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

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• 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 EFIGW LVKGR G
Glucagon: HSQGT FTSDY SKYLD SRRAQ DFVQW LMNT
Cotadutide: HSQGT FTSDX SEYLD SERAR DFVQW LEAGG

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
- Activates both GLP-1 and glucagon receptors
- Significantly upregulated after bariatric surgery (along with GLP-1)
- Reduces appetite and increases energy expenditure, leading to substantial weight loss in patients who are overweight and obese


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 ↓

Figure adapted from Müller et al. *Physiol Rev* 2017;97:721-766.
Exploratory, double-blind, placebo-controlled, phase 2a trial

**Eligibility Criteria**
- Aged ≥ 18 years
- BMI ≥ 27 and ≤ 40 kg/m²
- 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

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

**Cotadutide titrated from 100 µg to 300 µg**

**Once-daily placebo (SC) x 28 days**

**Metformin washout**
5 days

**Follow-up**
28 days

**Day**
-3
-1 to 1
26
28 to 29

**Post-MMTT (h)**
0 1 4 9 14 24

**MRS**
- MTTT end
- IP first dose
- IP last dose

**MRS**
- MTTT end
- IP first dose

**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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n = 9)</th>
<th>Cotadutide (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (67)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (33)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>69.3 (5.7)</td>
<td>65.8 (7.3)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)</td>
<td>32.7 (4.8)</td>
<td>31.8 (3.0)</td>
</tr>
<tr>
<td>Mean weight, kg (SD)</td>
<td>99.6 (20.1)</td>
<td>96.2 (7.7)</td>
</tr>
<tr>
<td>Mean HbA1c, % (SD)</td>
<td>6.30 (0.7)</td>
<td>6.51 (0.6)</td>
</tr>
<tr>
<td>Mean duration of T2DM, years (SD)</td>
<td>9.9 (6.1)</td>
<td>7.7 (5.4)</td>
</tr>
</tbody>
</table>

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<sub>0-4hr</sub>

**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

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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: $-45.98$, $-20.61$
  - $P = 0.006$

- **Placebo:** $-0.14\%$
  - 90% CI: $-13.52$, $13.23$

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

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Cotadutide</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucine</td>
<td>−0.353</td>
<td>−0.166</td>
<td>0.304</td>
</tr>
<tr>
<td>Lysine</td>
<td>−1.006</td>
<td>−0.242</td>
<td>0.020</td>
</tr>
</tbody>
</table>

### Ketogenic and Glucogenic AAs, mg/dL

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Cotadutide</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoleucine</td>
<td>−0.081</td>
<td>−0.069</td>
<td>0.900</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>−0.153</td>
<td>−0.085</td>
<td>0.418</td>
</tr>
<tr>
<td>Threonine</td>
<td>−0.523</td>
<td>−0.131</td>
<td>0.004</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>−0.239</td>
<td>−0.099</td>
<td>0.179</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>−0.430</td>
<td>−0.245</td>
<td>0.112</td>
</tr>
</tbody>
</table>

### Glucogenic AAs, mg/dL

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Cotadutide</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine</td>
<td>−1.337</td>
<td>−0.177</td>
<td>0.002</td>
</tr>
<tr>
<td>Arginine</td>
<td>−0.516</td>
<td>−0.359</td>
<td>0.270</td>
</tr>
<tr>
<td>Asparagine</td>
<td>−0.126</td>
<td>−0.108</td>
<td>0.775</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>−0.008</td>
<td>0</td>
<td>0.107</td>
</tr>
<tr>
<td>Cystine</td>
<td>−0.244</td>
<td>−0.106</td>
<td>0.244</td>
</tr>
<tr>
<td>Glutamate</td>
<td>−0.429</td>
<td>−0.085</td>
<td>0.005</td>
</tr>
<tr>
<td>Glutamine</td>
<td>−1.886</td>
<td>−1.355</td>
<td>0.598</td>
</tr>
<tr>
<td>Glycine</td>
<td>−0.385</td>
<td>−0.130</td>
<td>0.050</td>
</tr>
<tr>
<td>Histidine</td>
<td>−0.244</td>
<td>−0.091</td>
<td>0.324</td>
</tr>
<tr>
<td>Methionine</td>
<td>−0.092</td>
<td>−0.043</td>
<td>0.183</td>
</tr>
<tr>
<td>Proline</td>
<td>−0.633</td>
<td>−0.169</td>
<td>0.134</td>
</tr>
<tr>
<td>Serine</td>
<td>−0.254</td>
<td>−0.103</td>
<td>0.153</td>
</tr>
<tr>
<td>Valine</td>
<td>−0.633</td>
<td>−0.267</td>
<td>0.276</td>
</tr>
</tbody>
</table>

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.