# Cotadutide (MEDI0382), a Dual Receptor Agonist With Glucagon like Peptide-1 and Glucagon Activity, Modulates Hepatic Glycogen and Fat Stores

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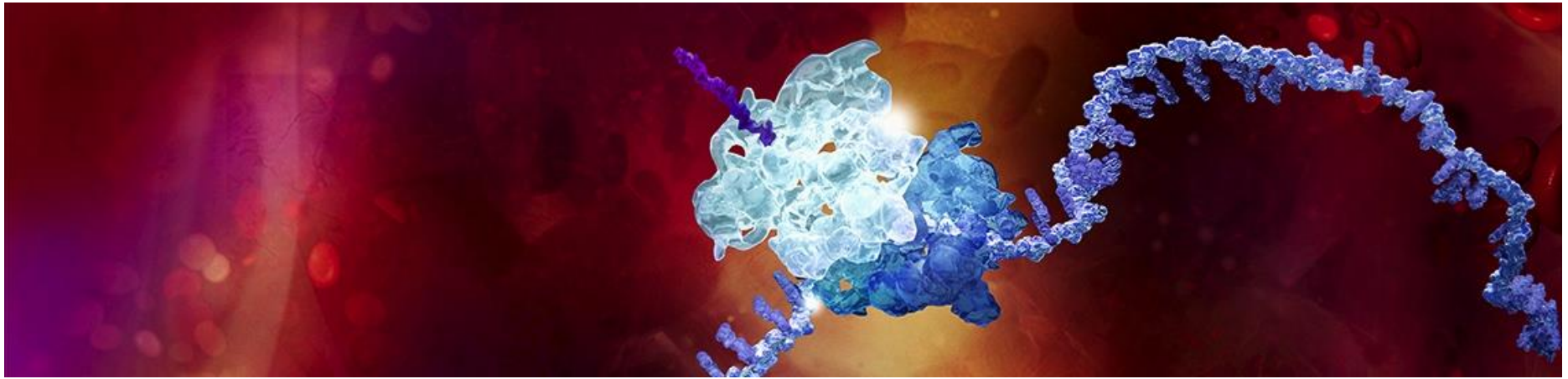
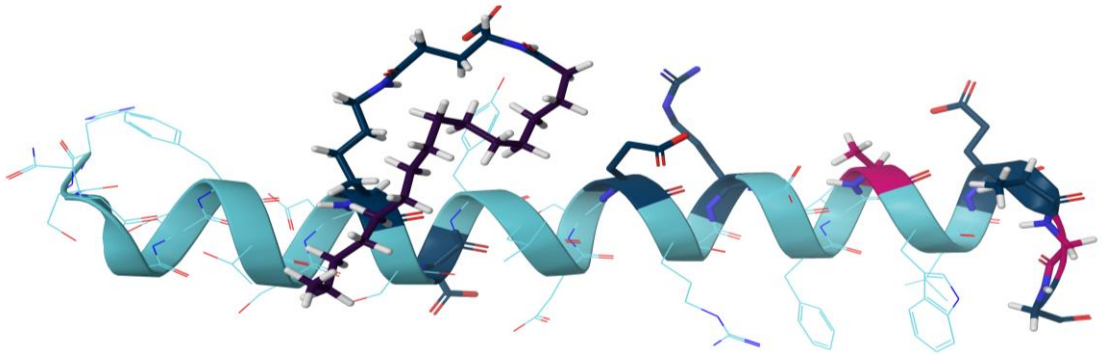


# Disclosures

- This study (NCT03555994) was sponsored by AstraZeneca
- Darren Robertson is an employee and a shareholder of AstraZeneca

# Cotadutide: A dual receptor agonist with GLP-1 and glucagon activity

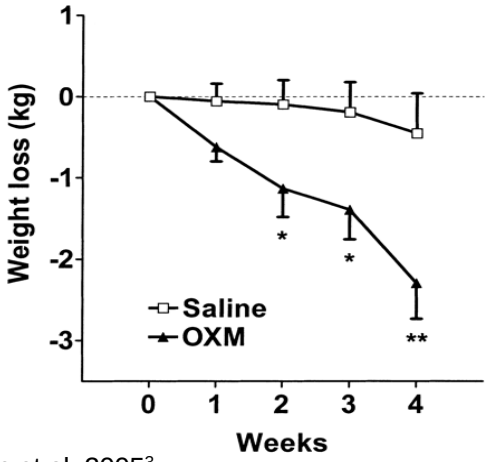


| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **GLP-1** | HAEGT | FTSDV | SSYLE | GQAAK | EFIAW | LVKGR | G |
| **Glucagon** | HSQGT | FTSDY | SKYLD | SRRAQ | DFVQW | LMNT | |
| **Cotadutide** | HSQGT | FTSDX | SEYLD | SERAR | DFVAW | LEAGG | |

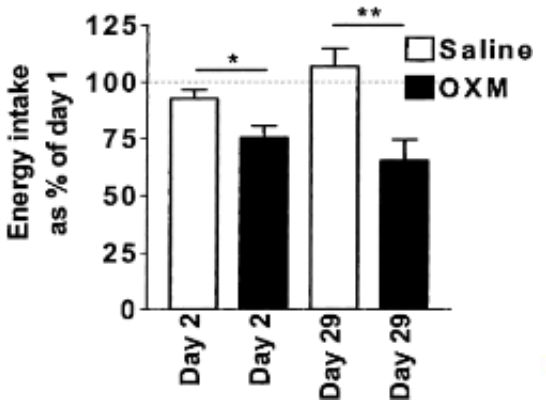
Ambery P et al. *Lancet.* 2018;391:2607–2618.
Amino acid sequence from Henderson et al. *Diabetes Obes Metab.* 2016;18:1176–1190.
GLP-1, glucagon-like peptide-1.

# Oxyntomodulin: An endogenous GLP-1 and glucagon receptor dual agonist

- Secreted along with GLP-1 in response to meals by enteroendocrine L-cells[1]
- Activates both **GLP-1** and **glucagon receptors**[2]
- Significantly upregulated after bariatric surgery (along with GLP-1)[1,2]
- **Reduces appetite** and **increases energy expenditure**, leading to substantial weight loss in patients who are overweight and obese[3,4]




Wynne et al. 2005[3]





1. Ionut et al. *Obesity.* 2013;21:1093–1103.
2. Laferrère et al. *J Clin Endocrinol Metab.* 2010;95:4072–4076.
3. Wynne et al. *Diabetes.* 2005;54:2390–2395.
4. Wynne et al. *Int J Obes.* 2006;30:1729–1736.

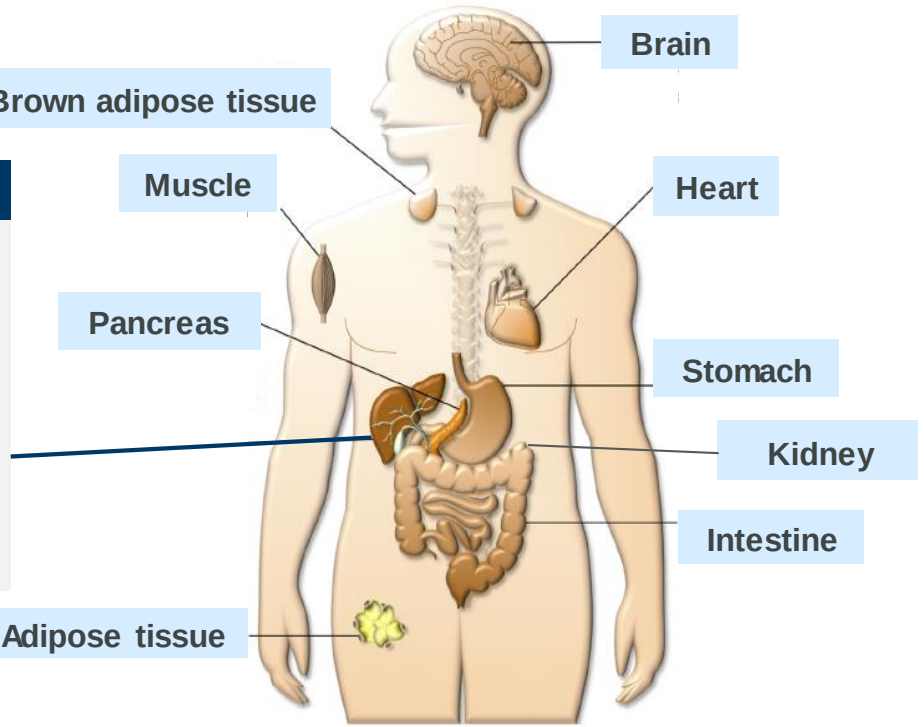

GLP-1, glucagon-like peptide-1; OXM, oxyntomodulin.

# Multiple effects of GLP-1 and glucagon on metabolism in the liver

**GLP-1 effects: ↑ ↓**

**Glucagon effects: ↑ ↓**

| Liver |
| --- |
| -Gluconeogenesis ↓ ↑ |
| -Glycogenolysis ↓ ↑ |
| -Hepatic steatosis ↓ |
| -Bile acid production ↑ |
| -Lipid oxidation ↑ |
| -Lipid synthesis ↓ |

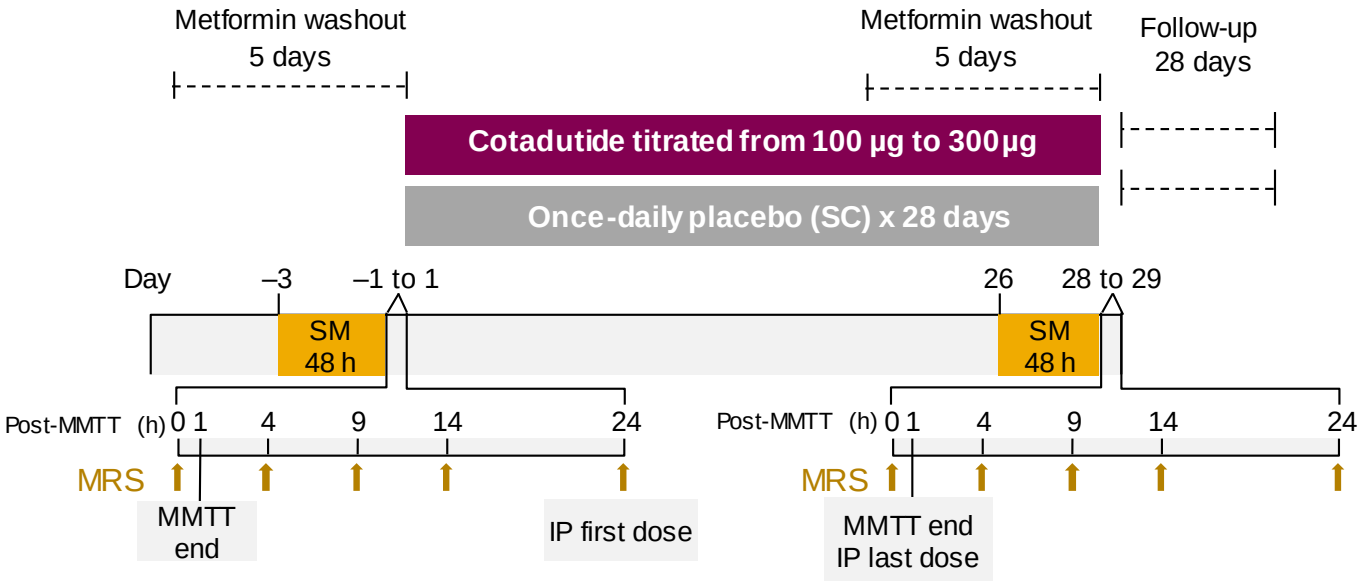



GLP-1, glucagon-like peptide-1.
Figure adapted from Müller et al. *Physiol Rev* 2017;97:721-766.

# Exploratory, double-blind, placebo-controlled, phase 2a trial

**Aim**

Investigate the effect of cotadutide on glycogen, as evidence for glucagon receptor engagement




**Eligibility Criteria**

- Aged ≥ 18 years
- BMI ≥ 27 and ≤ 40 kg/m$^2$
- T2DM on metformin monotherapy
- HbA1c ≤ 8.0%

**MRI/MRS Assessments**

- In vivo $^{13}$C MRS evaluating natural abundance $^{13}$C in glycogen
- Assessments of whole-liver PDFF
- All measurements were adjusted for liver volume

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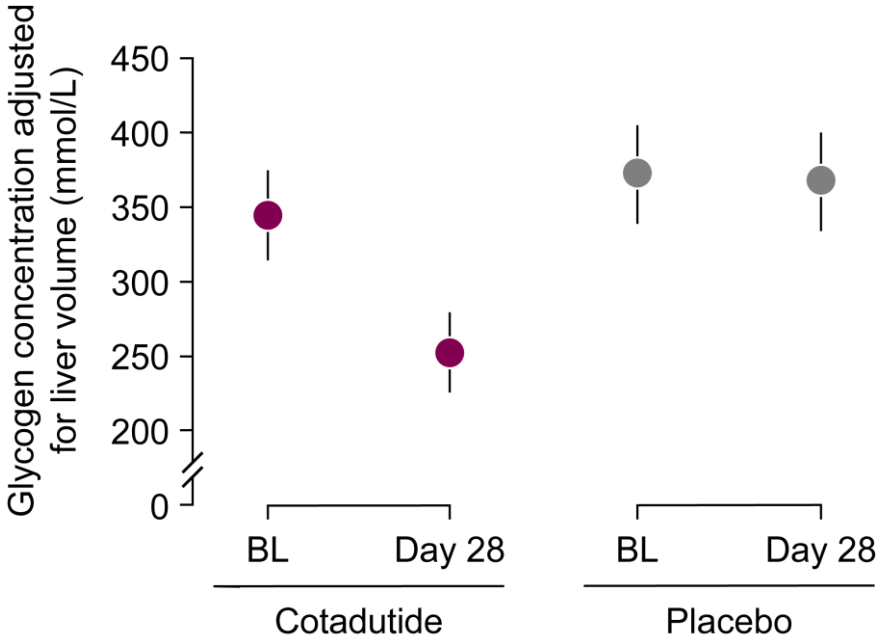
BMI, body mass index; HbA1c, glycated haemoglobin A1c; IP, investigational product; MMTT, mixed-meal tolerance test; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PDFF, proton density fat fraction; SC, subcutaneous; SM, standardised meal; T2DM, type 2 diabetes mellitus.

# Patient demographics and baseline characteristics

| Parameter | Placebo (n = 9) | Cotadutide (n = 12) |
|---|---|---|
| **Sex, n (%)** | | |
| Male | 6 (67) | 7 (58) |
| Female | 3 (33) | 5 (42) |
| **Mean age, years (SD)** | 69.3 (5.7) | 65.8 (7.3) |
| **Mean BMI, kg/m$^2$ (SD)** | 32.7 (4.8) | 31.8 (3.0) |
| **Mean weight, kg (SD)** | 99.6 (20.1) | 96.2 (7.7) |
| **Mean HbA1c, % (SD)** | 6.30 (0.7) | 6.51 (0.6) |
| **Mean duration of T2DM, years (SD)** | 9.9 (6.1) | 7.7 (5.4) |

BMI, body mass index; HbA1c, glycated haemoglobin A1c; SD, standard deviation; T2DM, type 2 diabetes mellitus.

# Cotadutide promoted a significant reduction in postprandial hepatic glycogen after a standardised meal




**Primary endpoint: Hepatic glycogen levels 4 hours post-MMTT**

**Cotadutide:** –100.2 mmol/L (–23.6%);
90% CI: –150.2, –50.1

**Placebo:** +5.5 mmol/L (+2.9%);
90% CI: –47.2, 58.3

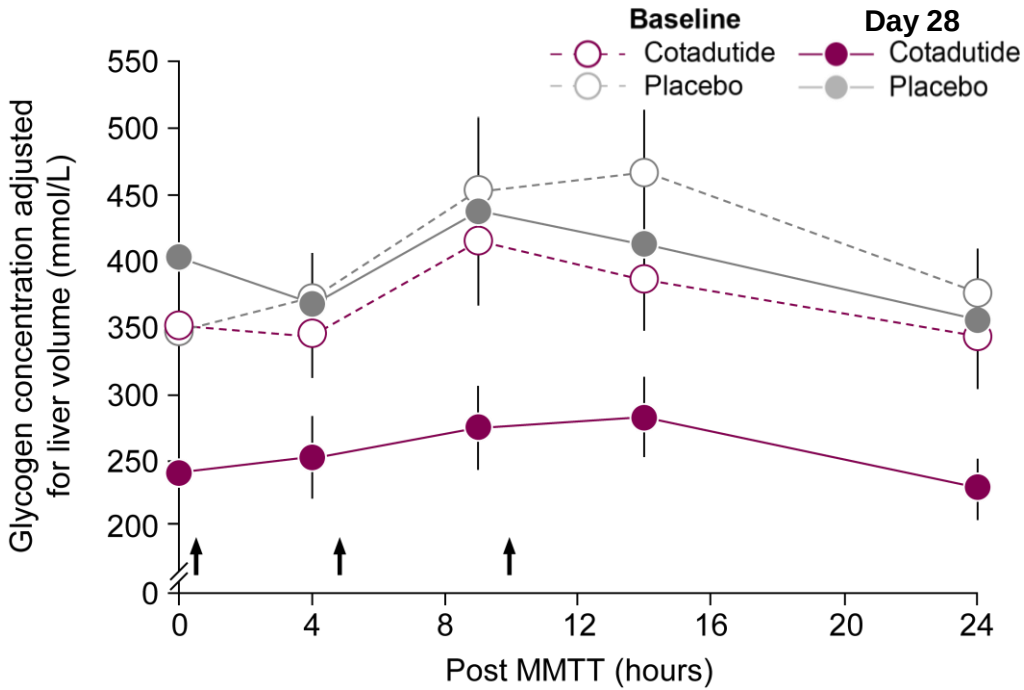
**LS mean change vs placebo:**
–105.7 mmol/L
90% CI: –178.8, –32.6

***P* = 0.023**

- Glycogen content, as measured by $^{13}C$ MRS 4 hours post-MMTT and adjusted for liver volume, was significantly lower with cotadutide vs placebo on day 28

Data are means ± standard error of means.
BL, baseline; CI, confidence interval; LS, least squares; MMTT, mixed-meal tolerance test; MRS, magnetic resonance spectroscopy.

# Cotadutide reduced fasting and postprandial hepatic glycogen levels, without completely depleting glycogen stores




**Hepatic glycogen $AUC_{24h}$**

**Cotadutide:** –29.04%
90% CI: –38.14, –19.95

**Placebo:** –1.78%
90% CI: –11.38, 7.81

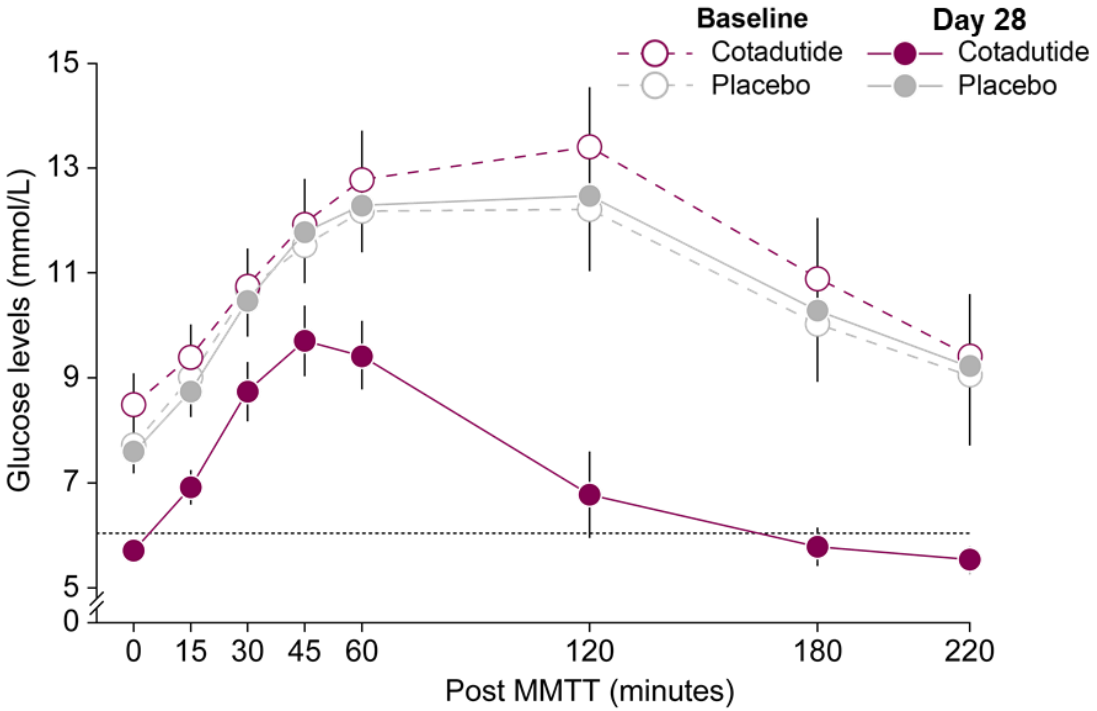
**LS mean change vs placebo:**
–27.26%
90% CI: –40.63, –13.89

***P* = 0.003**

- Hepatic glycogen concentrations across 24 hours were significantly lower with cotadutide vs placebo

Arrows denote timings of standardised meals.
Data are means ± standard error of means.
AUC, area under the concentration-time curve 0 to 24 hours; CI, confidence interval; LS, least squares; MMTT, mixed-meal tolerance test.

# Cotadutide promoted significant reductions in fasting and postprandial glucose levels




**Glucose $AUC_{0\text{-}4hr}$**

**Cotadutide:** –32.04%
90% CI: –37.26, –26.81

**Placebo:** +1.78%
90% CI: –3.73, 7.28

***P* < 0.001**

**Fasting glucose**

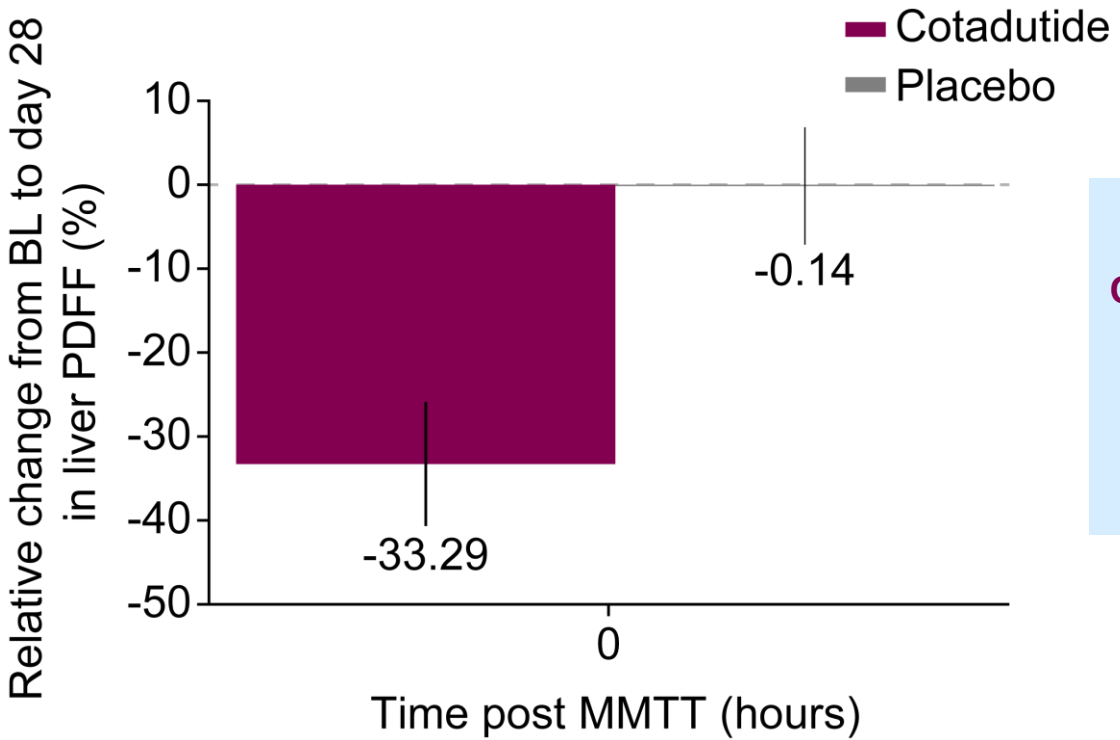
**Cotadutide:** –2.33 mmol/L
90% CI: –2.77, –1.90

**Placebo:** –0.29 mmol/L
90% CI: –0.75, 0.18

***P* < 0.001**

MMTT: 400 mL Ensure Plus (86 g carbohydrates [37 g sugars], 18 g fat, 22 g protein); 590 kcal.
Data are means ± standard error of means.
Dashed line represents cut-off for diagnosis of prediabetes; glucose = 6.1 mmol/L.
AUC, area under the curve; CI, confidence interval; MMTT, mixed-meal tolerance test.

# Cotadutide promoted a significant reduction in liver fat at 28 days




**Relative reduction in % liver fat**

**Cotadutide:** –33.29%
90% CI: –45.98, –20.61

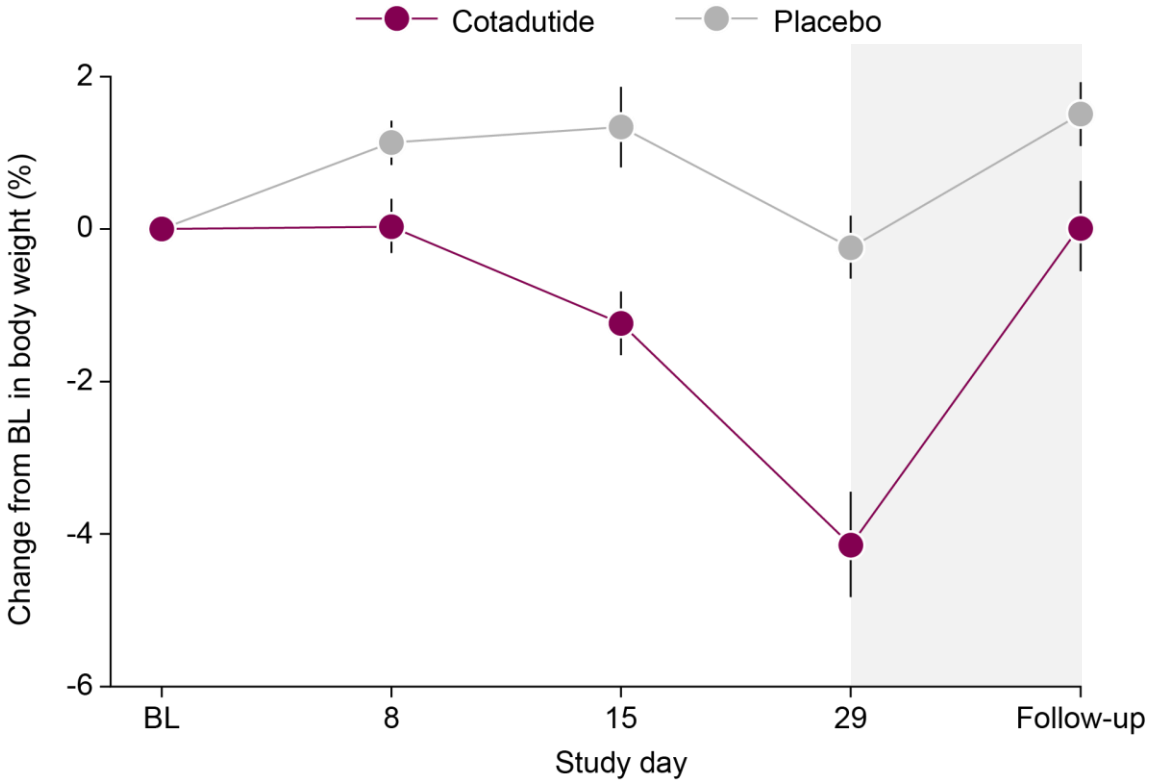
**Placebo:** –0.14%
90% CI: –13.52, 13.23

***P* = 0.006**



BL, baseline; CI, confidence interval; MMTT, mixed-meal tolerance test; PDFF, proton density fat fraction.

# Cotadutide promoted a significant loss in body weight




**Mean change from BL to day 29 in body weight**

**Cotadutide:** –4.03 kg
90% CI: –5.02, –3.04

–4.19%
90% CI: –5.20, –3.19

**Placebo:** –0.17 kg
90% CI: –1.21, 0.88

–0.16%
90% CI: –1.22, 0.90

***P* < 0.001**

Data are means ± standard error of means.
BL, baseline; CI, confidence interval.

# Cotadutide promoted significant reductions from BL in select AAs

- No clinically significant hypoaminoacidemia was observed after 28 days
- Numerical reductions in all AAs were observed with cotadutide
  - significant reductions in alanine, glutamate, glycine, lysine, and threonine levels were observed

| Ketogenic AAs, mg/dL | Cotadutide | Placebo | *P* Value |
|---|---|---|---|
| **Leucine** | –0.353 | –0.166 | 0.304 |
| **Lysine** | –1.006 | –0.242 | **0.020** |

| Ketogenic and Glucogenic AAs, mg/dL | Cotadutide | Placebo | *P* Value |
|---|---|---|---|
| **Isoleucine** | –0.081 | –0.069 | 0.900 |
| **Phenylalanine** | –0.153 | –0.085 | 0.418 |
| **Threonine** | –0.523 | –0.131 | **0.004** |
| **Tryptophan** | –0.239 | –0.099 | 0.179 |
| **Tyrosine** | –0.430 | –0.245 | 0.112 |

| Glucogenic AAs, mg/dL | Cotadutide | Placebo | *P* Value |
|---|---|---|---|
| **Alanine** | –1.337 | –0.177 | **0.002** |
| **Arginine** | –0.516 | –0.359 | 0.270 |
| **Asparagine** | –0.126 | –0.108 | 0.775 |
| **Aspartic acid** | –0.008 | 0 | 0.107 |
| **Cystine** | –0.244 | –0.106 | 0.244 |
| **Glutamate** | –0.429 | –0.085 | **0.005** |
| **Glutamine** | –1.886 | –1.355 | 0.598 |
| **Glycine** | –0.385 | –0.130 | **0.050** |
| **Histidine** | –0.244 | –0.091 | 0.324 |
| **Methionine** | –0.092 | –0.043 | 0.183 |
| **Proline** | –0.633 | –0.169 | 0.134 |
| **Serine** | –0.254 | –0.103 | 0.153 |
| **Valine** | –0.633 | –0.267 | 0.276 |



AA, amino acid; BL, baseline.

# Conclusions

- Cotadutide reduced fasting and postprandial hepatic glycogen levels
  - This suggests target engagement of the glucagon receptor and a different mechanism vs GLP-1 analogues
- Reductions in liver fat and levels of selected amino acids further support this conclusion
- Glycogen stores were not completely depleted following cotadutide therapy
- Reductions in fasting and postprandial glucose levels were observed with cotadutide despite reductions in glycogen

# Acknowledgments


- The authors thank the patients who participated in this study and their families, the study site personnel, and the cotadutide team