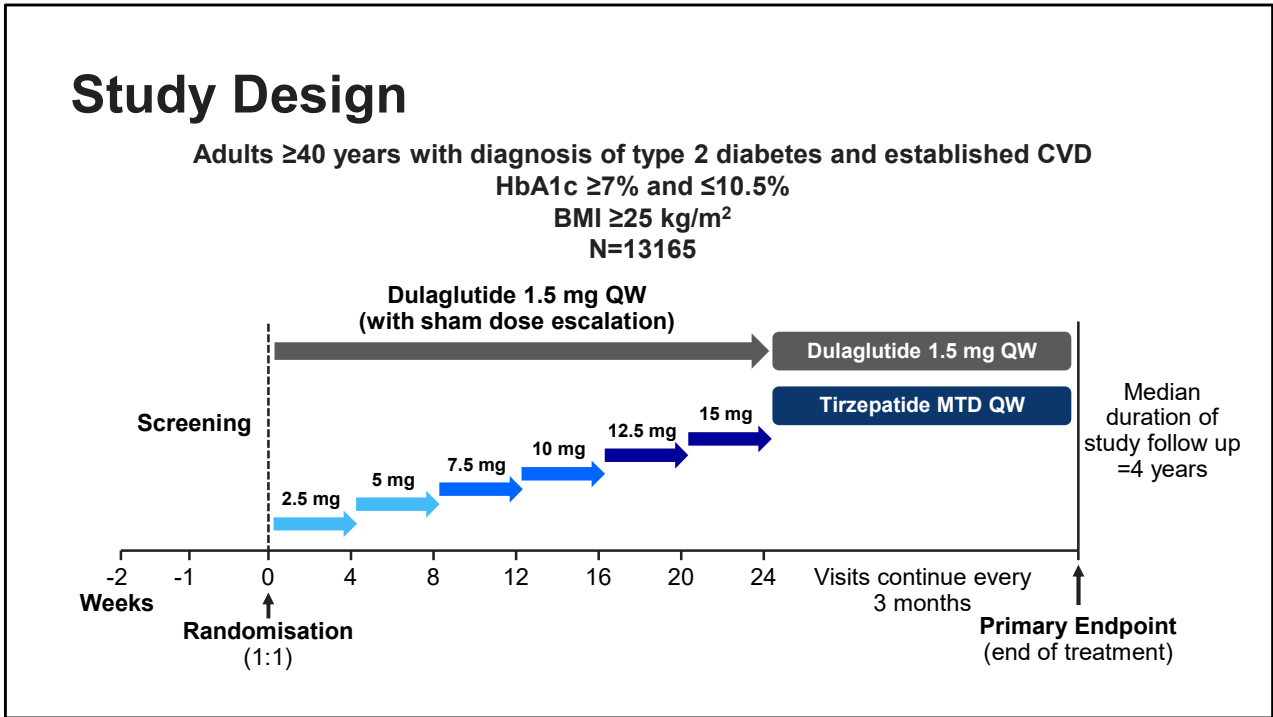
KDIGO: Prognosis of CKD by GFR and Albuminuria categories			Albuminuria Categories Description and Range		
			Normal to mildly increased <30 mg/g <3 mg/mmol	Moderately increased 30-300 mg/g 3-30 mg/mmol	Severely increased >300 mg/g >30 mg/mmol
GFR Categories (mL/min/1.73 m ²) Description and Range	Normal or high	≥90			
	Mildly decreased	60-89			
	Mildly to moderately decreased	45-59			
	Moderately to severely decreased	30-44			
	Severely decreased	15-29			
	Kidney failure	<15			

Note: Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

Abbreviations: *CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; GFR=glomerular filtration rate; KDIGO=kidney disease improving global outcomes;*

Study code: I8F-MC-GPGN

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Abbreviations: BMI=body mass index; CVD=cardiovascular disease; HbA1c=glycated haemoglobin; MTD=maximum tolerated dose; QW=once weekly.

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Major Kidney Outcomes

Primary endpoints:

- Time to first occurrence of the 4-component primary composite kidney endpoint

Secondary endpoints:

- Time to first occurrence of composite kidney endpoints 2-4
- Change in eGFR from baseline to 36 months^a
- Percent change in UACR from baseline to 36 months

	Primary Composite Kidney Endpoint
Persistent macroalbuminuria	✓
Persistent ≥50% reduction in eGFR	✓
ESKD ^a	✓
Death from kidney disease	✓

^aAnalysis in the high/very high-risk CKD population was a key secondary endpoint of the main SURPASS-CVOT study.
Notes: The primary composite kidney endpoint was not pre-specified in the main study statistical analysis plan.

Abbreviations: eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease; UACR=urine albumin-to-creatinine ratio.

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Statistical Analysis

- All analyses were based on data from all randomised participants
- The primary and secondary composite kidney outcomes were analysed using Cox proportional hazards models
- Change from baseline to 36 months in eGFR (creatinine-cystatin C) and percent change in UACR were assessed using analysis of covariance models treating missing values with a multiple imputation manner
- eGFR and percent change in UACR per treatment arm at each assessment ('visit') were estimated using mixed model for repeated measures
- All safety events were investigator reported, except for deaths due to kidney and cardiovascular disease, which were independently adjudicated

Abbreviations: *eGFR=estimated glomerular filtration rate; UACR=urine albumin-to-creatinine ratio.*

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Baseline Characteristics: High-Risk CKD Population

Parameter	TZP MTD (N=1520)	Dula 1.5 mg (N=1403)
Age, years, mean	67.2	67.2
Female, %	27.8	28.4
HbA1c, % (mmol/mol)	8.5 (69.4)	8.4 (68.6)
Weight, kg, mean	93.2	93.0
Body mass index, kg/m ² , mean	33.1	33.0
Type 2 diabetes duration, years, mean	17.7	17.7
eGFR, mL/min/1.73 m ² , mean	52.9	53.8
<60 mL/min/1.73 m ² , %	74.7	72.9
≥60 mL/min/1.73 m ² , %	25.3	27.1
UACR, mg/g, median	296.0	325.0
Normoalbuminuria (UACR <30 mg/g), %	12.4	12.0
Microalbuminuria (UACR 30-300 mg/g), %	37.9	35.3
Macroalbuminuria (UACR >300 mg/g), %	49.6	52.8

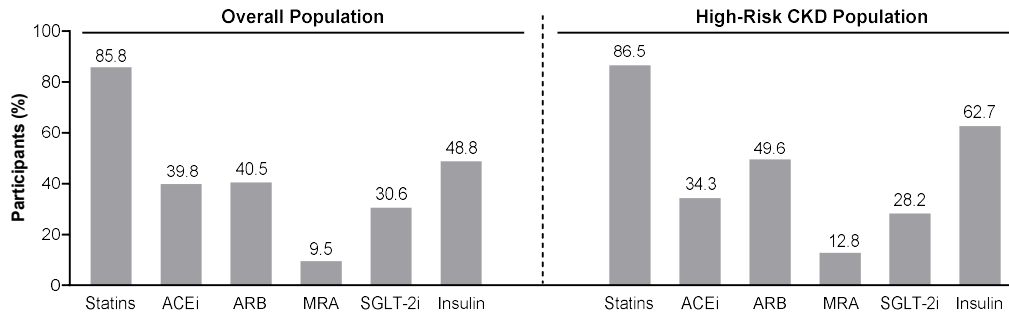
Abbreviations: CKD=chronic kidney disease; Dula=dulaglutide; eGFR=estimated glomerular filtration rate; HbA1c=glycated haemoglobin; MTD=maximum tolerated dose; TZP=tirzepatide; UACR=urine albumin-to-creatinine ratio.

Study code: I8F-MC-GPGN

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Medication Use

Baseline Medication Use



Study Drug Use

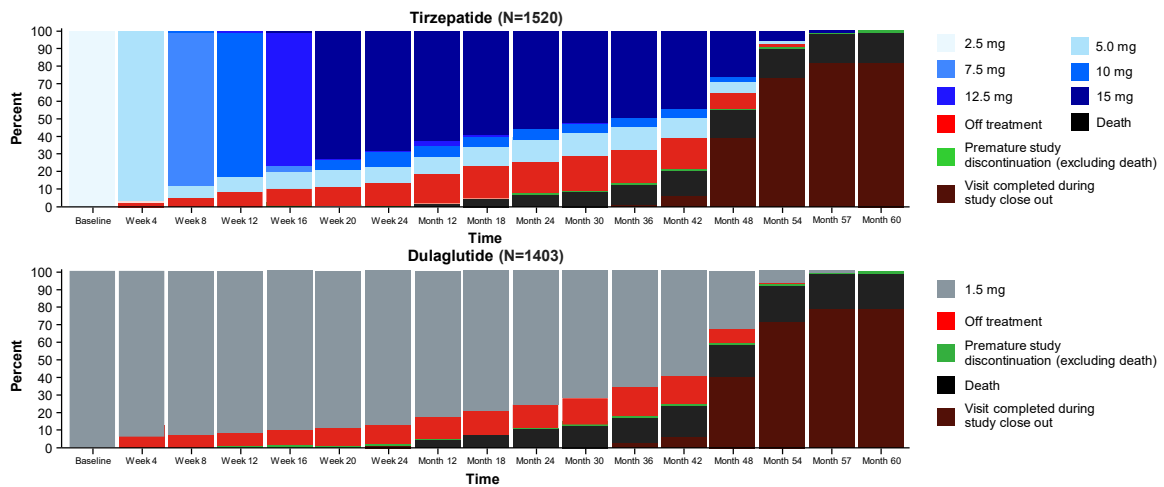
- Similar numbers of the overall population and the population with high-risk CKD were receiving the 15 mg dose of tirzepatide at 36 months, 72.7% vs 71.8%, respectively
- In the overall and high-risk CKD populations, premature study drug discontinuation occurred in 21.6% and 26.2% on tirzepatide, and 19.8% and 25.5% on dulaglutide, respectively

Abbreviations: ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blockers; CKD=chronic kidney disease; MRA=Mineralocorticoid receptor antagonist; SGLT-2i=sodium-glucose transporter-2 inhibitor.

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Dose Distributions and Permanent Discontinuations: High-Risk CKD Population

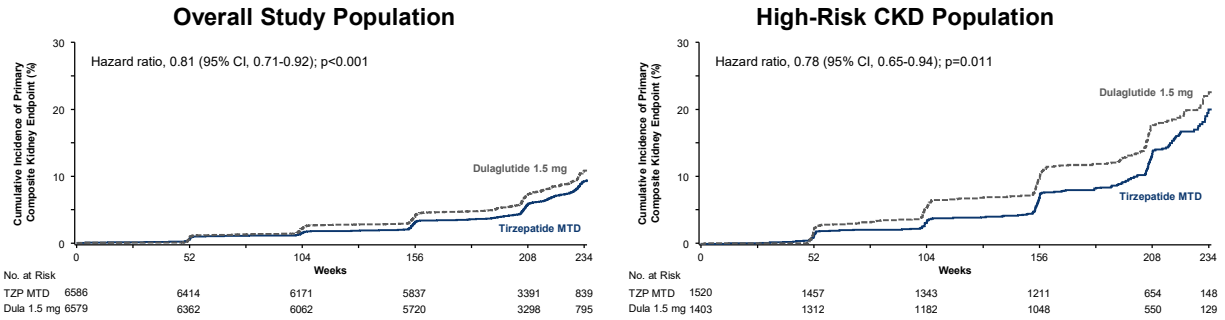


At 36 months, 71.8% of participants in the tirzepatide group were receiving the 15-mg dose

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Primary Composite Kidney Endpoint



Note: HR, 95% CI and p-value refer to the significance of the treatment effect, computed using a Cox proportional hazards model stratified by SGLT-2 inhibitor use at baseline.

Abbreviations: *CI=confidence interval; Dula=dulaglutide; HR=hazard ratio; MTD=maximum tolerated dose; SGLT-2=sodium-glucose transporter 2; TZP=tirzepatide.*

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Primary Composite Kidney Endpoint and Components

Parameter	Overall Population				High-Risk CKD Population			
	TZP MTD (N=6586)	Dula 1.5 mg (N=6579)	Hazard Ratio (95% CI)	p-value	TZP MTD (N=1520)	Dula 1.5 mg (N=1403)	Hazard Ratio (95% CI)	p-value
Primary composite kidney endpoint	441 (6.7)	532 (8.1)	0.81 (0.71 to 0.92)	<0.001	203 (13.4)	224 (16.0)	0.78 (0.65 to 0.94)	0.011
Components								
Persistent macroalbuminuria	238 (3.6)	322 (4.9)	0.72 (0.61 to 0.86)	<0.001	85 (5.6)	89 (6.3)	0.83 (0.62 to 1.12)	0.23
Persistent ≥50% reduction in eGFR	163 (2.5)	181 (2.8)	0.88 (0.71 to 1.09)	0.24	93 (6.1)	111 (7.9)	0.73 (0.55 to 0.96)	0.024
ESKD	106 (1.6)	93 (1.4)	1.12 (0.85 to 1.48)	0.42	73 (4.8)	73 (5.2)	0.88 (0.64 to 1.22)	0.45
Death from kidney disease	4 (0.1)	5 (0.1)			4 (0.3)	5 (0.4)		

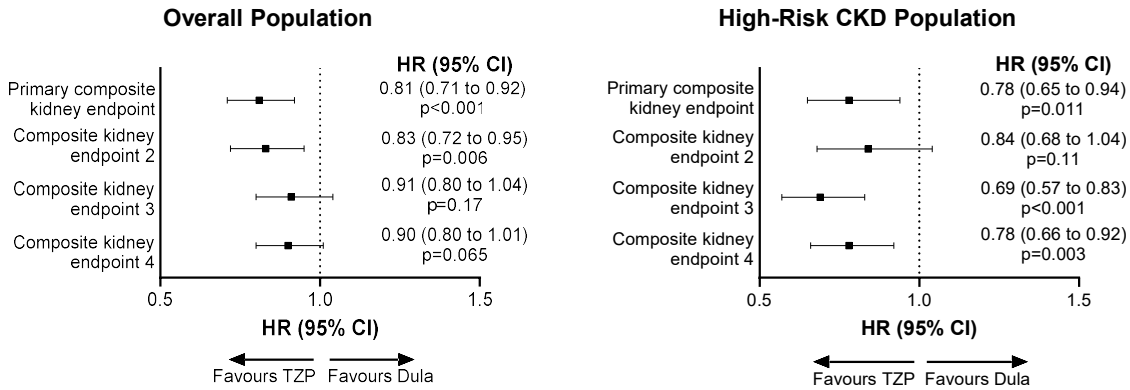
Notes: Data are n (%) unless stated otherwise. HR, 95% CI and p-values were analysed using a Cox proportional hazards model stratified by SGLT-2 inhibitor use at baseline. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine-cystatin C equation 2021.

Abbreviations: *CI=confidence interval; CKD=chronic kidney disease; Dula=dulaglutide; eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease; HR=hazard ratio; MTD=maximum tolerated dose; SGLT-2=sodium-glucose transporter-2; TZP=tirzepatide.*

Study code: I8F-MC-GPGN

Clinicaltrials.gov identifier: -NCT04255433

Composite Kidney Endpoints and Components



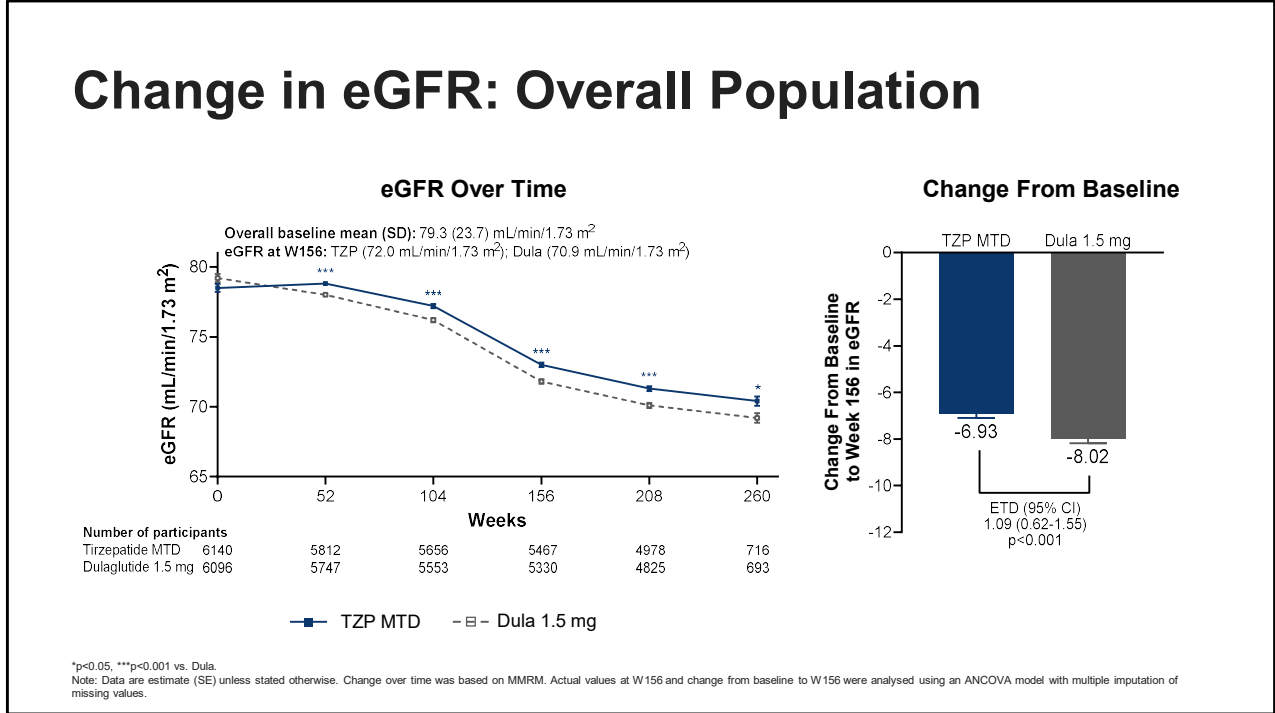
Notes: HR, 95% CI and p-values were computed using a Cox proportional hazards model stratified by SGLT-2 inhibitor use at baseline. Composite kidney endpoint 2 was defined as persistent macroalbuminuria, doubling of serum creatinine level and creatinine clearance per eGFR <45 mL/min/1.73 m², ESKD, and death from kidney disease. Composite kidney endpoint 3 was defined as persistent ≥40% reduction in eGFR, eGFR <15 mL/min/1.73 m² or initiation of chronic kidney replacement therapy, death from kidney disease. Composite kidney endpoint 4 was defined as persistent ≥50% reduction in eGFR, ESKD and death from kidney or cardiovascular disease. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine-cystatin C equation 2021.

Abbreviations: *CI=confidence interval; CKD=chronic kidney disease; Dula=dulaglutide; eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease; HR=hazard ratio; SGLT-2=sodium-glucose transporter-2; TZP=tirzepatide.*

Study code: I8F-MC-GPGN

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Change in eGFR: Overall Population

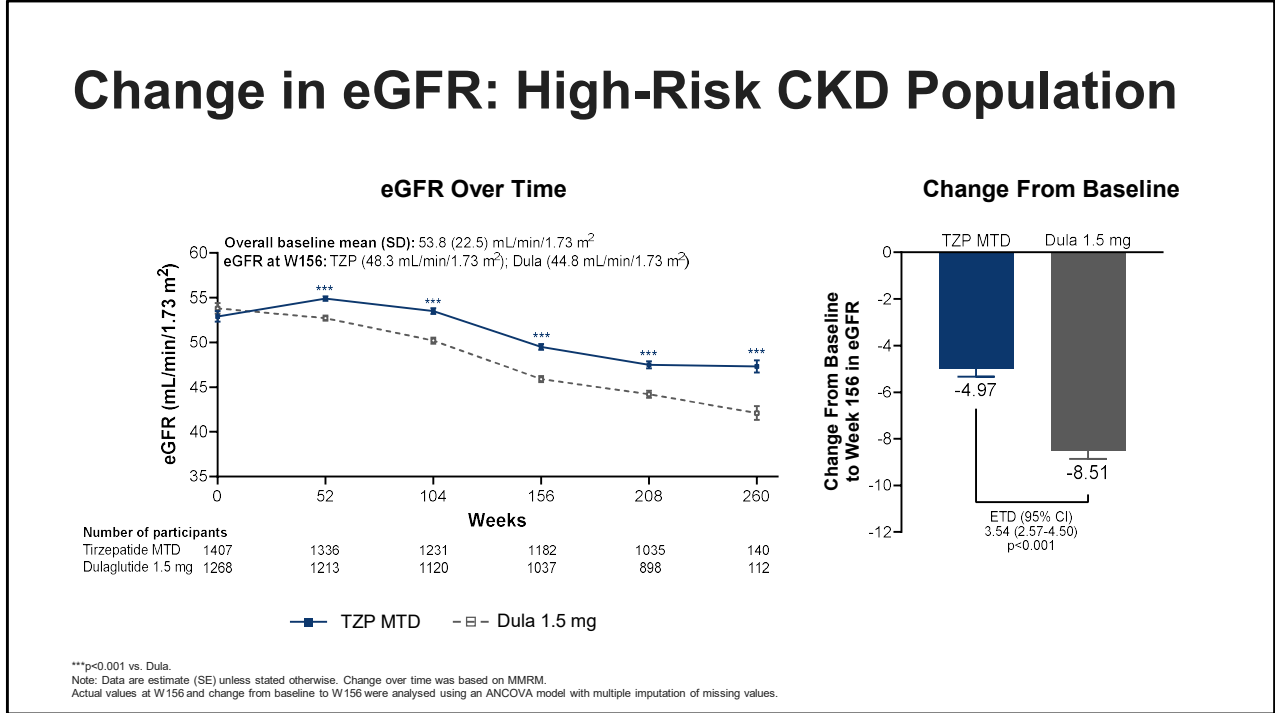


Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; Dula=dulaglutide; eGFR=estimated glomerular filtration rate; ETD=estimated treatment difference; MMRM=mixed model for repeated measures; MTD=maximum tolerated dose; SE=standard error; TZP=tirzepatide.

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Change in eGFR: High-Risk CKD Population

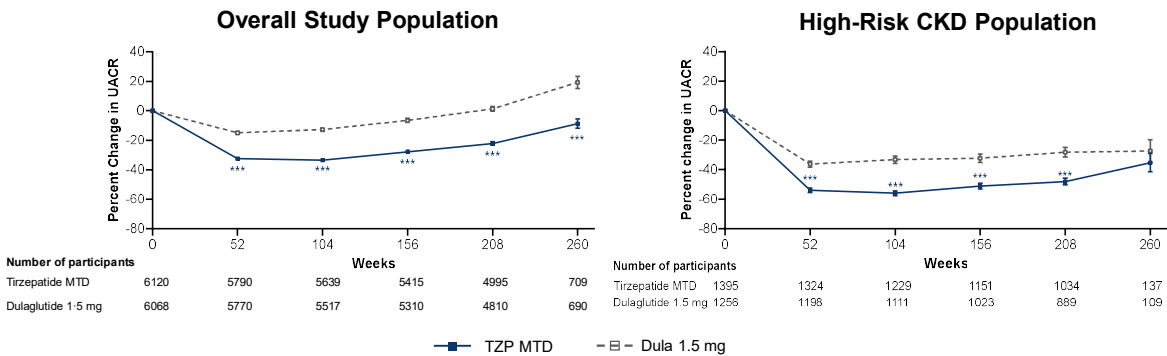


Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; CKD=chronic kidney disease; Dula=dulaglutide; eGFR=estimated glomerular filtration rate; ETD=estimated treatment difference; MMRM=mixed model for repeated measures; MTD=maximum tolerated dose; SE=standard error; TZP=tirzepatide.

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Change in UACR



	Overall Population			High-Risk CKD Population		
	TZP MTD	Dula 1.5 mg	Difference (95% CI)	TZP MTD	Dula 1.5 mg	Difference (95% CI)
% UACR change at W156, estimate (SE)	-28.2 (1.1)	-7.9 (1.5)	-22.0 (-25.2 to -18.7)***	-50.4 (2.1)	-33.1 (3.0)	-25.8 (-33.6 to -17.2)***

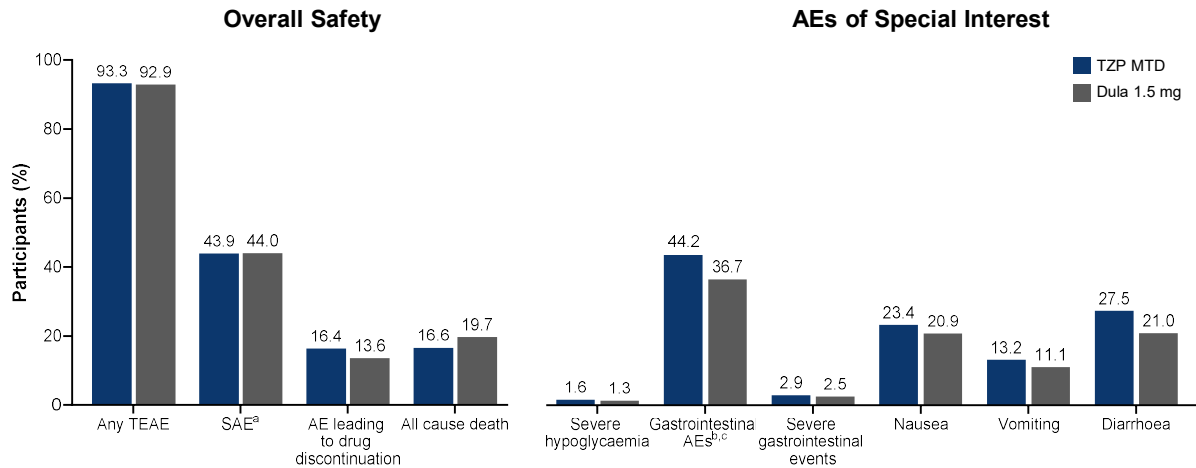
***p<0.001 vs. Dula.
 Note: Data are estimate (SE) unless stated otherwise. Change over time was based on MMRM. Actual values at W156 and change from baseline to W156 were analysed using an ANCOVA model based on log-transformed data, with multiple imputation of missing values.

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; CKD=chronic kidney disease; Dula=dulaglutide; MMRM=mixed model for repeated measures; MTD=maximum tolerated dose; SE=standard error; TZP=tirzepatide; UACR=urine albumin-to-creatinine ratio.

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Safety: High-Risk CKD Population



^aExcluding CV endpoint; ^bGastrointestinal events included nausea; vomiting; diarrhoea; ^cSeverity was determined by the investigators.

Abbreviations: AE=adverse event; CKD=chronic kidney disease; Dula=dulaglutide; MTD=maximum tolerated dose; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TZP=tirzepatide.

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Summary

- In participants with type 2 diabetes and established cardiovascular disease, tirzepatide (compared with dulaglutide):
 - Slowed the decline in kidney function
 - Reduced the progression of albuminuria
 - Reduced the risk of the major kidney composite outcome
- The lower risk of major kidney events was comparable in the high-risk CKD population, where the protective effects of tirzepatide were more apparent for eGFR decline
- Serious safety events and treatment emergent adverse events were reported in similar proportions for the tirzepatide and dulaglutide groups in the high-risk CKD population
 - Gastrointestinal adverse events were reported by more participants with high-risk CKD receiving tirzepatide than dulaglutide
- These findings add to the growing body of evidence of the kidney protective effects of tirzepatide in comparison to placebo or other glucose-lowering strategies

Abbreviations: *CKD=chronic kidney disease*

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Overall Summary

- SURPASS-CVOT demonstrated the following key findings in study participants:
 - Tirzepatide showed a cardioprotective benefit
 - Tirzepatide had significant and sustained effects on metabolic risk factors
 - Tirzepatide had favorable effects on renal outcomes
- These findings highlight the broad range of potential benefits in patients with type 2 diabetes and established atherosclerotic cardiovascular disease

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Acknowledgements

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