Effect of Tirzepatide Versus Insulin Degludec on Liver Fat Content and Abdominal Adipose Tissue in Patients With Type 2 Diabetes (SURPASS-3 MRI)

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Presenter Disclosure

Dr. Amalia Gastaldelli

Consultancy: Inventiva

Advisory boards: Boehringer Ingelheim

Speaker’s honorarium/other fees: Eli Lilly and Company, Gilead Sciences, and Novo Nordisk

Objectives

Primary Objective:

- To compare the effect of tirzepatide on the change from baseline in the percentage of LFC as measured by MRI-PDFF at 52 weeks, using data pooled from 10 mg and 15 mg dosing arms, versus insulin degludec

Secondary Objectives:

To compare each dose of tirzepatide (5, 10, and 15 mg) versus insulin degludec at 52 weeks for

- Hepatic and abdominal fat
  - Endpoint LFC
  - Proportion of patients with LFC ≤10%
  - Proportion of patients with a relative decrease from baseline in LFC ≥30%
  - Volume of abdominal visceral and SC adipose tissue and change from baseline
  - Ratio of abdominal visceral versus SC adipose tissue and change from baseline
- Serum biomarkers

Exploratory Objective:

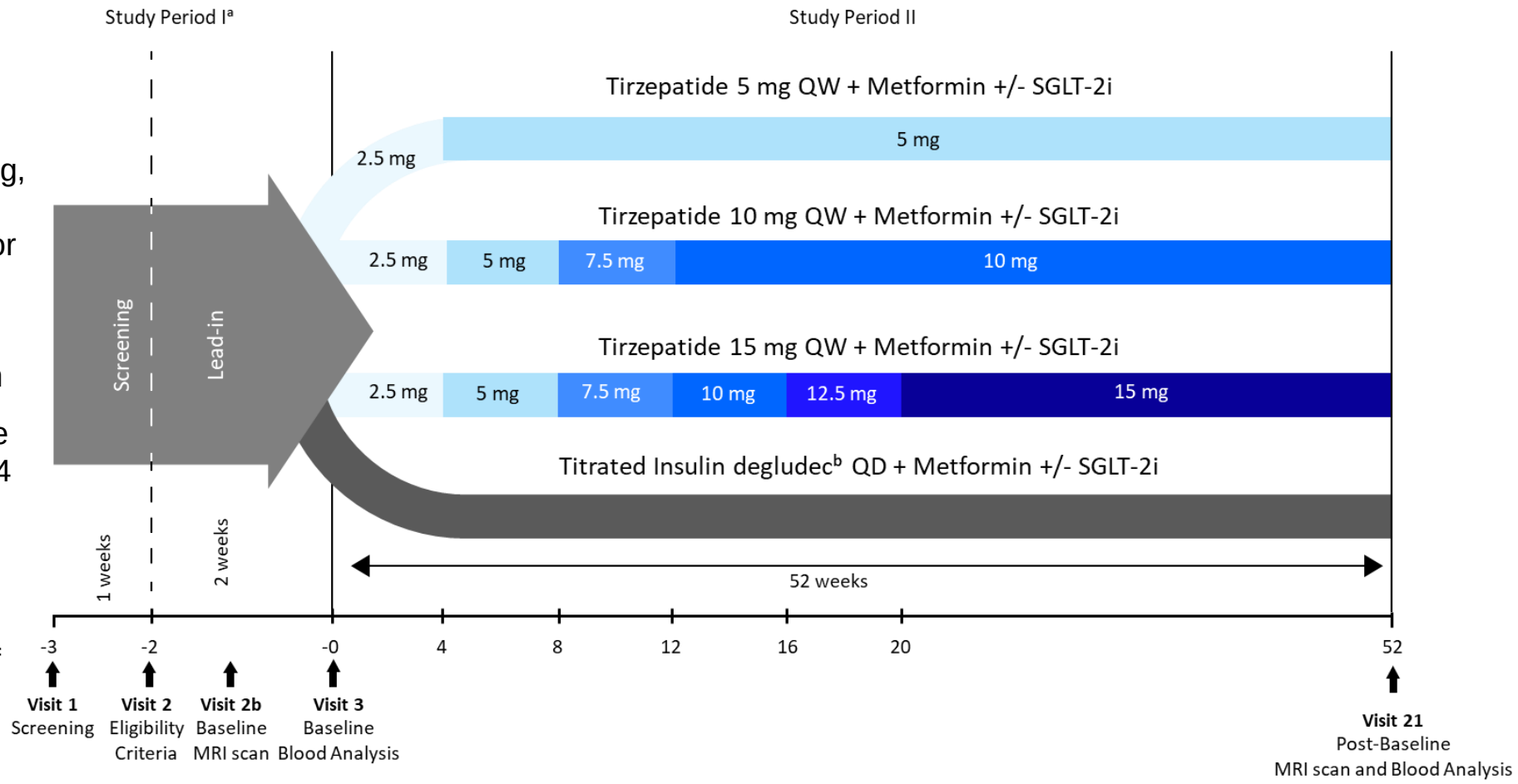
- To evaluate the relationship between laboratory data, MRI measures, and other efficacy, safety, and genomic variables

Abbreviations: LFC = liver fat content; MRI-PDFF = magnetic resonance imaging - estimated proton density fat fraction; SC = subcutaneous.

Study Design

Key Exclusion Criteria

- Fatty liver index value <60
- Contraindications for MRI scanning, such as the use of cardiac pacemakers and metal implants, or other contraindications for MRI
- Claustrophobia precluding completion of an MRI examination
- History of excessive alcohol intake (>21 units per week for males; >14 units per week for females)
- BMI >45 kg/m^2
- Are participating in Addendum 1 Continuous Glucose Monitoring of the SURPASS-3 main study



Participating Countries: Argentina, Austria, Greece, Hungary, Italy, Romania, Spain, and the USA.

[a]Stable doses of metformin (≥1500 mg/day) ± SGLT-2i for ≥3 months prior to Visit 1 and during the screening/lead-in period.

[b]The starting dose of insulin degludec was 10 U/day ideally at bedtime, titrated to a FBG <5 mmol/L (<90 mg/dL), following a treat-to-target algorithm.

Abbreviations: BMI = body mass index; FBG = fasting blood glucose; MRI = magnetic resonance imaging; QD = once daily; QW = once weekly; SGLT-2i = sodium-glucose cotransporter-2 inhibitor.

Baseline Demographics and Clinical Characteristics

Baseline demographics and clinical characteristics were well balanced across the treatment groups

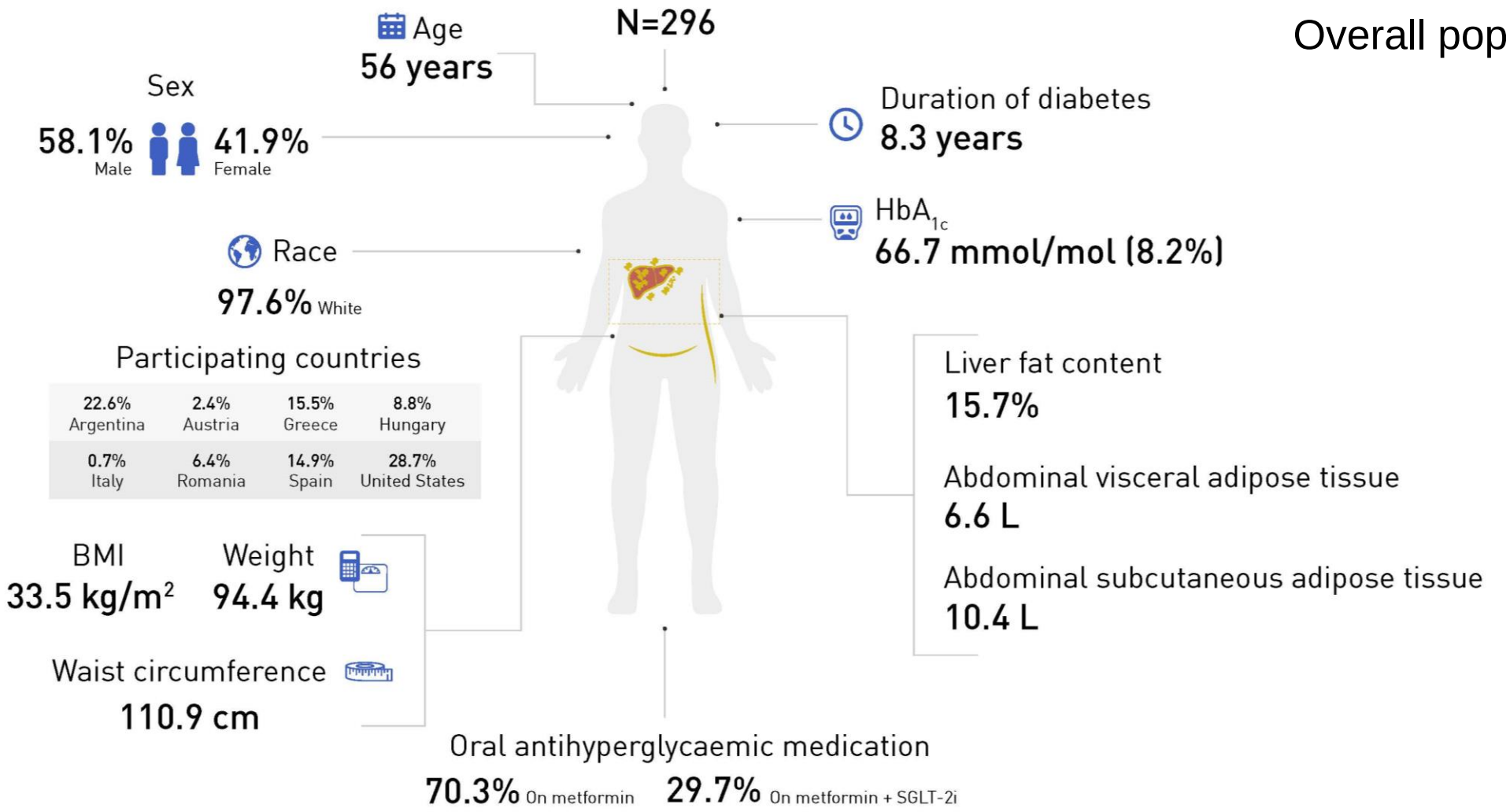
Parameter (mean ± SD, unless otherwise specified)	Tirzepatide 5 mg N=71	Tirzepatide 10 mg N=79	Tirzepatide 15 mg N=72	Insulin Degludec N=74	Total N=296
Age (years)	57 ± 10	56 ± 10	57 ± 10	57 ± 10	56 ± 10
Female, n (%)	27 (38.0)	38 (48.1)	25 (34.7)	34 (45.9)	124 (41.9)
Race, n (%)					
White	70 (98.6)	76 (96.2)	70 (97.2)	73 (98.6)	289 (97.6)
Duration of diabetes (years)	7.9 ± 6.0	9.4 ± 8.2	8.7 ± 6.7	7.0 ± 4.8	8.3 ± 6.6
HbA_{1c} (mmol/mol)	66.8 ± 9.7	68.4 ± 9.8	65.6 ± 9.5	65.6 ± 10.9	66.7 ± 10.0
HbA_{1c} (%)	8.3 ± 0.9	8.4 ± 0.9	8.2 ± 0.9	8.1 ± 1.0	8.2 ± 0.9
On metformin alone, n (%)	47 (66.2)	54 (68.4)	49 (68.1)	58 (78.4)	208 (70.3)
On metformin + SGLT-2i, n (%)	24 (33.8)	25 (31.6)	23 (31.9)	16 (21.6)	88 (29.7)
Body mass index (kg/m^2)	34.5 ± 5.3	33.1 ± 4.6	33.4 ± 4.5	33.0 ± 4.9	33.5 ± 4.8
Body weight (kg)	98.0 ± 18.3	93.1 ± 14.0	95.6 ± 16.0	91.2 ± 16.6	94.4 ± 16.3
Waist circumference (cm)	113.5 ± 11.4	109.5 ± 11.7	111.2 ± 10.3	109.8 ± 12.3	110.9 ± 11.5
Liver fat content (%)	14.9 ± 8.9	14.8 ± 8.8	16.7 ± 8.4	16.6 ± 9.6	15.7 ± 8.9
AVAT (L)	6.9 ± 2.1	6.2 ± 1.9	6.8 ± 1.9	6.3 ± 2.0	6.6 ± 2.0
ASAT (L)	11.0 ± 4.2	10.2 ± 4.5	10.3 ± 3.9	10.0 ± 4.0	10.4 ± 4.1

Country, n(%): Argentina 67 (22.6); Austria 7 (2.4); Greece 46 (15.5); Hungary 26 (8.8); Italy 2 (0.7); Romania 19 (6.4); Spain 44 (14.9); USA 85 (28.7)

Abbreviations: ASAT=abdominal subcutaneous adipose tissue; AVAT=abdominal visceral adipose tissue; HbA_{1c} = haemoglobin A_{1c}; n = number of patients in the specified category; N = all randomly assigned participants who took at least 1 dose of study drug and had a valid MRI at either baseline or postbaseline (enrolled MRI population); SD = standard deviation; SGLT-2i = sodium-glucose co-transporter-2 inhibitor.

Baseline Demographics and Clinical Characteristics

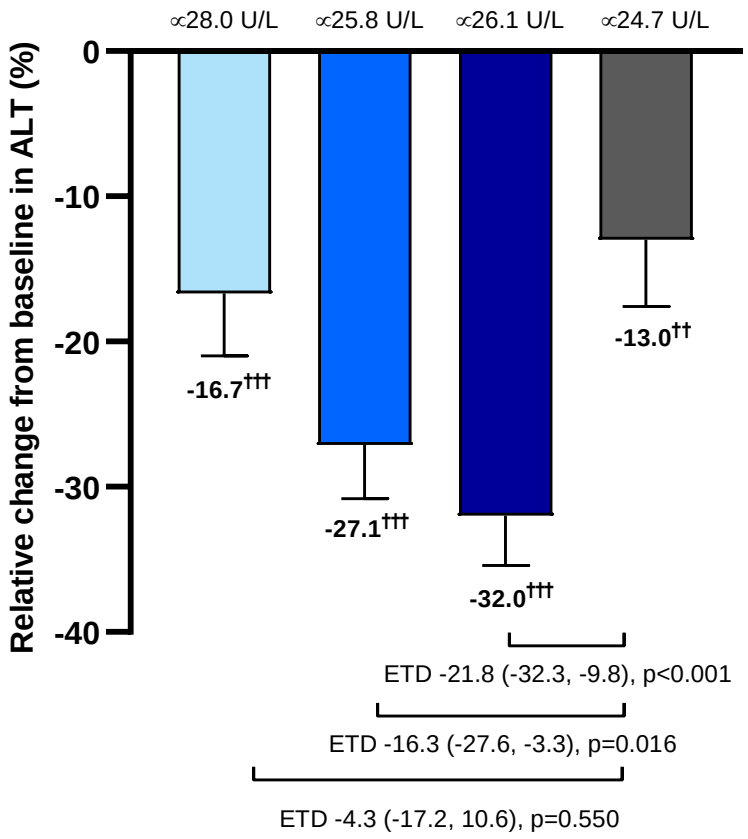
Overall population



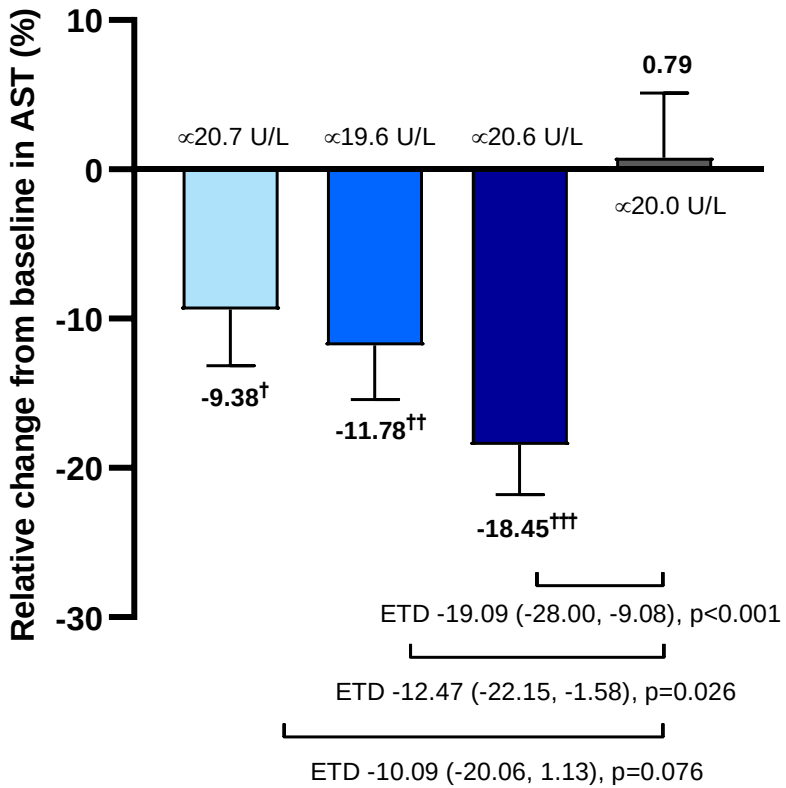
Abbreviations: BMI = body mass index; HbA_{1c} = haemoglobin A_{1c}; N = all randomly assigned participants who took at least 1 dose of study drug and had a valid MRI at either baseline or postbaseline (enrolled MRI population); SGLT-2i = sodium-glucose co-transporter-2 inhibitor.

ALT and AST

Alanine Aminotransferase (ALT) at Week 52



Aspartate Aminotransferase (AST) at Week 52



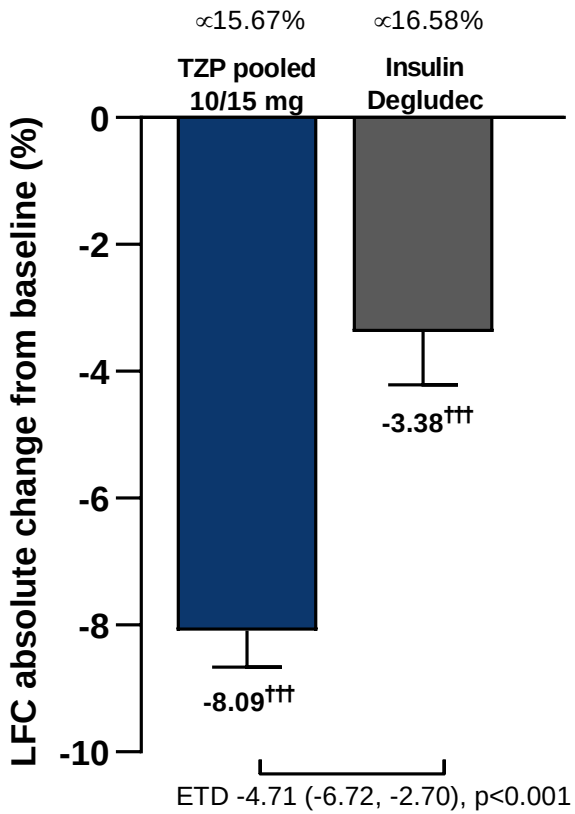
Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Insulin Degludec

Data are LSM (SE); MMRM analysis using log transformation. mITT (safety analysis set). Estimated treatment differences (ETD) are LSM (95% confidence interval) vs. insulin degludec. † p<0.05; †† p<0.01; ††† p<0.001 vs. baseline within treatment group. ∝ represents the mean value at baseline for the respective group.

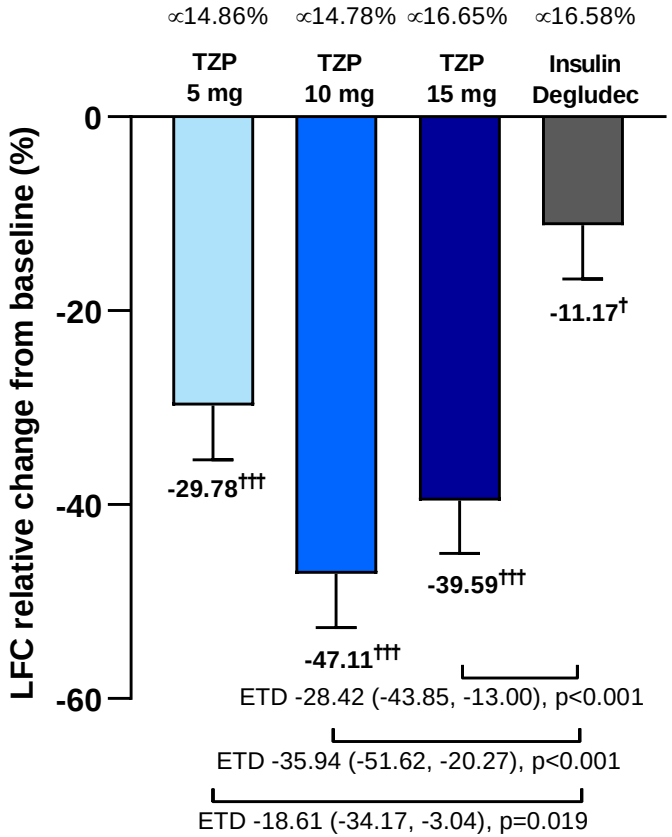
Abbreviations: LSM = least-squares mean; mITT = modified Intent-to-Treat; MMRM = mixed model repeated measures; SE = standard error.

Liver Fat Content

Comparison Between Pooled Data From Tirzepatide 10/15 mg and Insulin Degludec at Week 52



Comparison Between Individual Doses of Tirzepatide and Insulin Degludec at Week 52

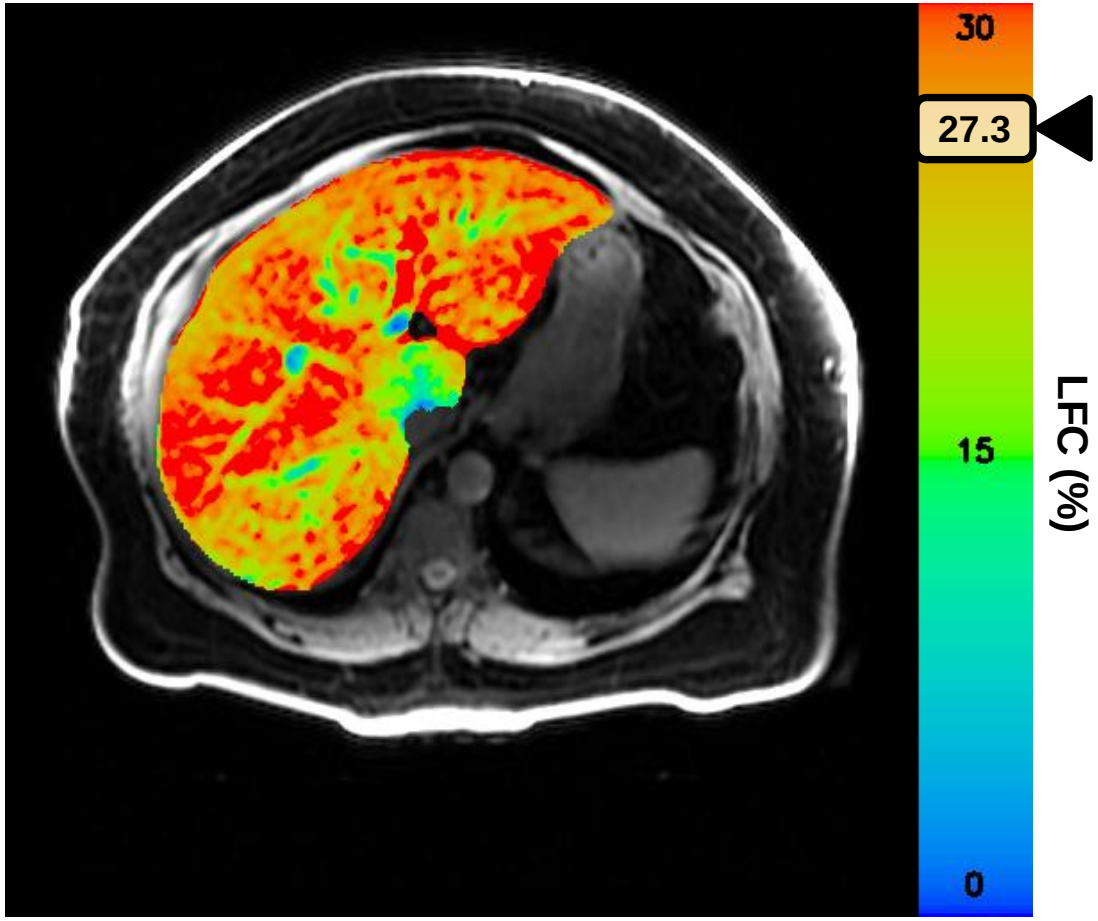


Data are LSM (SE); ANCOVA analysis. mITT (MRI analysis set). Estimated treatment differences (ETD) are LSM (95% confidence interval) vs. insulin degludec. † p<0.05; ††† p<0.001 vs. baseline within treatment group. ∝ represents the mean value at baseline for the respective group. Mean insulin degludec dose at Week 52 was 58.8 U/day (0.6 U/kg/day).

Abbreviations: ANCOVA = analysis of covariance; LFC = liver fat content; LSM = least-squares mean; mITT = modified Intent-to-Treat; MRI = magnetic resonance imaging; SE = standard error; TZP = tirzepatide.

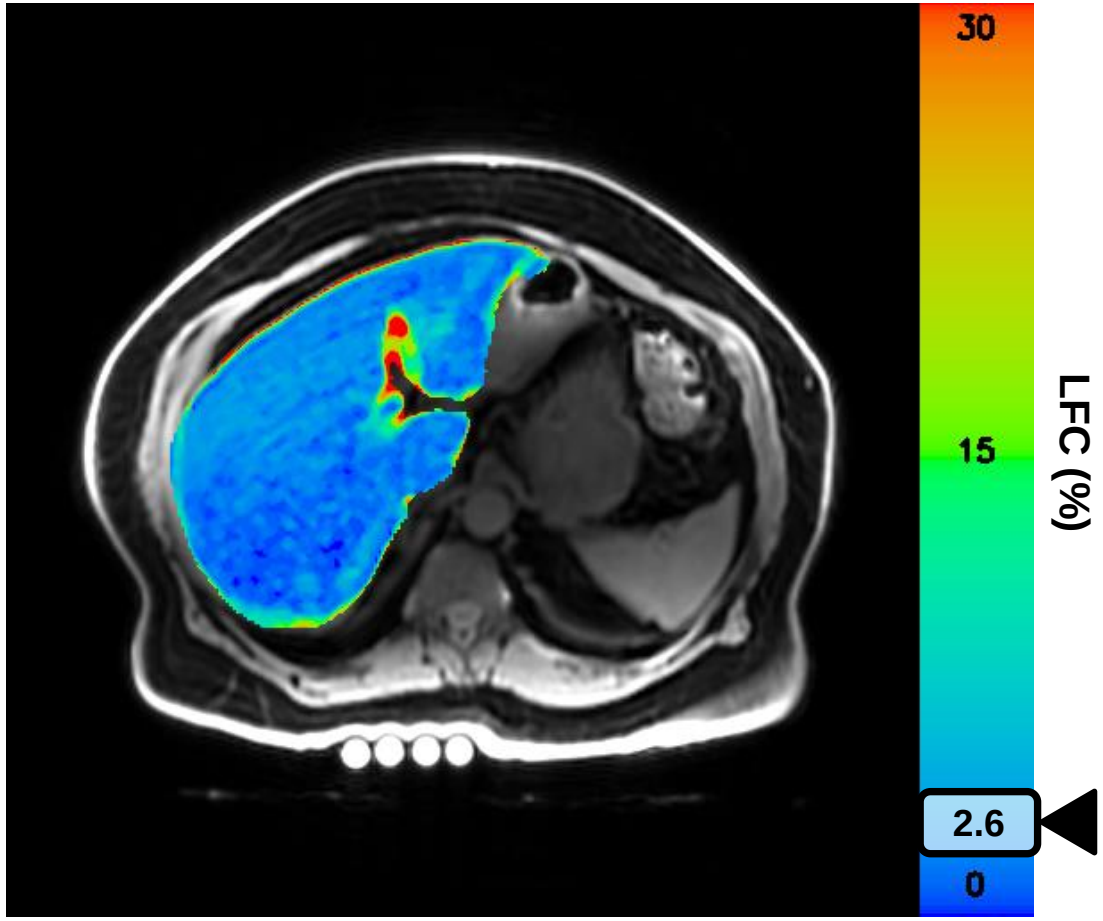
MRI Scan: Male, 59 Years, on Metformin + SGLT-2i Randomised to Tirzepatide 5 mg

At Baseline



BMI: 44.8 kg/m^2; body weight: 134.2 kg; WC: 139.7 cm
HbA_{1c}: 78.1 mmol/mol (9.3%)
FSG: 10.3 mmol/L (186 mg/dL)

At Week 52

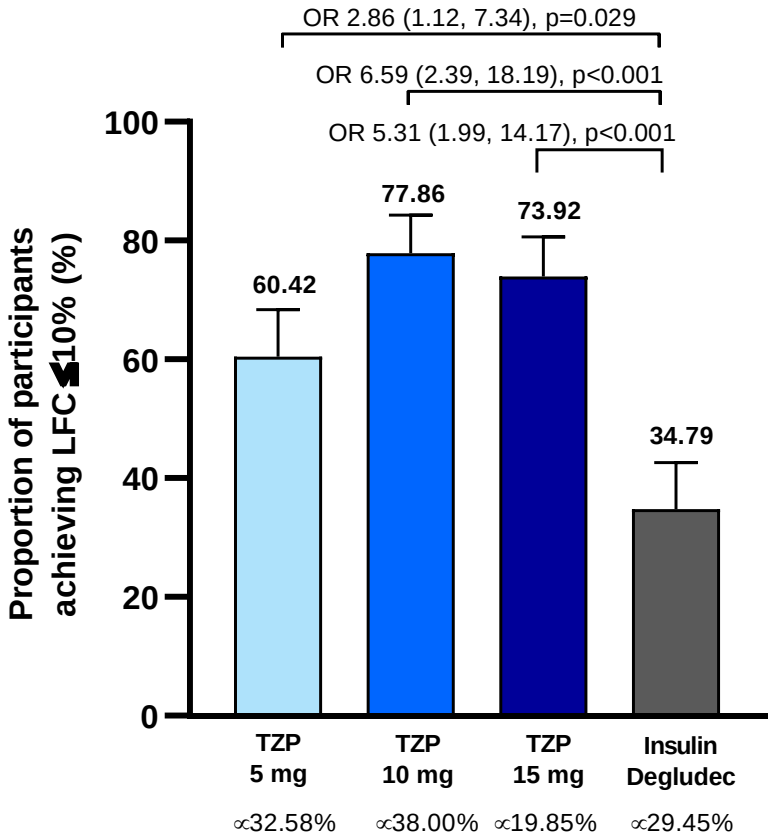


BMI: 36.2 kg/m^2; body weight: 108.4 kg; WC: 124.4 cm
HbA_{1c}: 43.2 mmol/mol (6.1%)
FSG: 5.9 mmol/L (107 mg/dL)

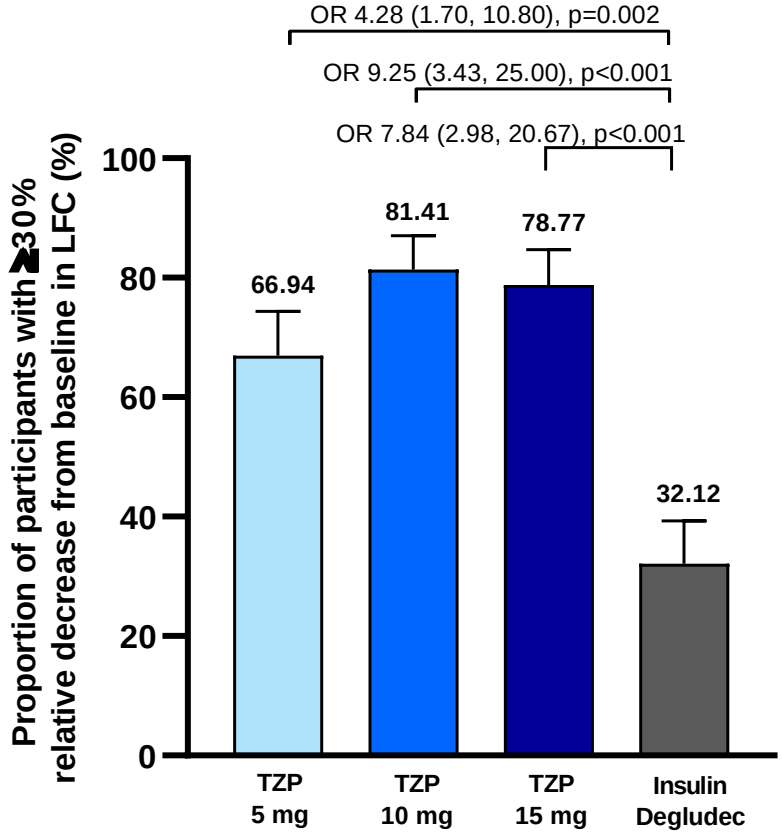
Abbreviations: BMI = body mass index; FSG = fasting serum glucose; HbA_{1c} = haemoglobin A_{1c}; LFC = liver fat content; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; WC = waist circumference.

Liver Fat Content Targets

Proportion of Participants With LFC ≤10% at Week 52



Proportion of Participants With ≥30% Relative Decrease From Baseline in LFC at Week 52

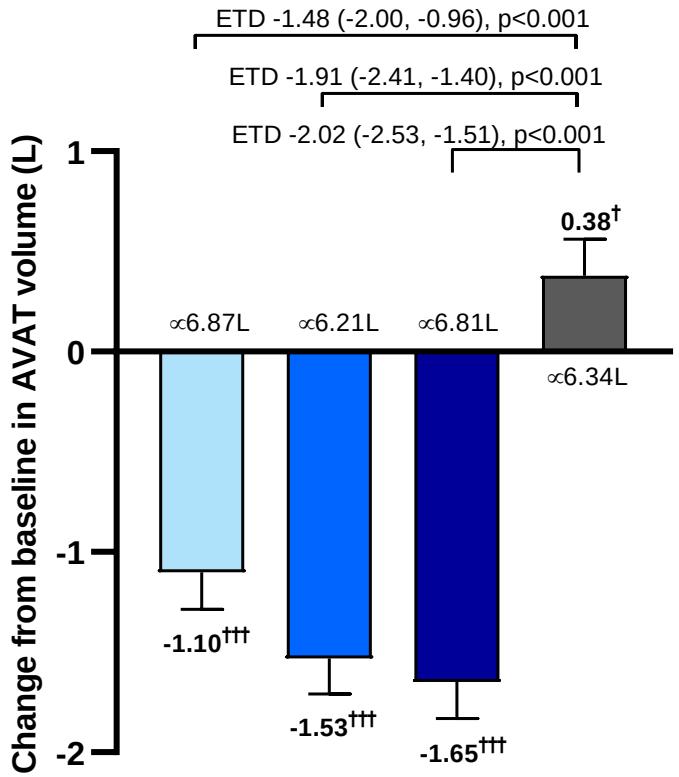


Data are LSM (SE); logistic regression analysis. mITT (MRI analysis set). Odds ratio (OR) are LSM (95% confidence interval) vs. insulin degludec. ∝ represents the mean value at baseline for the respective group.

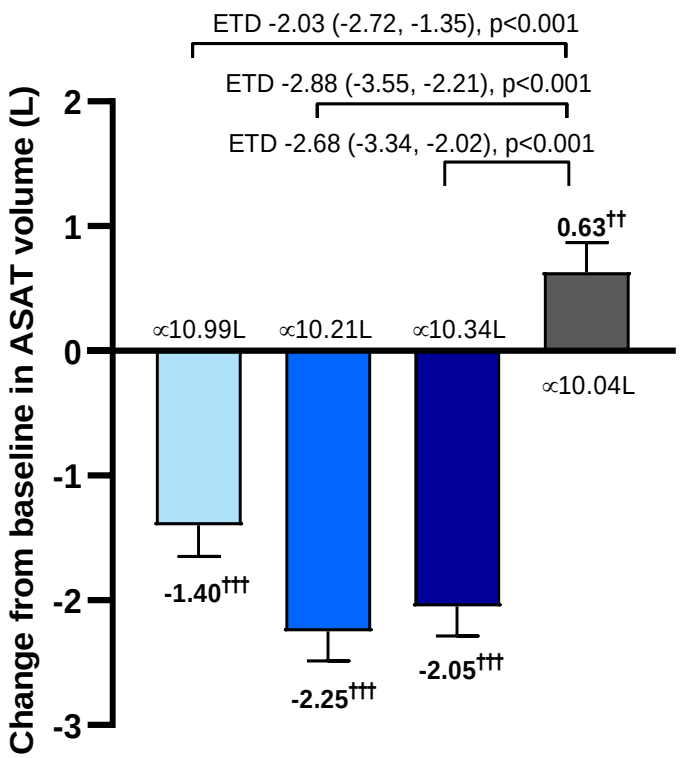
Abbreviations: LFC = liver fat content; LSM = least-squares mean; mITT = modified Intent-to-Treat; MRI = magnetic resonance imaging; SE = standard error; TZP = tirzepatide.

Distribution of Abdominal Adipose Tissue

Abdominal Visceral Adipose Tissue (AVAT) at Week 52



Abdominal SC Adipose Tissue (ASAT) at Week 52

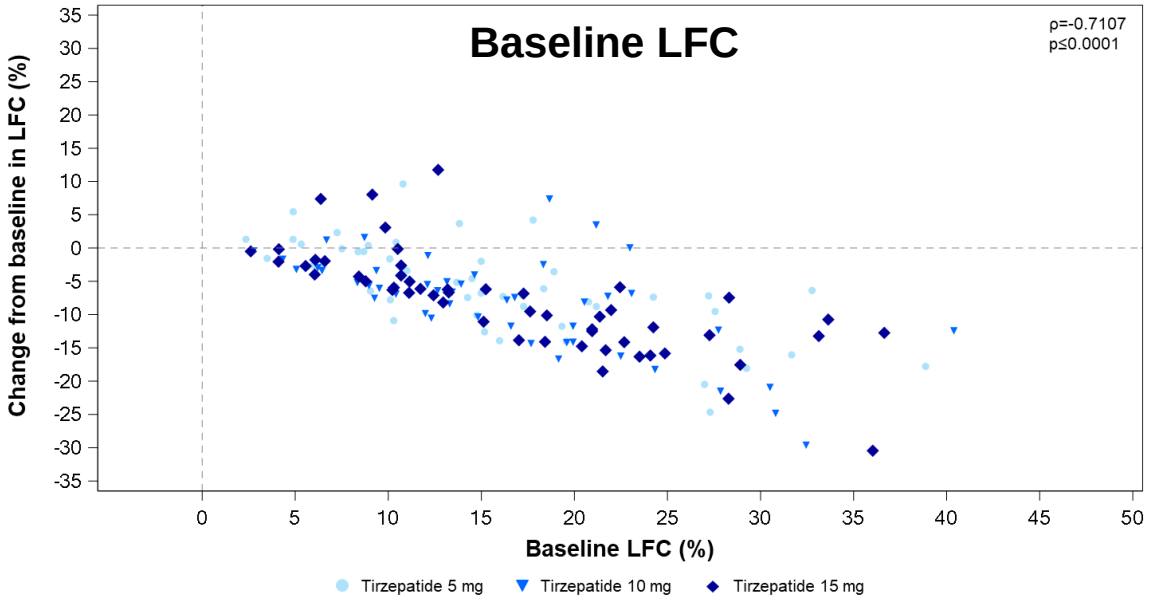


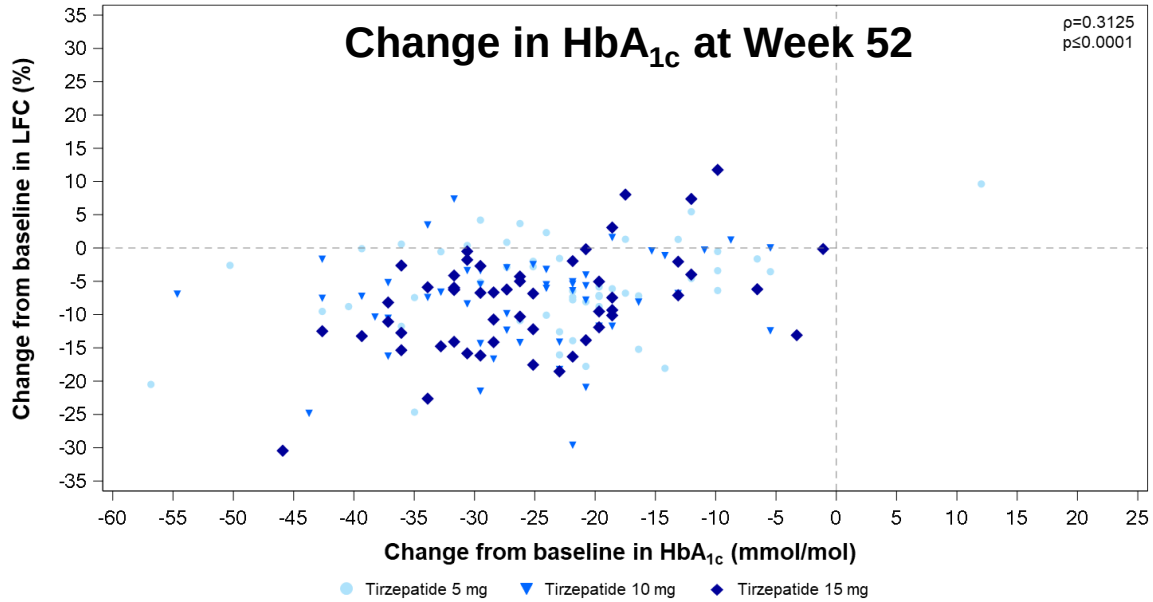
Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Insulin Degludec

Data are LSM (SE); ANCOVA analysis. mITT (MRI analysis set). Estimated treatment differences (ETD) are LSM (95% confidence interval) vs. insulin degludec. † p<0.05; †† p<0.01; ††† p<0.001 vs. baseline within treatment group. ∝ represents the mean value at baseline for the respective group.

Abbreviations: ANCOVA = analysis of covariance; LSM = least-squares mean; mITT = modified Intent-to-Treat; MRI = magnetic resonance imaging; SC = subcutaneous; SE = standard error.

Correlations Between Change in LFC and Baseline LFC, Change in HbA_{1c}, and Liver Enzymes





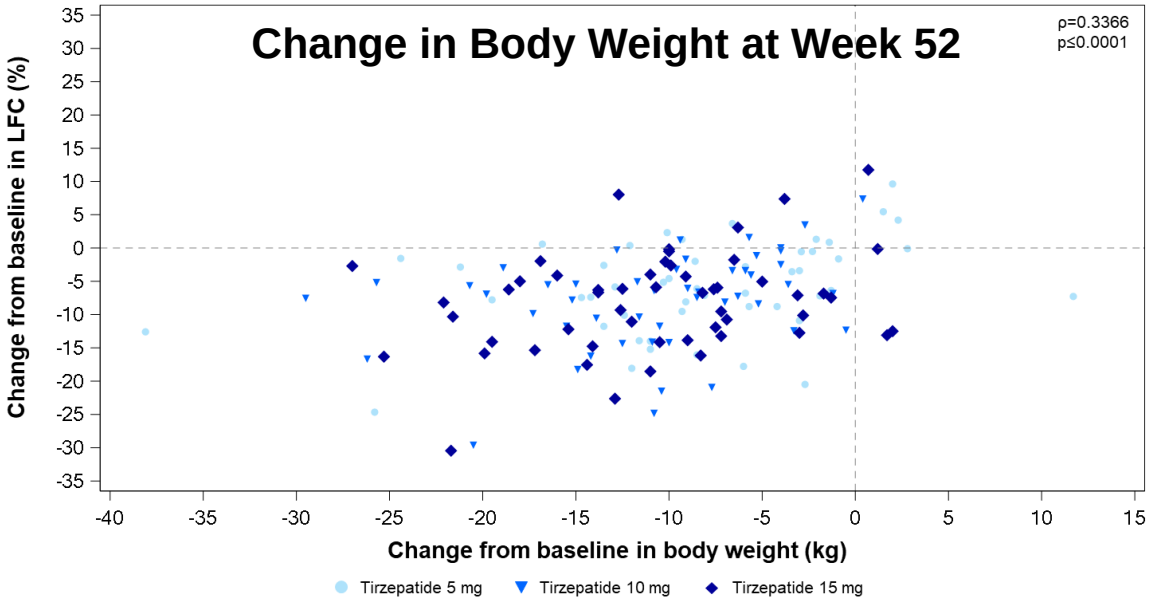
Change in Liver Enzymes at Week 52

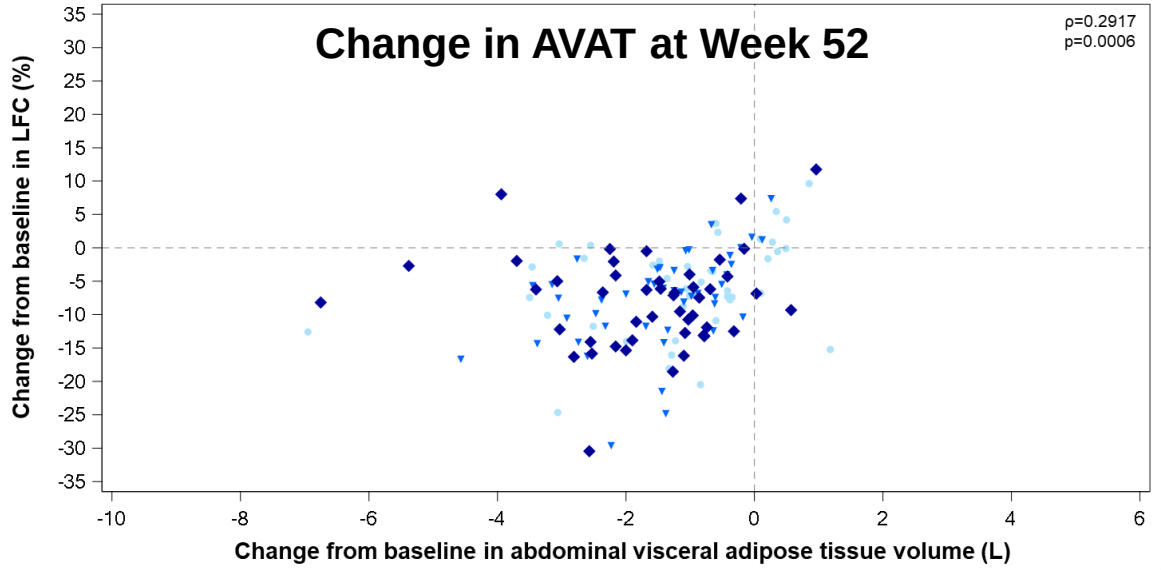
- There was a significant positive correlation between the change from baseline in LFC and
  - ALT concentration (ρ=0.35; p≤0.0001)
  - AST concentration (ρ=0.23; p≤0.01)

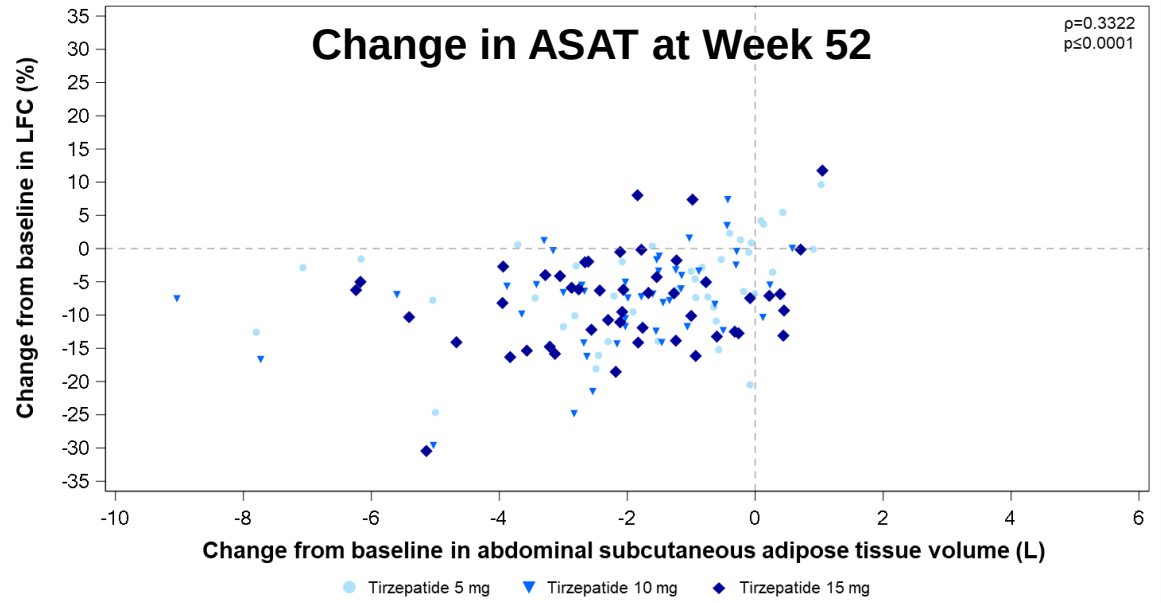
Correlations used pooled data from all tirzepatide arms. mITT (MRI analysis set).

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; HbA_{1c} = haemoglobin A_{1c}; LFC = liver fat content; mITT = modified Intent-to-Treat.

Correlations Between Change in LFC and Change in Body Weight, AVAT, and ASAT







Correlations used pooled data from all tirzepatide arms. mITT (MRI analysis set).
Abbreviations: ASAT = abdominal subcutaneous adipose tissue; AVAT = abdominal visceral adipose tissue; LFC = liver fat content; mITT = modified Intent-to-Treat.

Conclusion

- In patients with type 2 diabetes on metformin, with or without SGLT-2i, treatment with tirzepatide for 52 weeks is effective in reducing liver fat content and abdominal visceral and subcutaneous adipose tissue volumes.
- Further studies are needed to assess whether this liver fat reduction after treatment with tirzepatide leads to improvements in histopathological parameters in patients with NASH.

Abbreviations: NASH = non-alcoholic steatohepatitis; SGLT-2i = sodium-glucose cotransporter-2 inhibitors.

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