Efficacy and safety of cotadutide, a dual GLP-1 and glucagon receptor agonist in patients with T2DM and DKD

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Disclosures

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\textsuperscript{a} Employee at the time the study was conducted
Introduction

- Cotadutide is a dual GLP-1 and glucagon receptor agonist\textsuperscript{1,2} in development for the treatment of Non-Alcoholic Steatohepatitis as well as chronic kidney disease with type 2 diabetes mellitus.

- Chronic kidney disease with type 2 diabetes mellitus carries a significant health and economic burden for individuals\textsuperscript{3} and society\textsuperscript{4}, which increases as the disease progresses to later stages\textsuperscript{5}.

- Cotadutide may offer a particularly effective treatment for chronic kidney disease with type 2 diabetes because:
  - GLP-1 and glucagon are implicated in renal hemodynamics and promote natriuresis\textsuperscript{6,7}
  - the GLP-1 receptor is expressed in the renal vasculature; the glucagon receptor is highly expressed both in the liver and in the distal tubules of the kidney\textsuperscript{8,9}
  - GLP-1 receptor (GLP-1R) agonists influence various cellular pathways including inhibition of inflammation and apoptosis, and protection against oxidative stress for agonists
    - GLP-1R delay the onset of macroalbuminuria in chronic kidney disease with type 2 diabetes\textsuperscript{10–12}
  - This study assessed the glycemic and renal effects of short-term treatment with cotadutide in patients with type 2 diabetes and renal impairment.

Endpoints

- Primary endpoint: serum glucose concentration assessed using MMTT
- Secondary and exploratory: interstitial glucose concentration assessed using CGM, insulin dose, eGFR, UACR, body weight, safety and tolerability

Phase 2a, randomized, double-blind, placebo-controlled study in patients with T2DM, HbA1c, 6.5–10.5% (47.5–91.3 mmol/mol), CKD stage G3* and a BMI of 25–45 kg/m², receiving insulin and/or oral glucose-lowering drugs.

Study design

40 days

Screening

4 days 7 days 7 days 14 days 28 days

32 days dosing

Placebo: n = 20

Placebo

Cotadutide: n = 20

50 μg 100 μg 200 μg 300 μg

4 days 7 days 14 days 28 days

Run-in

Follow-up

V1 V2 V3 V4 V5 V6 V7 V8 V9/V10 V11 V12

MMTT ABPM ABPM ABPM ABPM MMTT

Overnight local stay or daily visits

* eGFR ≥ 30 to < 60 mL/min/1.73 m².

ABPM, ambulatory blood pressure monitoring; BMI, body mass index; CGM, continuous glucose monitoring; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MMT, mixed meal tolerance test; T2DM, type 2 diabetes mellitus; UACR, urinary albumin:creatinine ratio; V, visit
## Baseline demographics

<table>
<thead>
<tr>
<th></th>
<th>Cotadutide (n = 21)</th>
<th>Placebo (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, female: male, n</strong></td>
<td>9:12</td>
<td>11:9</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>71.1 (7.4)</td>
<td>70.9 (4.7)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>20 (95.2)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Hawaiian/Pacific Islander</td>
<td>1 (4.8)</td>
<td>0</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>32.4 (4.1)</td>
<td>32.9 (5.5)</td>
</tr>
<tr>
<td><strong>HbA₁c, %</strong></td>
<td>7.85 (0.74)</td>
<td>7.88 (1.27)</td>
</tr>
<tr>
<td><strong>HbA₁c, mmol/mol</strong></td>
<td>62.3 (8.1)</td>
<td>62.6 (13.9)</td>
</tr>
<tr>
<td><strong>eGFR, mL/min/1.73 m²</strong></td>
<td>44.73 (8.70)</td>
<td>47.63 (8.77)</td>
</tr>
<tr>
<td><strong>UACR, mg/g</strong></td>
<td>23.8 (32.8)</td>
<td>19.8 (22.5)</td>
</tr>
<tr>
<td><strong>Duration of T2DM, years</strong></td>
<td>16.3 (8.5)</td>
<td>15.9 (7.2)</td>
</tr>
<tr>
<td><strong>Insulin, n (%)</strong></td>
<td>16 (76)</td>
<td>15 (75)</td>
</tr>
<tr>
<td><strong>Total daily insulin dose (U/day)</strong></td>
<td>50.52 (61.96)</td>
<td>57.55 (49.37)</td>
</tr>
<tr>
<td><strong>Oral glucose-lowering medication, n (%)</strong></td>
<td>16 (76)</td>
<td>12 (60)</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless otherwise stated.
BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA₁c, glycated hemoglobin; T2DM, type 2 diabetes mellitus; UACR, urinary albumin:creatinine ratio.
Cotadutide significantly improved glycemic control

Serum glucose concentrations during MMTT

<table>
<thead>
<tr>
<th>Time post meal (minutes)</th>
<th>Mean glucose (mg/dL ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>150 ± 5</td>
</tr>
<tr>
<td>15</td>
<td>160 ± 5</td>
</tr>
<tr>
<td>30</td>
<td>170 ± 5</td>
</tr>
<tr>
<td>45</td>
<td>180 ± 5</td>
</tr>
<tr>
<td>60</td>
<td>190 ± 5</td>
</tr>
<tr>
<td>90</td>
<td>200 ± 5</td>
</tr>
<tr>
<td>120</td>
<td>210 ± 5</td>
</tr>
<tr>
<td>180</td>
<td>220 ± 5</td>
</tr>
<tr>
<td>240</td>
<td>230 ± 5</td>
</tr>
</tbody>
</table>

Change from baseline to day 32 in plasma glucose AUC$_{0-4h}$ was –26.71% with cotadutide versus +3.68% with placebo ($p = 0.001$)

Time in target blood glucose range across 32 days of dosing

- < 54 mg/dL (< 3.0 mmol/L)
- 54–< 70 mg/dL (3.0–< 3.9 mmol/L)
- ≥ 70 mg/dL (> 10 mmol/L)

Change from baseline to day 32 in time in target plasma glucose range was +14.8% with cotadutide versus –21.2% with placebo ($p < 0.001$)

AUC, area under the curve, CGM, continuous glucose monitoring, MMTT, mixed meal tolerance test
Body weight was reduced by $-3.69\%$ from baseline to day 32 with cotadutide and by $-0.21\%$ with placebo ($p < 0.001$).

In patients with a baseline total daily insulin dose ≥ 20 U in the cotadutide group (n = 14), daily insulin dose reduced by 35.2% from baseline to day 32 ($p = 0.012$).

Mean (SD) change from baseline in fasting C-peptide was $0.897 (0.965) \mu g/L$ with cotadutide and $-0.206 (0.577) \mu g/L$ with placebo ($p < 0.001$ between groups).
Cotadutide treatment may have a potential renoprotective effect

At day 32, eGFR was unchanged from baseline in both treatment arms. LS mean change from baseline, +1.17 mL/min/1.73 m² with cotadutide versus −1.10 mL/min/1.73 m², with placebo; \( p = 0.268 \)

Mean change in eGFR over time

In patients with baseline micro- or macroalbuminuria (\( n = 18 \)), UACR was reduced by 51%, independently of glucose control, at day 32 with cotadutide versus placebo (\( p = 0.0504 \))

Mean percent change in UACR over time (subgroup analysis)

NT-proBNP was reduced with cotadutide versus placebo (−79.73 vs −9.42 ng/L; \( p = 0.040 \))

eGFR, estimated glomerular filtration rate; LS mean, least square mean; NT-proBNP, N-terminal pro B-type natriuretic peptide; SE, standard error; UACR, urinary albumin:creatinine ratio;
Safety and tolerability

- There were no episodes of severe hypoglycemia*
  - CGM time < 54 mg/dL (3.0 mmol/L) was 1.65% with cotadutide vs 0.82% with placebo

- Safety and tolerability findings were consistent with the known mechanism of action of GLP-1 receptor agonists in patients without renal impairment
  - One death in the cotadutide group (SAE, diabetic ketoacidosis)
  - Three other SAEs (cotadutide, n = 1; placebo, n = 2); all patients were receiving insulin at ≥ 20 U/day
    - SAEs: cotadutide, hypertensive crisis (n = 1); placebo, carotid artery stenosis, (n = 1), syncope (n = 1)
  - Three patients (cotadutide, n = 2; placebo, n = 1) discontinued study treatment owing to AEs
  - Treatment-related AEs: cotadutide, 71% (15/21); placebo, 35% (7/20)
    - Higher incidence with cotadutide was largely driven by gastrointestinal side effects

- No clinically significant changes in blood pressure in either group but heart rate was increased with cotadutide versus placebo after 32 days of dosing (14.13 vs 3.14 bpm; \( p < 0.001 \))

*Requiring hospitalization or third-party assistance

bpm, beats per minute; CGM, continuous glucose monitoring; GLP-1, glucagon-like peptide 1; (S)AE, (serious) adverse event
Conclusions

• After 32 days of dosing cotadutide at a maximum dose of 300 µg/day, the overall tolerability of cotadutide in this renally impaired population was comparable to that observed in prior studies of cotadutide in subjects without renal impairment.

• Cotadutide significantly improved glycemic control and reduced body weight in patients with chronic kidney disease with type 2 diabetes mellitus.

• In patients receiving insulin therapy (50%), reductions in serum glucose were achieved alongside significant reductions in the total daily insulin dose requirement suggesting that cotadutide improved insulin sensitivity.

• There was a reduction in albuminuria in a subgroup analysis suggesting that cotadutide may have renoprotective potential in patients with renal impairment.

• Further evaluation in patients with chronic kidney disease with type 2 diabetes mellitus is warranted and a Phase 2b study studying cotadutide at a maximum doses of 300 and 600 µg/day, compared to Ozempic (semaglutide), is on-going.