Safety and Tolerability

- Consistent with the known metformin safety profile, the most common adverse events were gastrointestinal in nature: 13% for Met DR QAM, 8% for Met DR QPM, and 17% for Met DR BID.
- However, relative to the prescribing information for metformin, the incidence of gastrointestinal adverse events was low in all metformin treatment groups. This suggests that the majority of the population (88%) already taking metformin was tolerant to these adverse effects and is consistent with study entry criteria and the brief washout period.

Summary

- Met DR provided 24-h glucose-lowering with once-daily administration.
- Morning dosing (QAM) provided the lowest metformin exposure compared to evening (QPM) or BID dosing without compromising efficacies.

Conclusions

- Given the low total daily metformin plasma exposure with Met DR, these results support the hypothesis that metformin works predominantly in the gut and not in the circulation.
- By directly targeting the distal small intestine, Met DR may provide optimal efficacy at lower doses and with lower plasma exposure than currently available formulations.
- The reduction in systemic exposure would be expected to reduce the risk of lactic acidosis; Met DR administered in the morning could represent a potential treatment for patients with type 2 diabetes and renal impairment.

References


Abstract

Background and Aims: Metformin delayed-release (MetDR) is a gut-restricted formulation designed to release drug only when it reaches the ileum, a region of the gut where GLP-1 secreting L-cells are abundant and absorption is poor, leading to low bioavailability. MetDR was previously shown to have glucose-lowering activity comparable to immediate-release and extended-release metformin (both of which are absorbed in the upper bowel with ~50% bioavailability) but with ~40% lower doses and significantly lower (~75%) systemic exposure, consistent with the gut being metformin’s primary site of action. As the intestine is a major site of Met accumulation (300-1000X plasma), timing and frequency of daily metformin delivery to the lower bowel may not be important with repeated dosing (ie, at steady-state, the intestine effectively becomes a metformin reservoir that provides sustained activity). We tested this in the present study by comparing the pharmacokinetics (PK) and glucose-lowering efficacy of a total daily dose of 1000 mg Met DR administered twice-daily (BID) or once-daily (QD) in the morning (QAM) or evening (QPM).

Materials and Methods: 1000 mg MetDR QAM or QPM were compared to 500 mg MetDR BID in a 7-day randomized crossover design (n=26, mean FPG 9.33 mmol/L) in subjects with T2D not on Met ≥2 wks prior to dosing. All treatments were administered with meals and were separated by a 6- to 14-day washout.

Results: PK results indicate a diurnal effect in both the rate and extent of metformin absorption with QAM having the fastest gut transit time and the lowest plasma exposure compared to QPM. The time to reach the ileum was 4.5-5.8 h for morning dosing vs 7.1-8.5 h for evening dosing. QAM resulted in a 28% decrease in 24h Met plasma exposure (AUC) compared to QPM and BID (p<0.005 for both). Despite these differences in exposure, both once-dose regimens resulted in an ~9% reduction in 24h glucose AUC0-24 from baseline (both p<0.01) compared to a 5% reduction for BID dosing (p=0.099). QAM dosing also resulted in a 10% reduction in 24h maximum plasma glucose (Rmax) from baseline (p=0.006) compared to a 9% reduction for QPM (p=0.007) and a 6% reduction for BID (p=0.039). All treatments were well tolerated consistent with previous studies of MetDR.

Conclusion: Met DR delivered once-daily in the morning results in lower Met plasma exposure but the greatest reduction in plasma glucose compared to evening or BID administration. The observation that MetDR provides 24h glucose-lowering with once-daily administration supports the previous findings that Met works predominantly in the lower bowel and that the contribution of systemic exposure to glucose-lowering is small at best. As MetDR is being developed to limit metformin exposure in patients with renal impairment, once-daily morning administration of MetDR is the preferred dosing regimen.

Presented at the 51st Annual meeting of the European Association for the Study of Diabetes, 14-18 September 2015, in Stockholm.

Introduction

- The gut is a major reservoir for metformin and is potentially responsible for much of its glucose-lowering effects, including enhanced secretion of the L-cell products glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), which in turn affects systemic mechanisms including reducing hepatic glucose-production through glucagon suppression and enhanced glucose-dependent insulin secretion.1-4
- Currently available metformin tablets [immediate-release (Met IR) and extended-release (Met XRI)] dissolve in the stomach. Absorption occurs predominantly in the duodenum and upper jejunum with ~50% bioavailability.1-6 The remaining metformin is largely unabsorbed, not metabolized, and either accumulates in the bowel mucosa at up to 300 times plasma concentrations or is excreted in the feces (Figure 1).1-6
- To optimally target the gut-based mechanisms of metformin, we developed metformin delayed-release (Met DR), a gut-restricted metformin formulation that delivers metformin to the ileum where absorption is poor (approximately ≤25% bioavailability) and L-cell density is high.
- We previously showed that Met DR had increased glucose-lowering potency compared to Met IR/XR (ie, maintained glycemic effect at lower doses) in the face of reduced bioavailability (Figure 1).5

Funded by Ecelryx Therapeutics, Inc.

For more information, contact info@elcelyx.com.
Introduction (continued)

- Systemic exposure to metformin increases blood lactate concentrations.\textsuperscript{10,11} Metformin-associated lactic acidosis (MALA), a rare but serious risk of metformin use, is a consequence of metformin plasma accumulation.
- Because patients with poor renal clearance are at greater risk for metformin accumulation, metformin is contraindicated in patients with renal disease or renal dysfunction.\textsuperscript{12}
- As Met DR reduces plasma glucose with minimal metformin accumulation, it is being developed for glycemic control in patients with type 2 diabetes and renal impairment.
- The aim of the current study was to identify the optimal doses and dosing regimen for Met DR in patients with type 2 diabetes.

Objectives

To compare the effect of targeted delivery of metformin to the distal small intestine with a single daily dose of Met DR on metformin pharmacokinetics (PK) in patients with type 2 diabetes.

Study Overview

Patient Population
- Male and female adults with type 2 diabetes treated with diet/exercise alone or with metformin and/or a DPP-4 inhibitor

Study Design
- PK, randomized, 3-period, 7-day, crossover study
- N = 26
- 7.28 ± 1.0
- 31.5 ± 3.2

Results

Baseline Demographics and Characteristics

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51 ± 11</td>
<td></td>
</tr>
<tr>
<td>% Male</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>% White/Black</td>
<td>92/8</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>31.5 ± 3.2</td>
<td></td>
</tr>
<tr>
<td>FPG at Screening, mmol/L</td>
<td>9.33 ± 3.17</td>
<td></td>
</tr>
<tr>
<td>Hba1c at Screening</td>
<td>7.28 ± 1.0</td>
<td></td>
</tr>
</tbody>
</table>

Statistical Analyses

- PK and pharmacodynamic (PD) parameters were determined using non-compartmental analysis methods based on the individual concentration over time data. An ANOVA was performed on the Evaluable Population for the In-transformed parameters for each treatment. Each ANOVA model included status within subject nested within sequence as a random effect. The statistical model included status (pre-treatment, on-treatment), period, sequence, treatment arm, and status by treatment arm as fixed effects and LS means ratios of each pairwise comparison of the In-transformed parameters.
- Comparison of plasma glucose concentrations and PD parameters on-treatment vs. pre-treatment within each subject was conducted using ANOVA with the Evaluable Population. The statistical model included status on the individual concentration over time data. An ANOVA was performed on the Evaluable Population for the In-transformed parameters for each treatment. Each ANOVA model included treatment, sequence, and period as fixed effects. The LS means ratios of each pairwise comparison were back-transformed to obtain geometric least squares (LS) means for each treatment and geometric exposure:

$\text{PK} = \frac{\text{Peak concentration (Cmax)}}{\text{AUC}_0-24}\text{h}\text{, }\text{Efficacy} = \frac{\text{FPG}_24\text{h}}{\text{FPG}_0}\text{, }\text{Absorption} = \frac{\text{Cmax}_0-24\text{h}}{\text{Cmax}_0-24\text{h}}\text{, }\text{Systemic (plasma) exposure} = \frac{\text{FPG}_24\text{h}}{\text{FPG}_0}\text{, }\text{Dissolution} = \frac{\text{FPG}_24\text{h}}{\text{FPG}_0}$

Figure 1a. Glucose-Lowering Effect of Metformin is not Associated with Systemic (Plasma) Exposure

Figure 1b. Glucose-Lowering Effect of Metformin is Not Associated with Systemic (Plasma) Exposure

![Figure 1a. Glucose-Lowering Effect of Metformin is not Associated with Systemic (Plasma) Exposure](image1)

![Figure 1b. Glucose-Lowering Effect of Metformin is Not Associated with Systemic (Plasma) Exposure](image2)

Statistical Analyses

- There was a diurnal effect in both the rate and extent of metformin absorption with QAM dosing having the fastest gut transit time and the lowest plasma exposure compared to QPM.
- The time to reach the peak was 4.5–5.8 h for QAM dosing vs 7.1–8.5 h for QPM dosing.
- QAM dosing resulted in approximately 30% lower metformin exposure over 24 h at steady state (AUC\(_{0-24}\text{h}\)) compared to QPM and BID dosing.
- QAM dosing also resulted in the lowest peak plasma exposure (C\(_p\)) compared to QPM and BID dosing.

![Figure 2. Plasma Metformin Exposure with Met DR QAM, QPM, or BID](image3)