

A Triple GIP, GLP-1 and Glucagon Receptor Agonist, Retatrutide, Was Associated With Decreased Inflammatory CV Risk Biomarkers in People With Overweight or Obesity, With or Without Type 2 Diabetes

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Eli Lilly and Company, Indianapolis, USA

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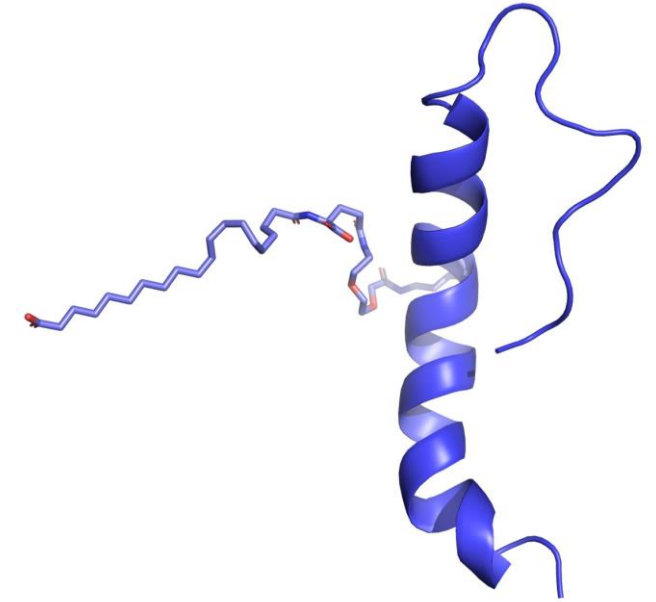


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Background

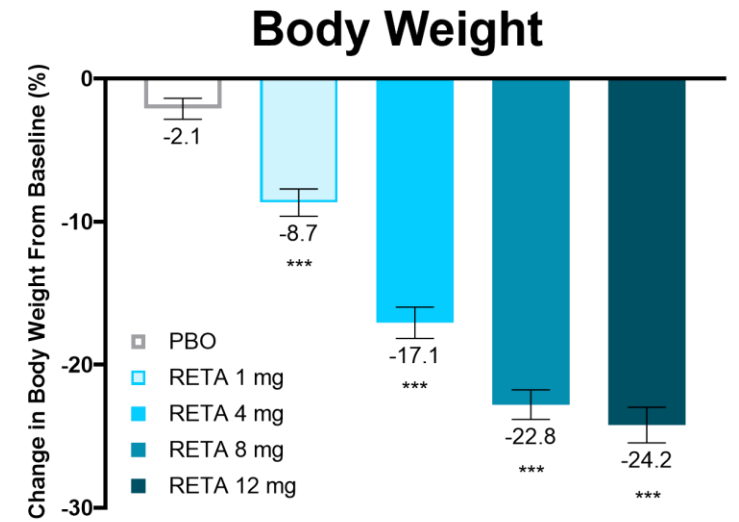
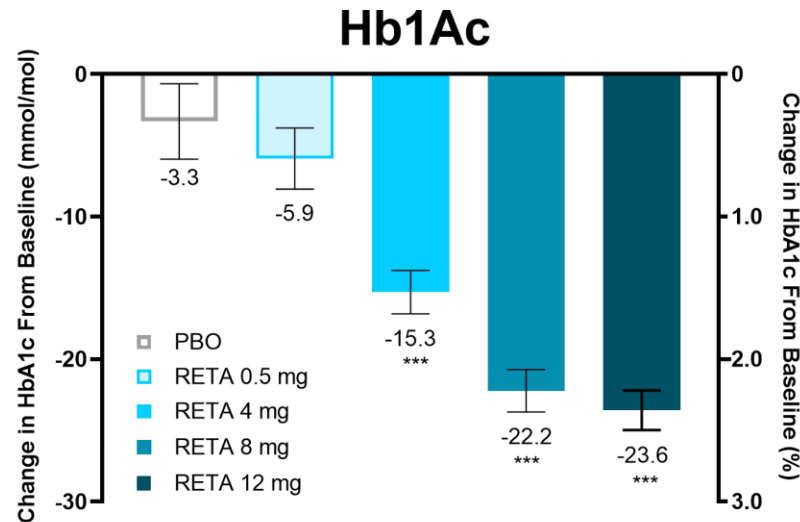
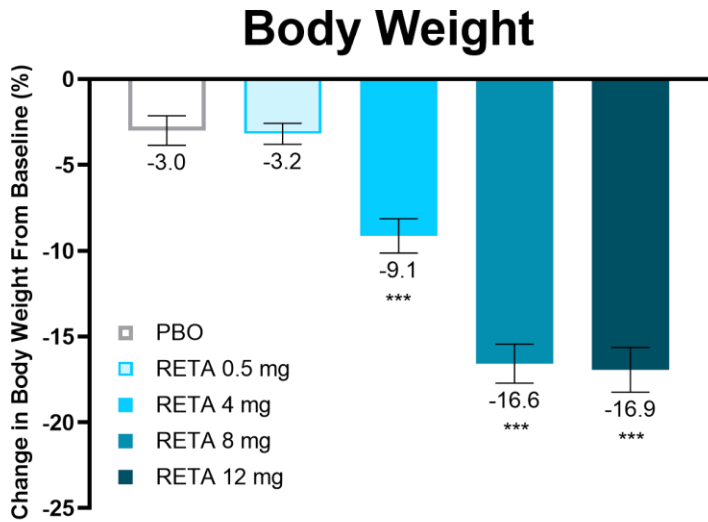
- Retatrutide is a novel synthetic molecule, which is an agonist of the glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1) and glucagon receptors
- Retatrutide is acylated, resulting in albumin-binding, half-life extension and weekly subcutaneous dosing
- Retatrutide has demonstrated reduction in glycated haemoglobin (HbA1c) and weight in people with type 2 diabetes (T2D)¹ and obesity²
- Biomarkers of inflammation, including high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-6 and tumour necrosis factor (TFN)- α , have been shown to be associated with increased cardiovascular (CV) risk³



Phase 2 Retatrutide Studies in People With T2D and People With Overweight/Obesity

T2D, 36 Weeks¹

Overweight/Obesity, 48 Weeks²



Key eligibility criteria

- Adults, 18-75 years of age
- T2D^a (baseline HbA1c: 53.0-91.3 mmol/mol [7.0-10.5%])
- Body mass index (BMI): 25-50 kg/m²
- On treatment with diet and exercise alone or with a stable dose of metformin^b

Key eligibility criteria

- Adults, 18-75 years of age
- No diagnosis of T1D or T2D
- Obesity (BMI ≥30-≤50 kg/m²), or overweight (BMI ≥27-<30 kg/m²) with a weight-related comorbidity

***p<0.001 vs. PBO.

^aAccording to the World Health Organization or other locally applicable diagnostic standards; ^b≥1000 mg/day and not more than the locally approved dose.

Note: Data are LSM (SEM) derived from a mixed model for repeated measures.

1. Rosenstock J, et al. *Lancet*. 2023;402:529-544. 2. Jastreboff AM, et al. *N Engl J Med*. 2023;389:514-526.

HbA1c=glycated haemoglobin; LSM=least squares mean; PBO=placebo; RETA=retatrutide; SEM=standard error of the mean; T1D=type 1 diabetes; T2D=type 2 diabetes.

Objective and Methods

Objective

- This post hoc analysis evaluated the association between retatrutide and CV risk by measuring the percent change from baseline in circulating levels of inflammatory biomarkers and adipokines in participants with obesity with or without T2D

Methods

- hsCRP, IL-6, leptin, adiponectin and TNF- α were measured by immunoassay in fasting plasma samples collected at baseline, Week 24 and either Week 36 (T2D) or Week 48 (overweight/obesity)
 - Samples collected after discontinuation or rescue were excluded from the analysis
 - Participants were required to have baseline and at least 1 post-baseline sample available for inclusion in the analysis
- Changes in biomarkers were analysed using mixed model for repeated measures with log transformation
 - The model included the treatment, time and time*treatment as fixed effects and the baseline biomarker as a covariate
- Correlation between change in log hsCRP and percent change from baseline in body weight was evaluated by Pearson correlation analysis in participants treated with retatrutide only

Baseline Demographics and Clinical Characteristics: Overall Populations

- At baseline, hsCRP levels were higher in participants with T2D than in those with overweight/obesity (p=0.005)

Characteristic	T2D (N=281)	Obesity and Overweight (N=338)
Age, years	56.2 (9.7)	48.2 (12.7)
Body weight, kg	98.2 (21.1)	107.7 (21.4)
BMI, kg/m ²	35.0 (6.3)	37.3 (5.7)
HbA1c, %	8.3 (1.1)	5.5 (0.4)
HbA1c, mmol/mol	66.9 (11.9)	36.9 (4.2)
Waist circumference, cm	111.8 (15.9)	115.5 (14.7)
Duration of diabetes, years	8.1 (7.0)	–
Duration of obesity, years	–	13.0 (10.8)
hsCRP, mg/L, geometric mean (SEM)	4.3 (0.3)	3.4 (0.2)
IL-6, pg/mL, geometric mean (SEM)	1.5 (0.1)	1.2 (0)
Leptin, µg/L, geometric mean (SEM)	25.4 (1.4)	32.9 (1.4)
Adiponectin, mg/L, geometric mean (SEM)	4.1 (0.2)	4.9 (0.2)
TNF-α, pg/mL, geometric mean (SEM)	2.7 (0.1)	1.8 (0)

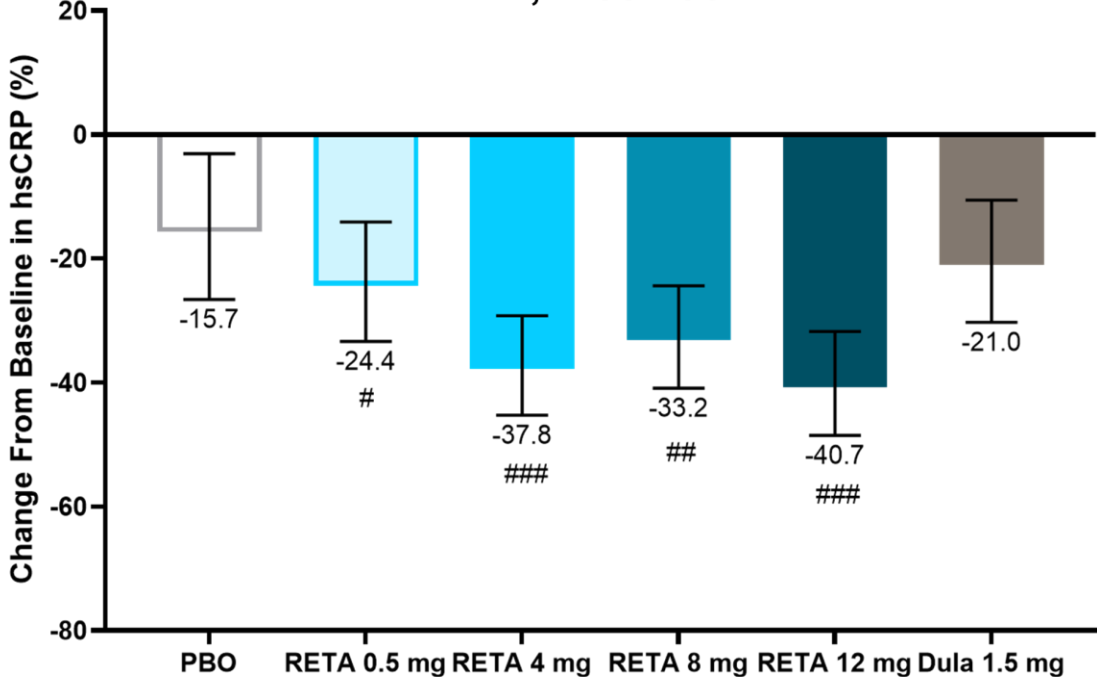
Note: Data are mean (SD) unless stated otherwise.

BMI=body mass index; HbA1c=glycated haemoglobin; hsCRP=high-sensitivity C-reactive protein; IL=interleukin; SD=standard deviation; SEM=standard error of the mean;

T2D=type 2 diabetes; TNF=tumour necrosis factor.

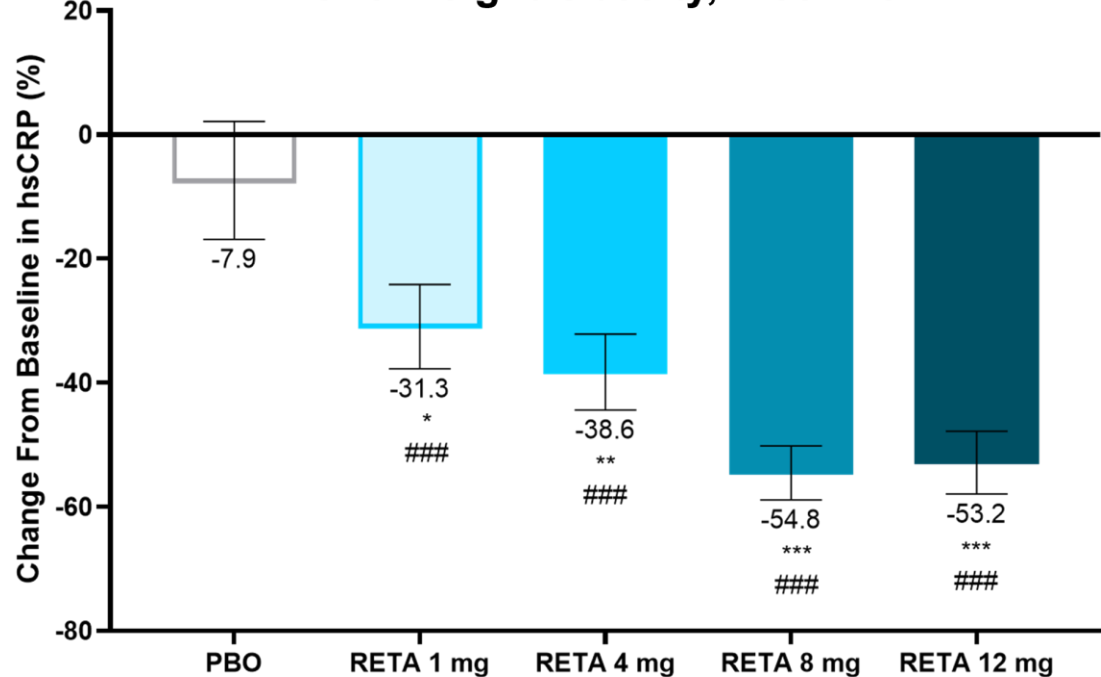
Change in hsCRP From Baseline to End of Treatment

T2D, Week 36



Baseline N	PBO	RETA 0.5 mg	RETA 4 mg	RETA 8 mg	RETA 12 mg	Dula 1.5 mg
Baseline N	32	39	37	40	32	40
Baseline hsCRP, mg/L	4.6 (0.8)	3.6 (0.6)	4.3 (0.7)	3.1 (0.5)	5.4 (1.0)	5.5 (0.9)

Overweight/Obesity, Week 48



Baseline N	PBO	RETA 1 mg	RETA 4 mg	RETA 8 mg	RETA 12 mg
Baseline N	56	58	57	60	50
Baseline hsCRP, mg/L	3.5 (0.5)	4.1 (0.6)	3.0 (0.4)	3.5 (0.5)	2.9 (0.4)

*p<0.05, **p<0.01, ***p<0.001 vs. PBO.

#p<0.05, ##p<0.01, ###p<0.001 vs. baseline.

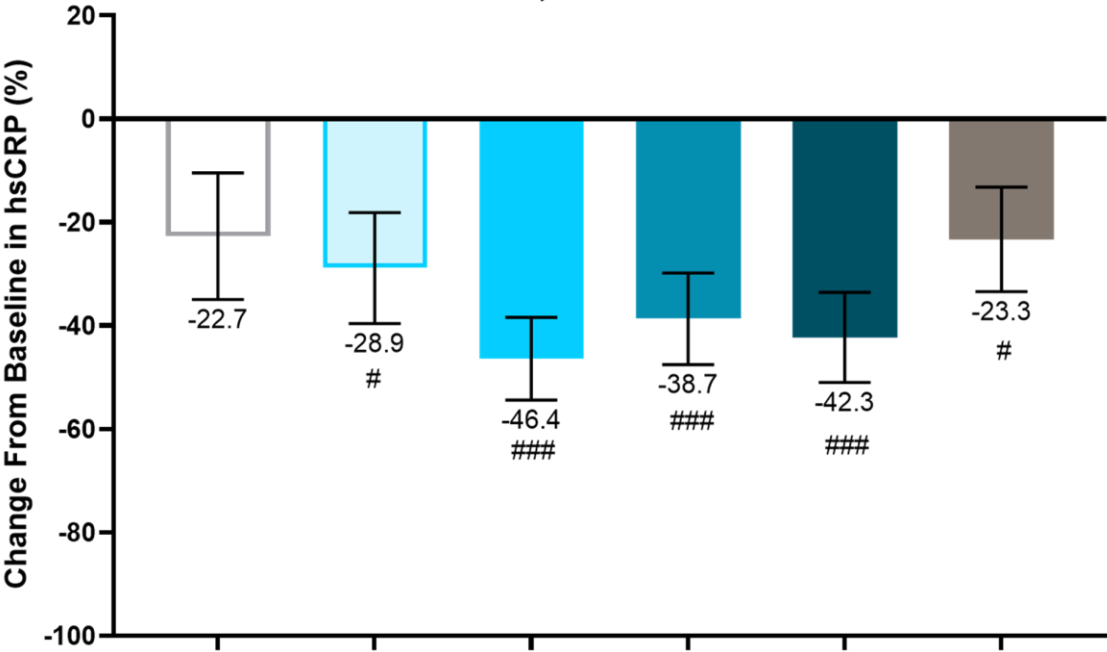
Note: Data are LSM (SEM).

Dula=dulaglutide; hsCRP=high-sensitivity C-reactive protein; LSM=least squares mean; PBO=placebo; RETA=retatrutide; SEM=standard error of the mean; T2D=type 2 diabetes.

Change in hsCRP From Baseline to End of Treatment in Participants With Baseline hsCRP >2 mg/L

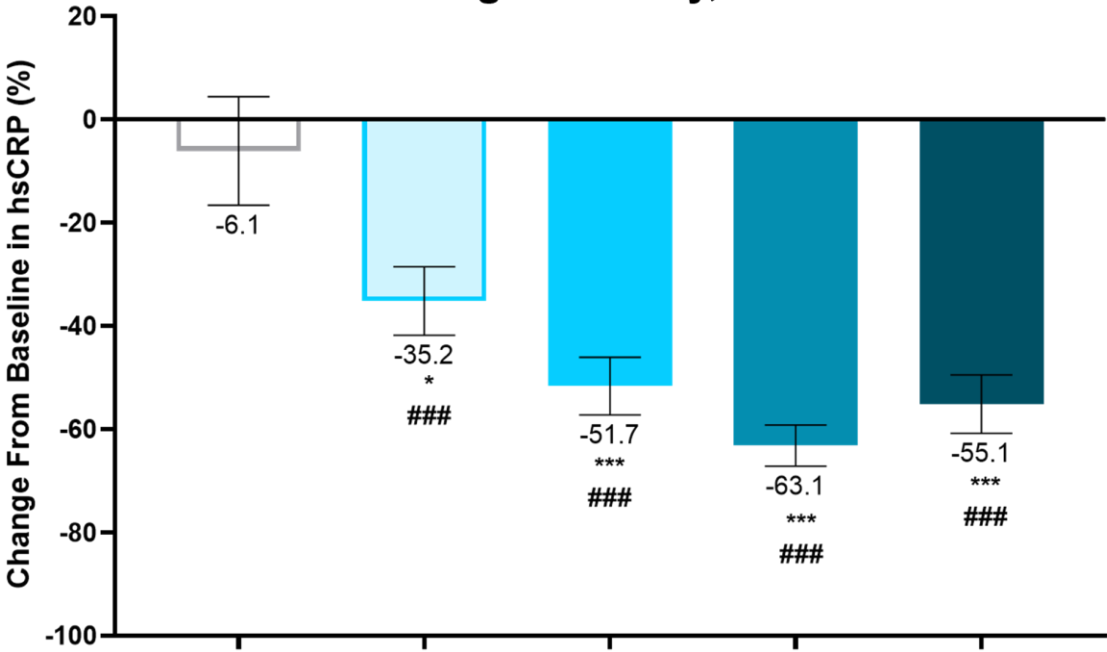
Participants With Baseline hsCRP >2 mg/L

T2D, Week 36



	PBO	RETA 0.5 mg	RETA 4 mg	RETA 8 mg	RETA 12 mg	Dula 1.5 mg
Baseline n	24	27	26	28	27	34
Baseline hsCRP, mg/L	7.2 (1.1)	6.3 (0.9)	7.1 (1.0)	5.3 (0.7)	7.3 (1.0)	7.2 (0.9)

Overweight/Obesity, Week 48



	PBO	RETA 1 mg	RETA 4 mg	RETA 8 mg	RETA 12 mg
Baseline n	44	50	38	44	34
Baseline hsCRP, mg/L	5.6 (0.6)	5.1 (0.5)	5.3 (0.6)	5.2 (0.5)	5.6 (0.6)

*p<0.05, ***p<0.001 vs. PBO.

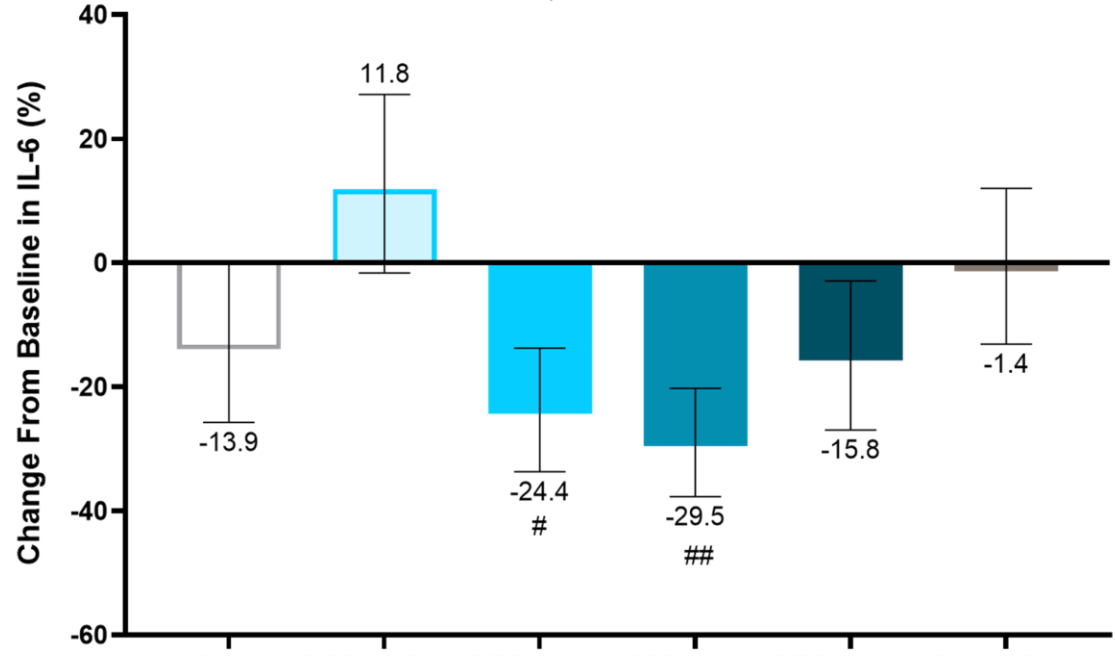
#p<0.05, ###p<0.001 vs. baseline.

Note: Data are LSM (SEM).

Dula=dulaglutide; hsCRP=high-sensitivity C-reactive protein; LSM=least squares mean; PBO=placebo; RETA=retatrutide; SEM=standard error of the mean; T2D=type 2 diabetes.

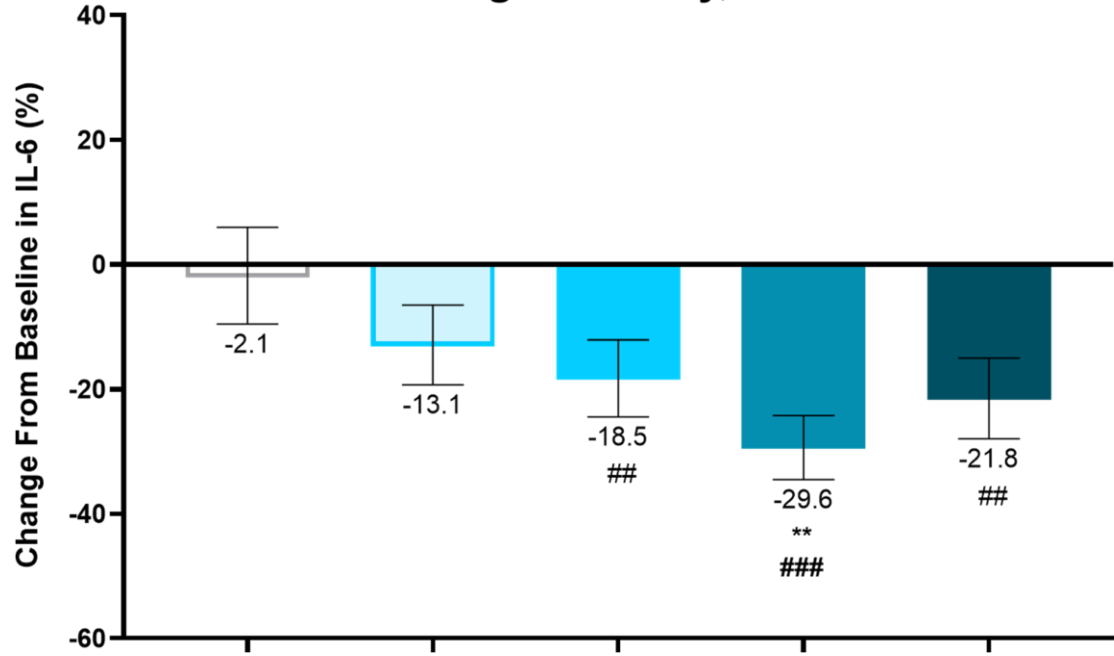
Change in IL-6 From Baseline to End of Treatment

T2D, Week 36



Baseline N	PBO	RETA 0.5 mg	RETA 4 mg	RETA 8 mg	RETA 12 mg	Dula 1.5 mg
Baseline N	30	40	37	41	33	40
Baseline IL-6, pg/mL	1.5 (0.2)	1.3 (0.1)	1.7 (0.2)	1.3 (0.1)	1.6 (0.2)	1.5 (0.1)

Overweight/Obesity, Week 48



Baseline N	PBO	RETA 1 mg	RETA 4 mg	RETA 8 mg	RETA 12 mg
Baseline N	55	59	56	60	49
Baseline IL-6, pg/mL	1.1 (0.1)	1.3 (0.1)	1.2 (0.1)	1.3 (0.1)	1.1 (0.1)

**p<0.01 vs. PBO.

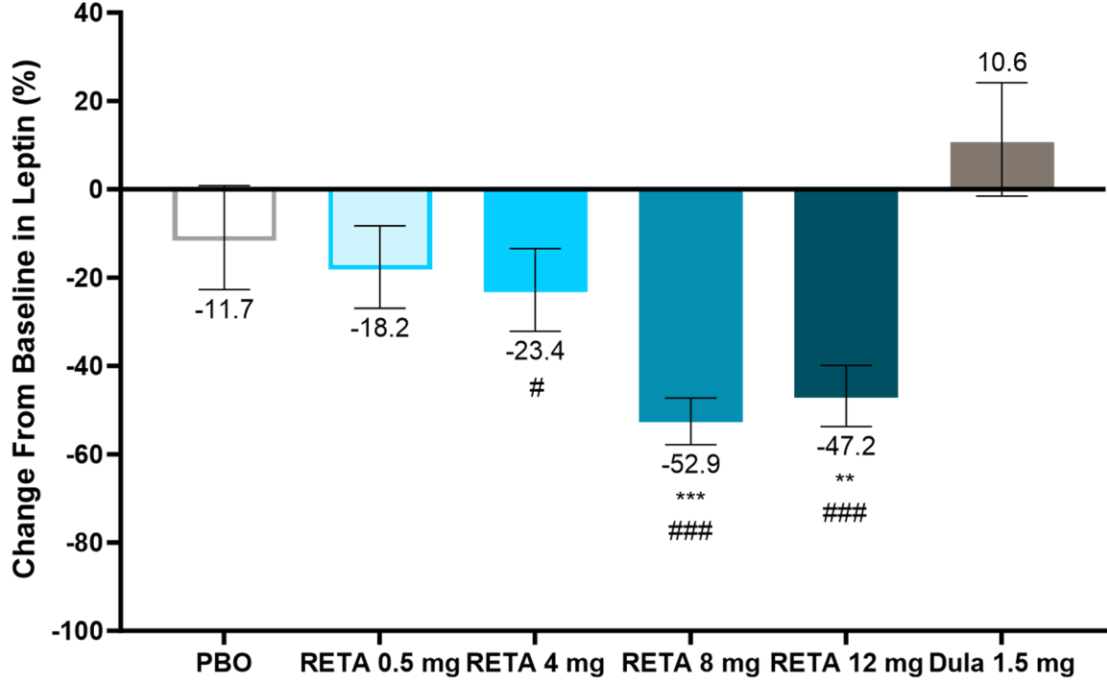
#p<0.05, ##p<0.01, ###p<0.001 vs. baseline.

Note: Data are LSM (SEM).

Dula=dulaglutide; IL=interleukin; LSM=least squares mean; PBO=placebo; RETA=retatrutide; SEM=standard error of the mean; T2D=type 2 diabetes.

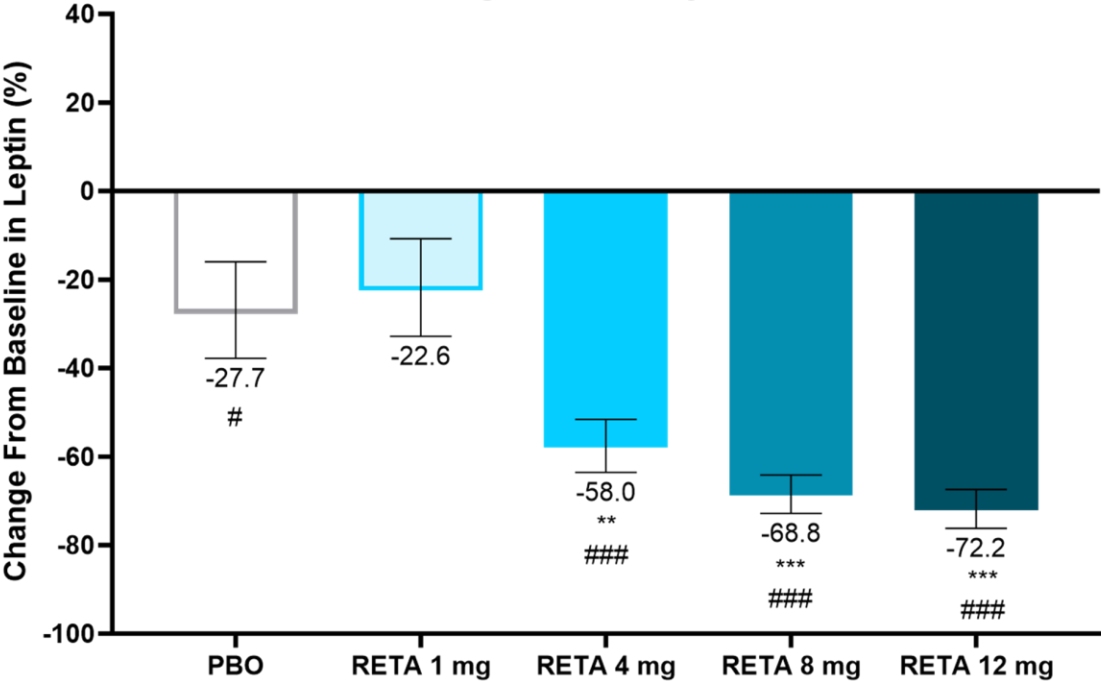
Change in Leptin From Baseline to End of Treatment

T2D, Week 36



Baseline N	PBO	RETA 0.5 mg	RETA 4 mg	RETA 8 mg	RETA 12 mg	Dula 1.5 mg
Baseline leptin, µg/mL	20.4 (2.9)	23.6 (2.9)	24.2 (3.2)	24.7 (3.0)	24.6 (3.4)	35.4 (4.4)

Overweight/Obesity, Week 48



Baseline N	PBO	RETA 1 mg	RETA 4 mg	RETA 8 mg	RETA 12 mg
Baseline leptin, µg/mL	37.1 (3.7)	31.8 (3.1)	31.4 (3.0)	32.9 (3.1)	31.7 (3.3)

p<0.01, *p<0.001 vs. PBO.

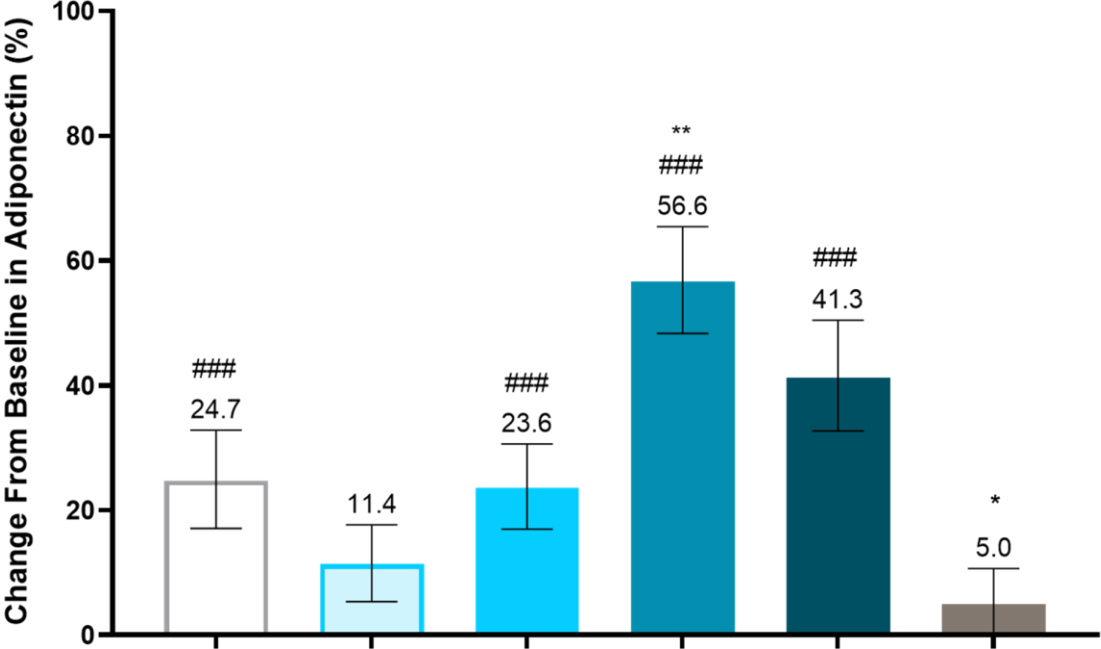
#p<0.05, ###p<0.001 vs. baseline.

Note: Data are LSM (SEM).

Dula=dulaglutide; LSM=least squares mean; PBO=placebo; RETA=retatrutide; SEM=standard error of the mean; T2D=type 2 diabetes.

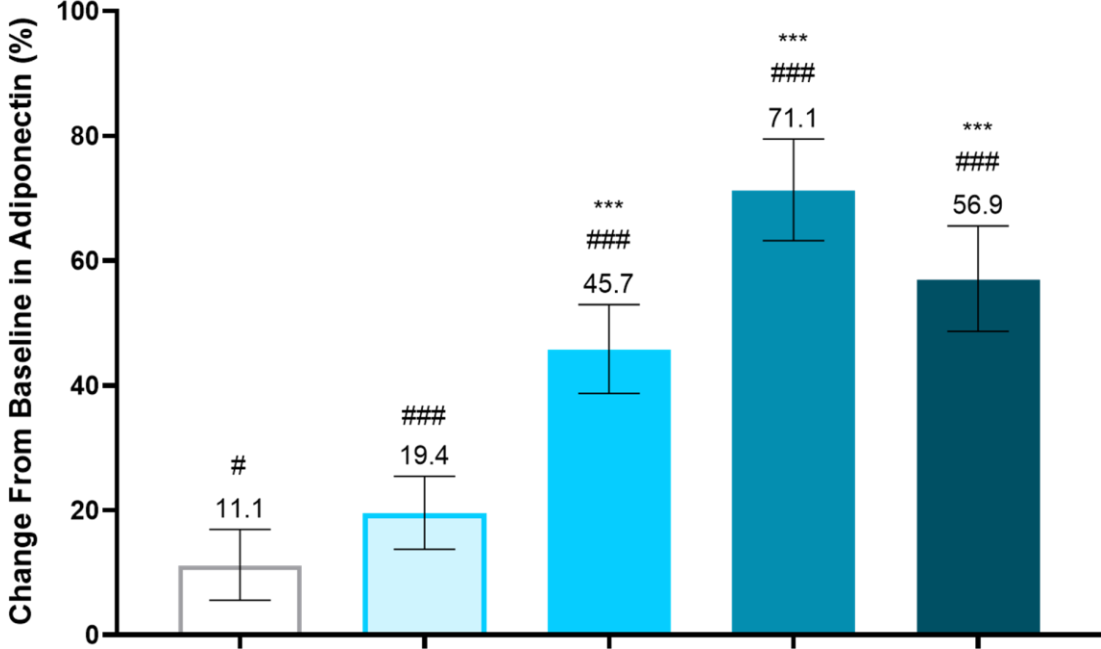
Change in Adiponectin From Baseline to End of Treatment

T2D, Week 36



Baseline N	PBO	RETA 0.5 mg	RETA 4 mg	RETA 8 mg	RETA 12 mg	Dula 1.5 mg
Baseline adiponectin, mg/L	4.7 (0.5)	4.0 (0.4)	3.9 (0.4)	4.2 (0.4)	3.9 (0.4)	3.9 (0.4)

Overweight/Obesity, Week 48



Baseline N	PBO	RETA 1 mg	RETA 4 mg	RETA 8 mg	RETA 12 mg
Baseline adiponectin, mg/L	5.0 (0.4)	5.1 (0.4)	4.9 (0.4)	4.8 (0.4)	4.8 (0.4)

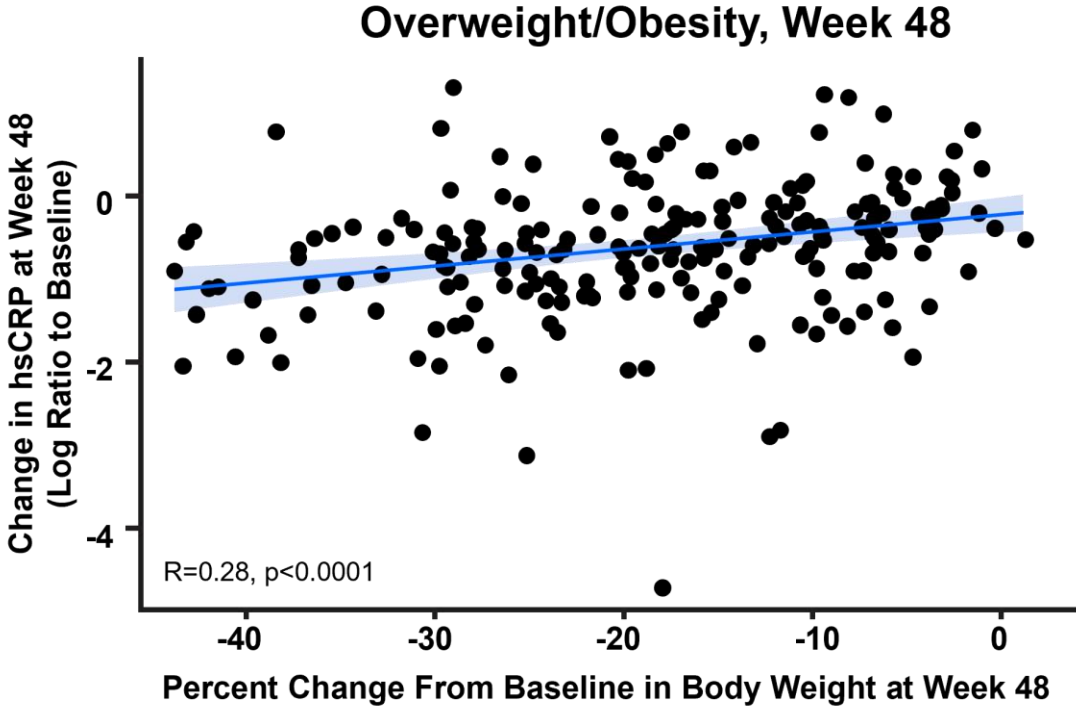
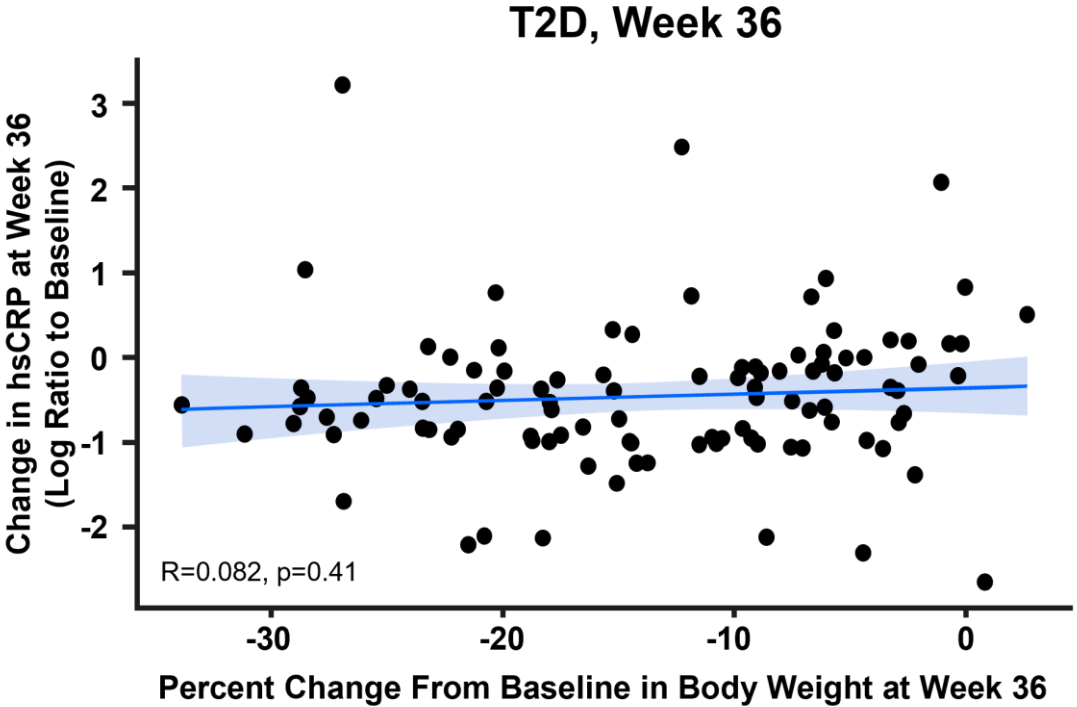
*p<0.05, **p<0.01, ***p<0.001 vs. PBO.

#p<0.05, ###p<0.001 vs. baseline.

Note: Data are LSM (SEM).

Dula=dulaglutide; LSM=least squares mean; PBO=placebo; RETA=retatrutide; SEM=standard error of the mean; T2D=type 2 diabetes.

Reduction in hsCRP Was Correlated With Weight Loss in Participants With Overweight/Obesity at Week 48



- There was a moderate but statistically significant correlation between reduction in hsCRP and weight loss in the overweight/obesity population, but not in the T2D population

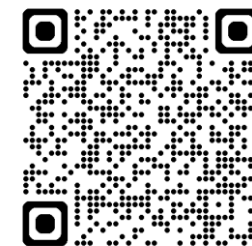
Note: Correlation analysis was conducted using Pearson correlation in participants receiving retatrutide.
hsCRP=high-sensitivity C-reactive protein; T2D=type 2 diabetes.

Limitations

- Several general limitations should be considered when interpreting the results:
 - Post hoc analysis
 - Limited sample size
- In addition, the lack of significant change in hsCRP with retatrutide compared with placebo in people with T2D may be related to:
 - Shorter duration of treatment (36 weeks)
 - Less pronounced weight loss treatment response in participants with T2D, as is commonly seen with incretins
 - An average of approximately 16% reduction from baseline levels observed in the placebo group
- Larger numbers of participants and body composition assessment could improve understanding of whether the relationship between hsCRP and weight loss is driven by changes in adipose tissue or visceral adipose tissue

Conclusions

- In this post hoc analysis of two Phase 2 trials in people with T2D or overweight/obesity, among participants treated with retatrutide:
 - hsCRP and IL-6 were reduced from baseline at the end of treatment in both populations; however, the changes were more clearly dose-dependent and statistically significant vs. placebo in the larger obesity trial
 - Leptin was reduced and adiponectin was increased from baseline and vs. placebo at the end of treatment in both populations
- Retatrutide appeared to be associated with an anti-inflammatory effect, which may be partially mediated by reduction in body weight
- The effect of retatrutide once weekly on CV outcomes is being evaluated in adults living with obesity in the Phase 3 study TRIUMPH-OUTCOMES (NCT06383390)



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Disclosures

- **G. Ruotolo, C. Harris, Y. Lin, M. K. Thomas, Y. Qu, J. Wilson, K. Duffin, M. L. Hartman, T. Coskun, Z. Milicevic and A. Haupt** are employees and shareholders of: Eli Lilly and Company
- Medical writing assistance was provided by Heidi Tran, PhD, and Joanna Best, PhD, of ProScribe – Envision Pharma Group, and was funded by Eli Lilly and Company