The Primary Glucose-Lowering Effect of Metformin Resides in the Gut Not the Circulation: Results from 7-Day and 12-Week Studies

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Summary

7-Day Study:

- **Once daily dosing of Met DR administered QAM has lower systemic bioavailability than when administered QPM or as divided doses (BID), yet maintains the glucose lowering effect observed with BID dosing.**

12-Week Study:

- **In patients with type 2 diabetes, all doses of Met DR produced statistically significant and clinically relevant and sustained reductions in FPG over 12 weeks of treatment.**
- **Improvements in FPG occurred in the presence of very low fasting plasma metformin concentrations.**
- **The mean change in FPG was similar for 600/800 mg Met DR and 1000 mg Met XR, despite 4–9 fold higher fasting plasma metformin concentrations with 1000 mg Met XR.**
- **The observed safety profile of Met DR was in general comparable to that seen with Met XR.**

Conclusions

- **Delivery of metformin to the distal small intestine increases the apparent potency of metformin; approximately 40% less Met DR than Met XR was needed to obtain a given glucose-lowering effect.**
- **Given the apparent increase in metformin potency and the low total daily metformin plasma exposure of Met DR, these results confirm 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 than typically used with currently available formulations.**
- **The reduction in plasma exposure would be expected to reduce the risk of lactic acidosis; Met DR could represent a potential treatment for patients with type 2 diabetes and renal impairment.**

Abstract

The intestine is a major site of metformin (Met) accumulation (300-1000X plasma), however its impact on glucose homeostasis is unknown. Met delayed-release (Met DR) is formulated to deliver Met to the lower bowel where bioavailability is 1/5th that of the upper bowel. Met DR was explored in two studies in subjects with T2D not on Met ≥2 wks prior to dosing. Study I compared 1000 mg Met DR QD vs 500 mg Met DR BID in a 7 day crossover design (n=26, mean FPG 168 mg/dL). Results: 1000 mg QD resulted in a 29% decrease in exposure vs. 500 mg BID ($p < 0.05$). 1000 mg QD dosing resulted in a 9% reduction in 24 hr plasma glucose from baseline ($p < 0.05$) and 5% reduction for 500 mg BID ($p=0.099$). Study II assessed the effect of 600 mg and 1000 mg Met DR QD on FPG over 12 wk in a randomized blinded study. Met extended release (Met XR) 1000 mg was included as a non-blinded reference (n=~40/group, mean FPG=173 mg/dL, mean HbA_{1c}=7.4%, mean Met dose prior to washout=1438 mg). Results: Mean 4-12 wk change in FPG from baseline was reduced for Met DR: -13.5 mg and -18.0 mg/dL for 600 mg and 1000 mg vs. -1.2 mg/dL for PBO (all $p<0.05$). The mean 4-12 wk FPG reduction for 1000 mg Met XR (-13.3 mg/dL, $p<0.05$ vs PBO) was similar to 600 mg Met DR with an apparent 40% increase in potency of Met DR vs. Met XR. The increased potency is more evident when considering that fasting Met plasma exposure was reduced by almost 90% with Met DR vs. Met XR (median plasma Met: 56 vs 515 ng/mL for 600 mg Met DR vs 1000 mg Met XR). The mean HbA1Cdifferences from placebo at 12 weeks were -0.48%, and -0.35% for 600 mg and 1000 mg Met DR respectively and -0.45% for 1000 mg Met XR. Treatments were all well tolerated. Increased efficacy with QD vs. BID dosing and markedly reduced exposure with Met DR strongly support a major role for Met bowel accumulation to mediate Met's glucose lowering effects. Restricting Met to the lower bowel may be a better alternative for patients with renal impairment to avoid met plasma accumulation associated with lactic acidosis.

Presented at the 75th Scientific Sessions of the American Diabetes Association, June 5–9, 2015, in Boston, MA.

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 though glucagon suppression and enhanced glucose-dependent insulin secretion.[1-4]
- Currently available metformin [immediate-release (Met IR) and extended-release (Met XR)] dissolves in the stomach. Absorption occurs predominantly in the duodenum and upper jejunum with ~50% bioavailability.[5,6] The remaining unabsorbed metformin is not metabolized and either accumulates in the bowel mucosa at 300–1000 times plasma concentrations or is excreted in the feces (Figure 1).[5-8]
- To optimize 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 increases the apparent glucose-lowering potency compared to Met IR/XR (i.e., maintained glycemic effect at lower doses) in the face of reduced bioavailability (Figure 1).[9]
- Systemic exposure to metformin increases blood lactate concentrations.[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.[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 moderate renal impairment.
- The aim of the current studies was to identify the optimal doses and dosing regimen for Met DR and the glucose-lowering effects of Met DR over 3 months in patients with type 2 diabetes.

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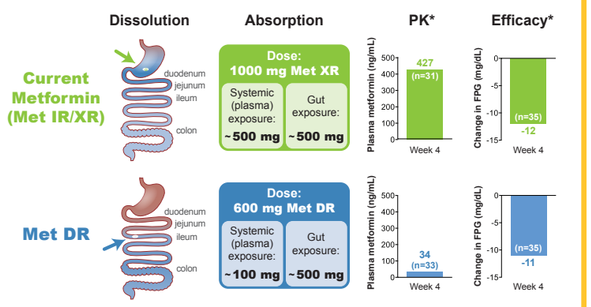
Figure 1. Glucose-Lowering Effect of Metformin is not Associated with Systemic (Plasma) Exposure[9]

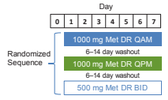
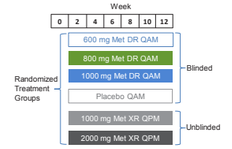


*Fasting plasma metformin pharmacokinetic (PK) data are median concentrations and efficacy data are the median change after 4 weeks of treatment in patients with type 2 diabetes who were washed out of metformin for 2 weeks prior to randomization. Abbreviations: IR = immediate-release, XR = extended-release, Met DR = metformin delayed-release, FPG = fasting plasma glucose.

Objectives

To compare the effect of targeted delivery of metformin to the distal small intestine with Met DR on metformin pharmacokinetics (PK), efficacy, and tolerability in patients with type 2 diabetes.

Study Overview

	7-Day Study	12-Week Study
Objective	Compare single daily dose PK of Met DR (1000 mg QD and 500 mg BID).	Compare the efficacy, safety, and tolerability of Met DR with placebo and unblinded Met XR.
Patient Population	Male and female adults with type 2 diabetes treated with diet/exercise alone or with metformin and/or a DPP-4 inhibitor	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 crossover study 	Randomized, multicenter, placebo-controlled, dose-ranging study 
Randomized/ITT Population	N=26	N=240
Evaluable Population	N=12	Week 4 (Primary Endpoint) N=215 Week 12 N=196

Note: In the 12-Week Study, 2000 mg Met XR was titrated with the final dose reached at Week 3. Abbreviations: BID = twice daily, DPP-4 = dipeptidyl peptidase-4, QAM = once daily in the AM, QPM = once daily in the PM.

Statistical Analyses

7-Day Study:

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

12-Week Study:

- **Efficacy Endpoints:** The primary endpoint was the change in FPG from baseline to Week 4. The change in FPG area under the curve (AUC) from Weeks 4 to 12 and the change in HbA_{1C} from baseline to Week 12 were also evaluated.
- **Analysis Populations:** All safety analyses were conducted using the intent to treat (ITT) population (randomized subjects who took at least one dose of study drug) and efficacy was evaluated using the Evaluable Populations (Evaluable Populations for Weeks 4 and 12 consisted of subjects who completed the corresponding treatment period without any major protocol violations and with non-missing FPG data at baseline and the corresponding endpoint).
- **Statistical Analysis Methods:** Changes in FPG from were assessed using an analysis of covariance (ANCOVA) model with treatment and baseline HbA_{1C} levels (<8% and ≥8%) as factors, and baseline FPG as a covariate. For change in HbA_{1C}, an ANCOVA model with treatment as a factor and baseline HbA_{1C} as a covariate was used. Notable departures from Gaussian assumption were detected for the change in FPG for all active treatment groups. Therefore, the main analyses used the Kruskal-Wallis test for comparisons to placebo and the Hodges-Lehmann method for confidence intervals (CIs) around the median differences from placebo. Analyses of HbA_{1C} employed parametric methods, as the departure from the Gaussian assumption for these did not require alternative methods to be used.

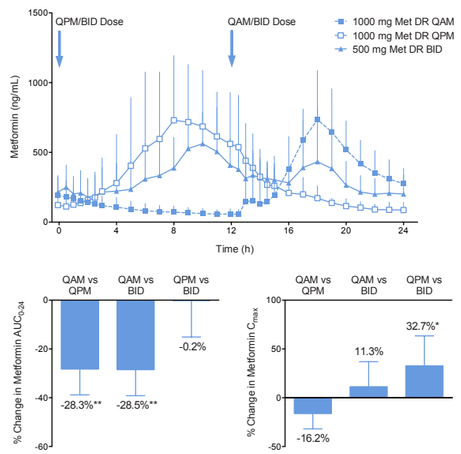
Results: 7-Day Study

Baseline Demographics and Characteristics

	N=26
Age, y	51 ± 11
% Male	38
% White/Black	92/8
BMI, kg/m^2	31.5 ± 3.2
% with Prior Metformin[a] Use, %	73
FPG at Screening, mg/dL	167.6 ± 57.0
HbA_{1C} at Screening, %	7.28 ± 1.0

Data are mean ± SD or percentage of patients for the ITT population. [a] Includes Met IR and Met XR.

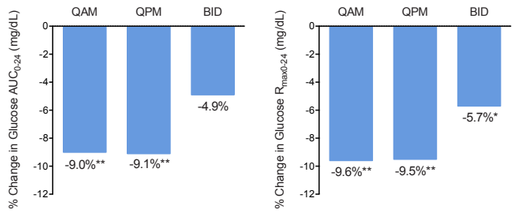
Figure 2. Plasma Metformin Exposure with Met DR QPM, QAM, or BID



Plasma metformin concentrations and plasma metformin relative bioavailability and exposure at steady state. Data are mean and SD (top graph) and % decrease in LS mean and 90% CI (bottom graph) for the Evaluable Population (N=12). Doses were administered at 0 h on Day 6 for QPM/BID dosing and 12 h on Day 7 for QAM/BID dosing. Meals were administered at t = 0, 3, 12, and 18 h. *p<0.05, **p<0.01. Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve over 24 h post-dose, BID = twice daily, Cmax = maximum drug concentration post-dose, DR = delayed-release, Met = metformin, QAM = once daily in the AM, QPM = once daily in the PM.

- QAM dosing resulted in approximately 30% lower metformin exposure over 24 h at steady state compared to QPM and BID dosing.
- Peak plasma exposure (C_{max}) was lowest for QAM dosing.

Figure 3. Change From Baseline in Plasma Glucose with Met DR QPM, QAM, or BID



Change from baseline in glucose and peak plasma glucose. Data are ratio of geometric LS mean of AUC_{0-24} (left) and peak plasma glucose (right) for the Evaluable Population (N=12). Doses were administered at 0 h on Day 6 for QPM/BID dosing and 12 h on Day 7 for QAM/BID dosing. Meals were administered at t = 0, 3, 12, and 18 h. *p<0.05, **p<0.01. Abbreviations: AUC0-24 = area under the plasma concentration-time curve over 24 h after standardized meals, BID = twice daily, DR = delayed-release, $R_{max0-24}$ = maximum observed glucose response over 24 h after standardized meals, Met = metformin, QAM = once daily in the AM, QPM = once daily in the PM.

- Both QAM and QPM dosing regimens resulted in similar and statistically significant decreases in plasma glucose AUC of approximately 9% after meal challenges compared to baseline. BID dosing resulted in a 4.9% reduction in plasma glucose AUC from baseline that did not achieve statistical significance (p=0.099).
- Mean FPG decreased from baseline in all treatment groups and though no statistically significant differences were observed between treatments, reductions were greatest with QAM and QPM compared to BID dosing.

Results: 12-Week Study

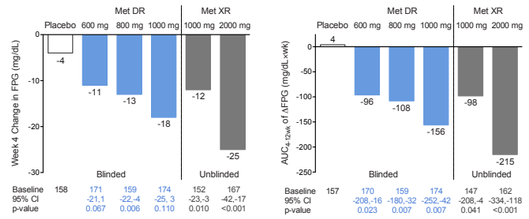
Baseline Demographics and Characteristics

	N=240
Age, y	52 ± 9
% Male	47
% White, Black, Other	68/28/4
BMI, kg/m^2	33.3 ± 5.4
% with Mild Renal Impairment[a]	35
% with Prior Met[b] Use	88
Mean Dose of Prior Met[b], mg	1438
FPG at Screening, mg/dL	144 ± 37
FPG at Baseline, mg/dL	173 ± 50
HbA_{1C} at Baseline, %	7.4 ± 0.9

Data are mean ± SD or percentage of patients for the ITT population. Other includes Asian, Pacific Islander/Native Hawaiian, American Indian/Alaska Native, or Other. [a] Mild renal impairment defined as eGFR ≥60 to <90 mL/min/1.73^2. [b] Includes Met IR and Met XR.

- Baseline demographics were similar across treatment groups.

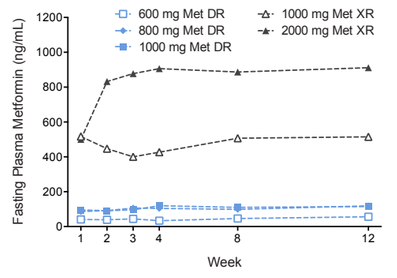
Figure 4. Lower FPG with Met DR Compared to Placebo



Median change in FPG from baseline to Week 4 and median Week 4–12 AUC of the change in FPG. Data are for the (left) Week 4 Evaluable Population (N=215) and (right) Week 12 Evaluable population (N=196). Nonparametric analysis based on Kruskal-Wallis test; 95% CI based on Hodges-Lehmann estimation of the median difference versus placebo; baseline is defined as the median measurement at Day 1. Abbreviations: AUC_{4-12wk} = baseline-corrected area under the FPG curve at steady state, DR = delayed-release, FPG = fasting plasma glucose, Met = metformin, XR = extended-release.

- There was a dose-dependent decrease in FPG from baseline for the Met DR and Met XR groups.
- 1000 mg Met DR produced a greater reduction in FPG than the same dose of Met XR.
- Changes in FPG with 600 mg Met DR was generally similar to that observed in the 1000 mg Met XR treatment group.
- Treatment with 2000 mg Met XR resulted in additional reductions in FPG compared to 1000 mg Met DR, suggesting that Met DR doses slightly greater than 1000 mg may provide additional efficacy.

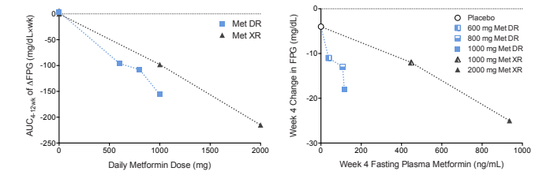
Figure 5. Median Fasting Plasma Metformin Concentrations



Median fasting plasma metformin concentrations. Week 12 Evaluable Population (N = 196). PK was measured in the morning. Met DR was dosed in the morning and Met XR was dosed in the evening after the PK assessment. Abbreviations: DR = delayed-release, Met = metformin, XR = extended-release.

- **Steady-state metformin concentrations were reached by Week 2 for all Met DR groups and 1000 mg Met XR or by Week 4 for 2000 mg Met XR, which required dose titration through Week 3.**
- **The low plasma metformin exposure at the time of FPG collection with Met DR vs Met XR provides further evidence that continuously elevated plasma metformin concentrations are not necessary to elicit or maintain the glucose-lowering effect.**

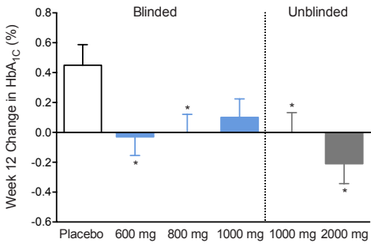
Figure 6. Met DR Reduces FPG with Lower Fasting Plasma Metformin Concentrations



Week 4-12 AUC of the median change in FPG by daily Met dose and Week 4 median change in FPG by fasting plasma metformin concentration in each treatment group. Week 12 Evaluable Population (N = 196; left) and Week 4 Evaluable Population (N = 215; right). Abbreviations: DR = delayed-release, Met = metformin, XR = extended-release.

- The dose-response (left) and exposure response (right) were left shifted for Met DR vs Met XR, indicating that lower doses of Met DR produce equivalent glucose-lowering effect as Met XR.

Figure 7. Mean Change in HbA_{1C} at Week 12

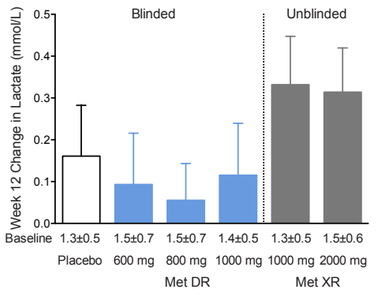


LS mean (SE) change from baseline to Week 12 in HbA_{1C} (%). Week 12 Evaluable Population (N = 196). Analysis of covariance model for change from baseline to post-baseline visit with factor for treatment and baseline HbA_{1C} as a covariate; baseline is defined as the mean measurement at Day 1. *p<0.05 vs placebo. Abbreviations: DR = delayed-release, Met = metformin, XR = extended-release.

- Met DR doses of 600, 800, and 1000 mg prevented the increase in HbA_{1C} observed with placebo, even though all Met DR doses were lower than the 1438 mg/day mean dose of Met IR or XR prior to study entry.
- Treatment with 2000 mg Met XR produced a 0.21% decrease in HbA_{1C} that is consistent with increasing the metformin dose from the 1438 mg/day mean dose prior to study entry.

Safety and Tolerability

Figure 8. Met DR was Associated with Small Changes in Lactate in the 12-Week Study



Baseline and mean (SE) change from baseline to Week 12 in lactate (mmol/L). ITT Population (N = 240). Note: Normal lactate range is 0.5 to 2.2 mmol/L. Abbreviations: DR = delayed-release, Met = metformin, XR = extended release.

- Met XR resulted in a modest increase in plasmas lactate relative to placebo that was not observed with any dose of Met DR.

Gastrointestinal Adverse Events

- Consistent with the known metformin safety profile, the most common adverse events were gastrointestinal in nature:
  - **7-Day study:** 13% for Met DR QAM, 8% for Met DR QPM, and 17% for Met DR BID
  - **12-Week study:** 7% placebo vs 13% to 18% for all Met DR and Met XR treatment groups
- However, relative to the prescribing information of 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 had developed tolerance to the adverse effects and is also consistent with study entrance criteria and the short washout period.