

Comparison of Treatment Persistence with Two Formulations of Metformin

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ABSTRACT

Purpose: Evidence shows that tight glycemic control mitigates the adverse microvascular and macrovascular effects of diabetes. Metformin, an oral anti-hyperglycemic agent, is commonly prescribed as first-line treatment for type 2 diabetes. Despite metformin's demonstrated efficacy, low rates of treatment persistence (the proportion of patients remaining on medication for a period of time) are typical among diabetes patients.¹ We examined persistence rates associated with immediate-release metformin (MIR) versus a novel extended-release metformin (MER) formulation designed to improve tolerability and efficacy.

Methods: The study was a phase III, 24-week, randomized, double-blind, active-controlled, fixed-dose trial comparing MIR 1500 mg/day, b.i.d. (MIR-1500B) versus MER at three doses [1,500 mg/day q.d. (MER-1500Q), 1,500 mg/day b.i.d. (MER-1500B), or 2,000 mg/day q.d. (MER-2000Q)]. Participants were adults with type 2 diabetes who were medication naïve or received prior oral hypoglycemic monotherapy. Titration to study dose was achieved over 3 weeks. Analyses were conducted using a modified intent-to-treat (ITT) approach, whereby participants who completed the study titration phase, received one week of study dose, and had at least one A1C follow-up from baseline were included. Reasons for study withdrawal (initiated by investigator or patient) included lack of efficacy, serious or non-serious adverse events, death, patient desire to withdraw, patient non-compliance with protocol, and lost to follow-up. Patients who prematurely terminated for any reason were defined as non-persistent; those who were titrated to the full study dose and completed the study through week 24 were considered to be persistent.

Results: The ITT analysis included 647 participants with a mean baseline A1C of 8.3% (SD 1.5). Treatment groups had similar demographics and disease-related characteristics at baseline. Patients who received MER-2000Q were approximately half as likely to prematurely terminate from the study as those receiving MIR-1500B (Odds Ratio: 0.52, 95% CI 0.28 to 0.96, p=0.04). Patients receiving MER-2000Q had a lower rate of withdrawal due to lack of efficacy (1.8%) compared with those receiving MIR-1500B (9.9%, NS) and MER-1500Q (11.4%, p=0.03). Groups were similar with respect to the number, type, and severity of adverse events.

Conclusions: Higher treatment persistence is associated with better glycemic control and lower healthcare costs.² Persistence rates were two times higher with extended-release versus immediate-release metformin, possibly due to enhanced tolerability and/or efficacy associated with the maximum Glumetza 2000 mg QD dose.

BACKGROUND

Diabetes mellitus is a metabolic disorder characterized by the presence of chronic hyperglycemia (high blood glucose) due to defects in insulin secretion, insulin action, or both. Type 2 diabetes, which accounts for 90-95% of all diabetes cases, occurs in response to impaired insulin secretion, insulin resistance, or excessive hepatic glucose production. Risk factors include obesity and physical inactivity.

Long-term micro- and macrovascular complications, including retinopathy, neuropathy, nephropathy, and cardiovascular disease, may be mitigated by intensive glycemic control.³⁻⁵

The glycosylated hemoglobin (A1C) laboratory test provides a long-term (3 to 4 month) measure of average glycemic control and predicts the risk for diabetes-related microvascular and macrovascular complications.

A consensus algorithm recently set forth by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends lifestyle changes with metformin medication as the first step to intensive control of type 2 diabetes.⁶

OBJECTIVES

We sought to answer the following questions:

- Are there differences in persistence rates associated with immediate-release metformin (MIR) versus a novel extended-release metformin (MER) formulation?
- If there are differences in persistence, do these differences affect A1C outcomes?

METHODS

This was a multicenter, randomized, double-blind (double-dummy), active-controlled, dose-ranging, non-inferiority, parallel-group clinical study designed to compare the efficacy and safety of a novel metformin extended-release (MER) formulation at doses of 1500 once daily (MER1500Q), 500 mg in the morning and 1000 mg in the evening (MER1500B), and 2000 once daily (MER 2000Q), to immediate-release metformin 500 mg in the morning and 1000 mg in the evening (MIR 1500B).

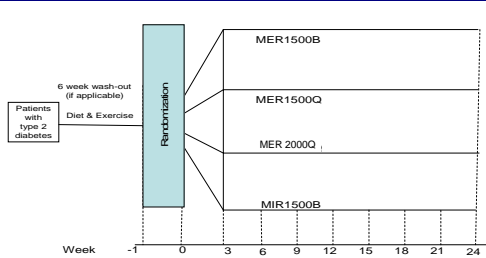
The MIR dosage was chosen because it is the most commonly used dosage of metformin and is accepted as being safe and effective with a tolerable side effect profile. The MIR dose regimen used was as described in the product insert.

The MER1500Q and MER 1500B dosages were chosen to examine the possible advantages of once-daily vs. twice-daily doses of MER at a comparable dose to that of the control group. The MER2000Q dose was designed to compare the safety and efficacy of this higher dosage to the standard MIR dose.

We report persistency and efficacy results of the highest MER dose (MER 2000Q) versus the MIR control (MIR 1500B).

Participants were adults with type 2 diabetes who were drug naïve or previously treated with anti-hyperglycemic agents.

Figure 1. Study Design

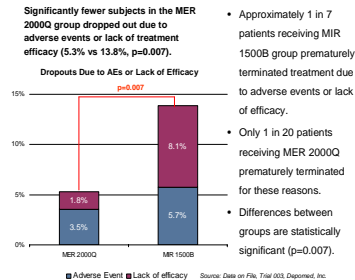


RESULTS

Baseline Characteristics

	MER2000Q (N=158)	MIR1500B (N=159)	p-value	
Demographics				
Female (%)	45.6%	44.0%	0.7822	
Race (%)	Caucasian	64.6%	64.1%	0.9652
	Black	10.7%	13.2%	
	Hispanic	20.9%	20.1%	
	Asian	1.9%	1.3%	
	Other	1.9%	1.3%	
Mean Age (SD)	55.5 (11.4)	52.9 (12.4)	0.0541	
Medical Characteristics				
Mean Body Mass Index (SD)	33.6(6.7)	34.0 (6.9)	0.5074	
Mean duration (years) diabetes (SD)	3.9(4.3)	4.3 (5.5)	0.5557	
Mean A1C (SD)	8.2(1.3)	8.3 (1.3)	0.3982	

Premature Termination by Metformin Treatment Group

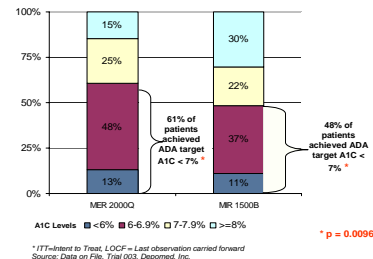


Treatment Persistence

Patients who received MER 2000Q were approximately half as likely to prematurely terminate from the study as those receiving MIR 1500B.

Odds Ratio=0.522 95% CI = 0.283 to 0.964, p=0.0299

% of Patients Achieving ADA Target A1C (< 7%)



CONCLUSIONS

- Superior efficacy, as demonstrated by a significantly greater percentage of patients achieving A1C at the ADA target of < 7%, was achieved with MER 2000Q.
- The higher dose of MER 2000Q appears to have been well tolerated.
- Persistence rates were two times higher with extended-release versus immediate-release metformin, possibly due to enhanced tolerability and/or efficacy associated with higher dose.

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