Cotadutide (MEDI0382), A Dual Receptor Agonist With Glucagon-like Peptide-1 and Glucagon Activity, Is Well-tolerated (≤ 600 µg) With Robust Effects On Blood Glucose In Patients With T2DM

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Disclosures

• This study (NCT03745937) was sponsored by AstraZeneca
• D Robertson is an employee and a shareholder of AstraZeneca
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Introduction

- For patients with T2DM, significant weight loss (≥ 5% of bodyweight) can promote improvements in glycemic control, cardiovascular risk, and mortality rates, and may slow or reverse disease progression\(^1,2\)

- Cotadutide, a dual receptor agonist with GLP-1 and glucagon receptor activity, is under development for T2DM and nonalcoholic steatohepatitis (NCT03555994, NCT04019561)

- A previous randomized, double-blind, placebo-controlled, phase 2b study (NCT03235050), with an open-label, active-comparator (liraglutide) arm, demonstrated significant decreases in HbA1c and bodyweight from BL to week 14 vs placebo at all cotadutide doses (100 μg, 200 μg, and 300 μg) in patients with T2DM who were also overweight or obese

Objective: To evaluate the safety and efficacy of cotadutide in doses up to 600 μg in patients with T2DM

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BL, baseline; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; T2DM, type 2 diabetes mellitus.
Study design

- This randomized, parallel-group, placebo-controlled, double-blind, phase 2a study evaluated the safety, tolerability, pharmacokinetics, and efficacy of cotadutide in overweight or obese adults with T2DM (NCT03745937)

Inclusion Criteria:
- T2DM
- 18–74 years old
- BMI 27–35 kg/m²
- HbA1c 6.5%–8.5%
- Glucose control managed with metformin monotherapy

Cohort 1: cotadutide (n = 6) + placebo (n = 2)
- Initial up titration
- 20 – 50 – 100 – 200 – 300 µg
- 5 weeks
- 400 µg
- 500 µg
- 600 µg
- Treatment extension 600 µg
- DEC 72 h data review
- DEC
- DEC
- Primary Analysis
- Escalation approved by DEC
- Escalation not approved by DEC.
- Proceed to treatment extension at prior dose level

Cohort 2: cotadutide (n = 9) + placebo (n = 3)
- Initial up titration period
- Up to 8-week up titration period
- 20 – 50 – 100 – 200 – 300 – 400 – 500 – 600 µg
- Treatment extension 300 µg
- Treatment extension 400 µg
- Treatment extension 500 µg
- Treatment extension 600 µg
- Primary Analysis

Primary Endpoints:
- Safety and tolerability of cotadutide titrated up to the HCTD

Secondary Endpoints:
- Efficacy as assessed by changes in:
  - Estimated HbA1c from CGM
  - Daily and 7-day average glucose levels from CGM
  - Percent time in hyperglycemia (> 140 mg/dL), normoglycemia (70–140 mg/dL), and clinically significant hypoglycemia (< 54 mg/dL) from CGM
  - Bodyweight
  - PK profile and cotadutide antidrug antibodies

BMI, body mass index; CGM, continuous glucose monitoring; DEC, dose-escalation committee; h, hour; HbA1c, hemoglobin A1c; HCTD, highest clinically tolerated dose; PK, pharmacokinetic; R, randomization; T2DM, type 2 diabetes mellitus.
# Patient demographics and key baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n = 5)</th>
<th>Cotadutide (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>64.8 (4.5)</td>
<td>66.4 (5.5)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2 (40.0)</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>Male</td>
<td>3 (60.0)</td>
<td>12 (80.0)</td>
</tr>
<tr>
<td>Weight, kg, mean (SD)</td>
<td>87.10 (5.11)</td>
<td>92.79 (10.71)</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>29.85 (2.11)</td>
<td>30.22 (1.93)</td>
</tr>
<tr>
<td>Duration of T2DM, years, mean (SD)</td>
<td>18.82 (13.36)</td>
<td>14.20 (6.02)</td>
</tr>
<tr>
<td>HbA1c, %, mean (SD)</td>
<td>7.54 (0.32)</td>
<td>7.41 (0.52)</td>
</tr>
<tr>
<td>Daily CGM glucose level, mg/dL, mean (SD)</td>
<td>161.81 (28.35)</td>
<td>154.11 (20.91)</td>
</tr>
<tr>
<td>Time spent in hyperglycemia over 24 h, %, mean (SD)</td>
<td>66.67 (30.87)</td>
<td>57.99 (24.89)</td>
</tr>
<tr>
<td>ALT level, U/L, mean (SD)</td>
<td>32.2 (17.0)</td>
<td>32.1 (11.7)</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; CGM, continuous glucose monitoring; HbA1c, glycated hemoglobin A1c; SD, standard deviation; T2DM, type 2 diabetes mellitus.
Safety summary

<table>
<thead>
<tr>
<th>Parameter, n (%)</th>
<th>Placebo</th>
<th>Cotadutide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 5)</td>
<td>(n = 15)</td>
</tr>
<tr>
<td>Safety summary</td>
<td></td>
<td></td>
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<tr>
<td>Treatment-related adverse events</td>
<td></td>
<td></td>
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<tr>
<td>≥ Grade 3 severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leading to study discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
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<tr>
<td>Deaths</td>
<td></td>
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</tbody>
</table>

### Most Frequent (≥ 20%) TEAEs

<table>
<thead>
<tr>
<th>Parameter, n (%)</th>
<th>Placebo (n = 5)</th>
<th>Cotadutide (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-site reaction</td>
<td>0</td>
<td>7 (46.7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (20.0)</td>
<td>6 (40.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>Appetite disorder</td>
<td>0</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (20.0)</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Early satiety</td>
<td>0</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Injection-site erythema</td>
<td>0</td>
<td>4 (26.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3 (60.0)</td>
<td>3 (20.0)</td>
</tr>
</tbody>
</table>

**Parameter details:**
- TEAEs
  - Placebo: 5 (100)
  - Cotadutide: 14 (93.3)
- Treatment-related
  - Placebo: 3 (60.0)
  - Cotadutide: 14 (93.3)
- ≥ Grade 3 severity
  - Placebo: 0
  - Cotadutide: 1<sup>a</sup> (6.7)
- Leading to study discontinuation
  - Placebo: 0
  - Cotadutide: 3<sup>b</sup> (20.0)
- Serious AEs
  - Placebo: 0
  - Cotadutide: 0
- Deaths
  - Placebo: 0
  - Cotadutide: 0

*Grade 3 ventricular extrasystoles.

Blood pressure diastolic increased (n = 1); atrial fibrillation, ventricular extrasystoles, and supraventricular extrasystoles (n = 1); and constipation and abdominal pain (n = 1).

- **Cotadutide did not appear to have a dose-dependent relationship with nausea and vomiting**.
- **Cotadutide increased pulse rate from baseline to day 77 vs placebo (6.19 vs -6.24); but there were no notable changes in ABPM**.
- **Cotadutide-treated patients had larger reductions in mean ALT (-30.70% vs -4.52%) and AST levels (-19.56% vs 1.89%) from baseline to day 77 vs placebo**.
- **1 Patient tested positive for cotadutide-specific antidrug antibodies at baseline**.
  - 7 Patients tested positive for cotadutide-specific antidrug antibodies postbaseline.

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ABPM, ambulatory blood pressure measurements; AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.
Cotadutide significantly reduced 7-day average estimated HbA1c and glucose levels

Statistical analyses are least squares means (90% confidence intervals); *P-value < 0.05; †P-value < 0.001.

CGM, continuous glucose monitoring; HbA1c, hemoglobin A1c; LOCF, last observation carried forward; LS, least squares; SEM, standard error of the mean.

<table>
<thead>
<tr>
<th>Parameter, %</th>
<th>Placebo (n = 5)</th>
<th>Cotadutide (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median HbA1c at day 77 90% CI</td>
<td>6.87, 6.81 to 8.51</td>
<td>5.35, 4.56 to 8.30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter, mg/dL</th>
<th>Placebo (n = 5)</th>
<th>Cotadutide (n = 15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS mean change from baseline in 7-day average glucose levels at days 71–77 90% CI</td>
<td>-8.0, -35.3 to 19.3</td>
<td>-48.4, -65.1 to -32.3</td>
<td>0.042</td>
</tr>
</tbody>
</table>
Cotadutide reduced time in hyperglycemia (>140 mg/dL) and increased time in normoglycemia as measured by CGM over 7 days.

- No significant difference was observed between treatment groups in time spent in clinically significant hypoglycemia.

**Statistical analyses are least-square means (90% confidence intervals); *P-value ≤ 0.05.**

CGM, continuous glucose monitoring; SEM, standard error of the mean.
Cotadutide reduced bodyweight vs placebo

Post hoc analysis showed a larger reduction in least-squares mean from baseline in ALT levels with cotadutide vs placebo at day 77 (-7.17%, 90% CI: -12.21 to -2.14; unadjusted P = 0.025)

Statistical analyses are least squares means (90% confidence intervals). ALT, alanine transaminase; SEM, standard error of the mean.
Conclusions

• Overall, cotadutide, at doses up to 600 µg, was safe and well-tolerated, improved glucose control, reduced HbA1C levels, improved liver enzymes, and showed a linear pharmacokinetic profile

• Safety:
  – One ≥ grade 3 TEAE was reported
  – Changes in heart rate and blood pressure were generally similar to those observed in other studies for cotadutide (doses up to 300 µg)
  – The incidence of nausea and vomiting with cotadutide was low, with no apparent dose-dependent relationship

• Glucose control and bodyweight showed improvements with cotadutide vs placebo (without adjustment for multiplicity):
  – Patients in the cotadutide group lost an average of 5.92% of their bodyweight, with reduced hyperglycemia, HbA1c levels, and ALT levels
  – Glucose reduction did not change with higher doses of cotadutide