

# ROLE OF GENDER ON RESPONSE TO ANTI-DIABETIC MEDICATION

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## ABSTRACT

**Purpose:** In patients with type 2 diabetes, some long-term health outcomes differ by gender, for example, the likelihood for cardiovascular-related mortality is greater for women than men.<sup>1</sup> Little is known, however, about gender differences in response to oral anti-diabetics. We examined the effect of dose and formulation of metformin on glycosylated hemoglobin (A1C) in men and women with type 2 diabetes.

**Methods:** The study was a phase III, 24-week, randomized, double-blind, active-controlled, fixed-dose trial comparing metformin immediate-release 1500 mg/day, b.i.d. (MIR-1500B) versus metformin extended-release (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 naive or received prior oral hypoglycemic medication. Analyses were conducted on the intent-to-treat (ITT) sample, defined as those who received at least one dose of medication and had at least one A1C follow-up measurement from baseline.

**Results:** Female and male participants did not differ in terms of baseline A1C. Overall, mean A1C at study endpoint was significantly lower for the MER-2000Q group than the other groups: 7.0±1.1 (MER-2000Q), 7.4±1.5 (MER-1500B), 7.5±1.4 (MER-1500Q), 7.4±1.5 (MIR-1500B), p=0.004. In the total sample, survival analysis indicated a significantly higher likelihood of achieving A1C below 7% for the MER-2000Q group at 12 weeks, 20, weeks and 24 weeks of treatment (p=0.0007); for example, among those receiving MER-2000Q, there was a 62.4% likelihood of achieving A1C below 7% at 24 weeks, compared to 40.9% likelihood for MER-1500B, 43.5% for MER-1500Q, and 46.3% for MIR-1500B. When analysis was stratified by gender, this significant effect held for females (p=0.0024), but not males.

**Conclusion:** Findings suggest that there are gender differences in response to metformin, with a significantly higher likelihood of achieving the American Diabetes Association's target cut-point for A1C (<7%) using the highest once-daily metformin dose for females but not for males. Given that female gender is independently associated with higher risk of cardiovascular-related mortality, these findings suggest that aggressive treatment of females with metformin may be especially appropriate.

## 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.<sup>2-4</sup>

The glycosylated hemoglobin (A1C) laboratory test provides a long-term (3 to 4 months) 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.<sup>5</sup>

## OBJECTIVE

We sought to determine whether there are differences by gender in A1C outcomes associated with immediate-release metformin (MIR) versus a novel extended-release metformin (MER) formulation.

## 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).

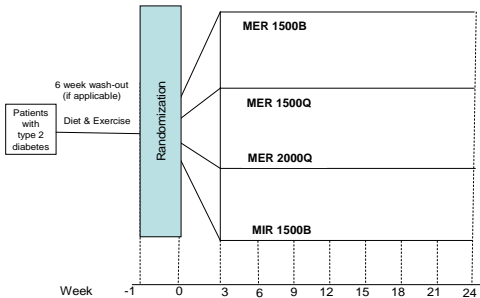
The MIR dosage was chosen because it is the most commonly used dosage of metformin and is accepted as being safe and effective with a tolerable side effect profile. The MIR dose regimen used was as described in the product insert.

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 naive or previously treated with anti-hyperglycemic agents.

Figure 1. Study Design



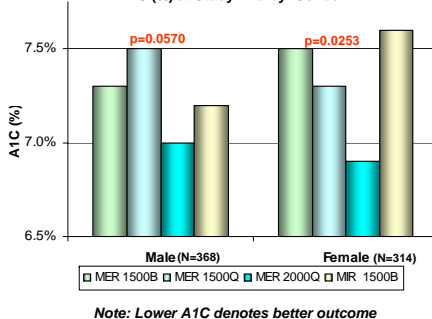
## RESULTS

### Baseline Characteristics

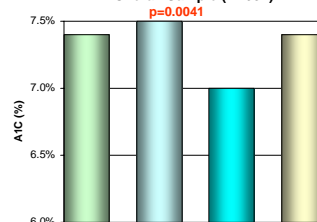
There were no significant differences at baseline in mean A1C % levels or mean fasting plasma glucose by gender.

	Female (N=314)	Male (N=368)	p-value
Mean A1C% (SD)	8.3 (1.4)	8.4 (1.5)	0.1832
Mean Fasting Plasma Glucose (SD)	191 (58)	193 (57)	0.6106

A1C (%) at Study End by Gender



A1C (%) at Study End  
Overall Sample (N=682)  
p=0.0041



Note: Lower A1C denotes better outcome

## CONCLUSIONS

- Overall, mean A1C at study endpoint was significantly lower for the MER-2000Q group than the other treatment groups.
- We found gender differences in response to metformin formulation and dose such that:
  - Females receiving 2000 mg extended release metformin showed significantly greater improvement in A1C at study end than females receiving immediate release metformin or lower doses of the extended release formulation.
  - Among men, there was a trend toward greater effect in A1C reduction in those receiving MER 2000Q.
- Findings suggest that aggressive treatment of females with the maximum tolerated dose of extended-release once-daily metformin may provide important clinical effect.

## REFERENCES

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**DISCLOSURES:** Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation: C Hankin, Z Wang, A Bronstone; Consultants to Depomed. J Wu and B Brener; Employees of Depomed