**Effects of New Metformin Formulation in Stage 3 and 4 CKD: A Pilot Study**

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Background: Metformin (Met) is contraindicated in patients with renal dysfunction (eg, eGFR <60 ml/min/1.73 m²) due to increased risk of lactic acidosis. Low-dose Met is sometimes used off-label in patients with Stage 3b CKD to limit exposure. Delayed-release (DR) Met targets delivery to its site of action in the ileum where absorption is poor, resulting in a greater glucose-lowering effect and lower plasma Met for a given dose. We previously showed that 1000 mg Met DR produces a greater reduction in glucose and lower plasma metformin concentrations compared to 1000 mg extended-release (XR) Met in patients with normal renal function (RF). Hence, Met DR may provide an option for metformin use by patients with advanced stage nephropathy.

Methods: This study used a randomized crossover design to assess plasma PK of a single dose of Met DR, Met XR, and placebo in 39 patients with T2DM and eGFR ≥90 ml/min/1.73 m² (normal renal function), 60–89 ml/min/1.73 m² (Stage 2 CKD), 30–59 ml/min/1.73 m² (Stage 3 CKD), or 15–29 ml/min/1.73 m² (Stage 4 CKD).

Results: Data are mean ± SD. Patients were predominantly Caucasian (87%) males (82%) with BMI 32 ± 4 kg/m², 12 ± 9 y duration of T2DM, fasting glucose 157 ± 48 mg/dl, and HbA1c 7.6 ± 1.2%. Compared to Met XR, Met DR was associated with a 48, 26, 43, and 48% reduction in Met exposure in patients with an eGFR ≥90, 60–89, 30–59, and 15–29 ml/min/1.73 m², respectively. Met exposure in patients with Stages 3 and 4 CKD is shown in Figure 2. Plasma lactate and anion gap were not increased in any group.

Conclusion: In patients with T2DM, including those with an eGFR <60 ml/min/1.73 m², Met DR had lower plasma metformin concentrations than similar doses of currently available Met XR without increased lactate or anion gap. Together with previous data showing the glucose-lowering effect of Met DR, these findings support further study of Met DR in patients with T2DM and advanced CKD.

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**Summary**

- In patients with type 2 diabetes and CKD:
  - Single-dose Met DR resulted in lower plasma metformin concentrations compared to single-dose Met XR.
  - At the single 1000 mg doses studied, metformin administration (with either formulation) was not associated with persistent elevations in plasma lactate.
  - Study medication was well tolerated across renal function groups.

**Conclusions**

- Delivery of metformin to the ileum with Met DR is associated with lower plasma metformin concentrations than Met XR in patients with CKD or normal renal function.
- These results support the Population PK model that predicts maximally effective doses of Met DR in patients with Stage 3 or 4 CKD would result in plasma concentrations maximally effective doses of Met IR/XR used on label (Normal or Stage 1 CKD).  
- These data support future longer-term safety and efficacy studies of Met DR in patients with diabetes and moderate to severe renal impairment.

**References**


**Metformin Use in CKD (Figure 1)**

- Metformin-associated lactic acidosis (MALA), a rare but serious risk of metformin use, results from plasma metformin accumulation.  
- Patients with poor renal clearance are at greater risk for metformin accumulation, therefore, metformin is contraindicated in patients with Stage 3 and 4 CKD.
- When metformin is implicated as the cause of lactic acidosis, metformin plasma levels are generally >5 μg/ml (concentrations are typically <2 μg/ml when used according to labeling recommendations).
- For a given dose, Met DR would result in lower plasma metformin and higher efficacy than Met IR/XR in patients with Stage 3 and 4 CKD due to targeted delivery, reducing the risk of plasma metformin accumulation and MALA.
- Population PK modeling that predicts maximally effective doses of Met DR (1200 mg) in patients with Stage 3 or 4 CKD result in plasma concentrations maximally effective doses of Met IR/XR (≤2000 mg) used on label (Normal and Stage 2 CKD).

Funded by Elcelyx Therapeutics, Inc.

For more information, contact info@elcelyx.com.

**Note:** Submitted abstract based on interim data (N=31). Abstract has been updated to reflect final data (N=39).
Results

<table>
<thead>
<tr>
<th>N</th>
<th>Stage 2 CKD</th>
<th>Stage 3 CKD</th>
<th>Stage 4 CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>11</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

**Baseline demographics and characteristics**

- **N = 9**
- **Stage 4 CKD**
- **48/50/13**
- **BMI, kg/m²**: 33.4 ± 32.4 ± 30.3 ± 33.4
- **eGFR, ml/min/1.73M²**: 101.1 ± 85.9 ± 41.3 ± 7.4 ± 21.8 ± 4.1
- **HbA1c, %**: 7.2 ± 7.6 ± 7.4 ± 7.1 ± 6.1
- **Fasting Lactate, mmol/L**: 1.0 ± 1.1 ± 1.0 ± 0.9 ± 0.9
- **Duration of T2DM, y**: 4.4 ± 1.7 ± 17.1 ± 13.6 ± 0.4
- **Systolic Blood Pressure, mmHg**: 120.0 ± 130.1 ± 114.2 ± 127.1 ± 11
- **Diastolic Blood Pressure, mmHg**: 76.0 ± 81.9 ± 79.1 ± 75.9 ± 1
- **% taking diabetes medication**: 80 ± 45 ± 83 ± 13 ± 0
- **% taking antihypertensive medication**: 63 ± 91 ± 100 ± 88 ± 0
- **% taking ACE inhibitors**: 25 ± 64 ± 50 ± 1 ± 0
- **% taking dipeptidyl peptidase-4 inhibitors**: 38 ± 16 ± 58 ± 36 ± 0
- **% taking metformin exposure**: 25 ± 16 ± 50 ± 33 ± 0

**Objectives**

- **In patients with type 2 diabetes and Stage 3 or 4 CKD**
  - Evaluate the single-dose PK of Met DR compared to Met XR.
  - Characterize the single-dose exposure relationship between plasma metformin concentrations and plasma lactate.

**Study Design**

- This was a Phase 2, randomized, placebo-controlled, crossover study.
- **Treatments**: Met DR 1000 mg, Met XR 1000 mg, or placebo.
- **Patients**: 35 patients with type 2 diabetes mellitus were randomized.

**Results**

- **Fasting plasma metformin (PK) data are median concentrations and efficacy data are the median change after 4 weeks of treatment.**
- **Abbreviations**: Met XR = metformin extended-release, Met DR = metformin delayed-release, FPG = fasting plasma glucose.
- **These effects of Met DR support a gut-mediated mechanism of metformin action.**

**Figure 3. Plasma Lactate During Single-Dose Metformin Administration**

- **Left**: Placebo-adjusted change in lactate concentration after single-dose Met DR or Met XR. Evaluate population. Time: 0 h to 24 h. Study medication administered at t=0 h. Estimate reduction of placebo-adjusted change in lactate at 0–1 h: 0.3 (0.1, 0.5) with Met XR, 1.2 (0.6, 1.9) with Met DR. Placebo-adjusted change in lactate and metformin concentrations after single-dose Met DR or Met XR. Evaluate population. Estimate reduction of placebo-adjusted change in lactate at 0–1 h: 0.1 (0.0, 0.2) with Met XR, 0.1 (0.0, 0.3) with Met DR.
- **Right**: Placebo-adjusted change in lactate and metformin concentrations after single-dose Met DR or Met XR. Evaluate population. Data are No. (%).

- **There was an increase in plasma lactate from baseline after single-dose Met XR administration, but not single-dose Met DR administration.**

- **A significant relationship between plasma metformin concentrations and change in plasma lactate from baseline was observed with Met XR (p = 0.0021) but not Met DR (p = 0.34).**

**Table 2. Additional Single-Dose Plasma and Urine Metformin PK Parameters**

<table>
<thead>
<tr>
<th>Plasma PK</th>
<th>Met DR</th>
<th>Met XR</th>
<th>Met XR</th>
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<tbody>
<tr>
<td>N/0</td>
<td>N/7</td>
<td>N/7</td>
<td></td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;, h</td>
<td>10.9 (4.2)</td>
<td>10.2 (4.3)</td>
<td>17.5 (4.1)</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, ng/ml</td>
<td>81.2 (46.4)</td>
<td>50.2 (20.2)</td>
<td>52.0 (31.0)</td>
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**Urine PK**

<table>
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<th>N/7</th>
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<tr>
<td>A&lt;sub&gt;UC&lt;/sub&gt;, mg</td>
<td>156 (50.2)</td>
<td>249 (19.1)</td>
</tr>
<tr>
<td>FE&lt;sub&gt;UC&lt;/sub&gt;, %</td>
<td>164.0 (34.1)</td>
<td>32.0 (18.1)</td>
</tr>
<tr>
<td>C&lt;sub&gt;UC&lt;/sub&gt;, L/h</td>
<td>15.9 (29.6)</td>
<td>5.4 (21.7)</td>
</tr>
</tbody>
</table>

**Table 3. Adverse Events**

| Patients experiencing any TEAE | 2 (18) | 2 (20) | 1 (11) | 4 (40) | 2 (20) | 1 (13) |
| Patients experiencing any hyperglycemia | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

**Data are mean (CV).**

**Statistical Analysis**: Statistical comparisons of treatment for PK parameters within each renal function group were performed using a linear mixed-effects model with treatment, treatment sequence, period, renal function group, and random effect as fixed factors. Within-subject comparison of exposure parameters between different renal function groups was performed using an analysis of variance (ANOVA) model with treatment, period, and random effect as fixed factors and subject as a random factor. PK parameters were back-transformed for analysis and model results were back-transformed to original scale.

**Dose: 1000 mg Met XR**

<table>
<thead>
<tr>
<th>PK*</th>
<th>Absorption</th>
<th>Dissolution</th>
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<tbody>
<tr>
<td>47 (0.5)</td>
<td>1000 mg Met XR</td>
<td>1000 mg Met XR</td>
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</table>

**Dose: 600 mg Met DR**

<table>
<thead>
<tr>
<th>PK*</th>
<th>Absorption</th>
<th>Dissolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>42 (0.5)</td>
<td>600 mg Met DR</td>
<td>600 mg Met DR</td>
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