

Efficacy and Safety of Acarbose in Insulin-Treated Patients With Type 2 Diabetes

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OBJECTIVE — To demonstrate the efficacy, tolerability, and safety of acarbose compared with placebo in patients with type 2 diabetes inadequately controlled with diet and insulin.

RESEARCH DESIGN AND METHODS — A multicenter randomized double-blind placebo-controlled parallel-group comparison study was conducted. The trial was 26 weeks with a 2-week screening period and a 24-week period of treatment with acarbose or placebo, with forced titration from 25 mg t.i.d. to 50 mg t.i.d. after 4 weeks, and titration of 50 mg t.i.d. to 100 mg t.i.d. after 12 weeks based on glucose control. The dosage of insulin was to remain stable. The primary efficacy variable was mean change from baseline in HbA_{1c}, and secondary efficacy variables included mean changes in fasting and postprandial plasma glucose and triglyceride levels.

RESULTS — The addition of acarbose to the treatment of patients receiving background insulin and diet therapy resulted in a statistically significant reduction in mean HbA_{1c} of 0.69% compared with placebo. There were statistically significant reductions in postprandial plasma glucose and glucose area under the curve, and in postprandial serum triglyceride levels in the acarbose-treated patients. Gastrointestinal side effects were more frequently reported in the acarbose-treated patients. There were no significant differences in hypoglycemic events or liver transaminase elevations between groups.

CONCLUSIONS — This study demonstrated that the addition of acarbose to patients with type 2 diabetes who are inadequately controlled with insulin and diet is safe and generally well tolerated and that it significantly lowers HbA_{1c} and postprandial glucose levels.

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Abbreviations: AUC, area under the curve.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

It can be difficult to control postprandial hyperglycemia in patients with type 2 diabetes. Impaired insulin secretion, particularly during the early prandial phase, is a key factor in an inefficient prandial suppression of endogenous glucose production (1–5). Insulin resistance of peripheral tissues impedes glucose uptake during the postprandial phase of metabolism and therefore prolongs the elevated plasma glucose levels. Among the pharmacological options for the treatment for type 2 diabetes, α -glucosidase inhibition has as its principal therapeutic objective the lowering of prandial hyperglycemia. The mechanism by which α -glucosidase inhibition reduces prandial hyperglycemia has been well described (6) and entails retarding hydrolysis of complex carbohydrates and thereby slowing glucose absorption. Acarbose, which is the α -glucosidase inhibitor approved for use in the U.S., has been found to be effective in both reducing postprandial glucose excursions and improving overall glycemic control in patients with type 2 diabetes when used as an adjunct to diet, either as monotherapy or in combination with sulfonylureas (7–11). Also, data demonstrate that acarbose can be effective when used in combination with either metformin or insulin (7,12,13).

Insulin and acarbose have different mechanisms of action with respect to glucose homeostasis, so it is logical to anticipate that the combination of insulin and acarbose would be complementary in the therapy of type 2 diabetes. In a 6-month, placebo-controlled, double-blind trial, the addition of acarbose to insulin therapy did reduce HbA_{1c} by ~0.4% in patients with type 2 diabetes (10). However, in that trial, adjustments of daily insulin dosages were permitted. Mean daily dosages of insulin were reduced in the acarbose-treated group and slightly increased in the placebo-treated group, which confounds the interpretation of the efficacy of acarbose in the study. Similarly, in a 1-year, multicenter, placebo-controlled Canadian study in which acarbose was given to insulin-treated type 2 diabetic patients, the placebo-subtracted treatment effect at end point for HbA_{1c} showed a non-

statistically significant improvement of 0.4% ($P = 0.07$) (7); however, insulin dose was reduced by $\geq 15\%$ in 36% of the acarbose-treated patients compared with 6% of the placebo-treated patients. Therefore, the current study was undertaken to examine the efficacy of acarbose when used with fixed doses of insulin in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

The study was designed as a 26-week multicenter randomized double-blind placebo-controlled two-arm parallel-group comparison of acarbose and insulin therapy versus placebo and insulin therapy for patients with type 2 diabetes. Eight investigation sites participated in this study and recruited patients with type 2 diabetes, defined according to established criteria (14), whose disease was inadequately controlled on diet and insulin. All patients had to be ≥ 30 years of age. Patients with type 1 diabetes were excluded, as were patients taking oral antidiabetic medications. Patients were also excluded from the study for any of the following reasons: the presence of significant diseases or conditions likely to alter the course of the diabetes or the patient's ability to complete the study; documented gastrointestinal diseases likely to be associated with abnormal gut motility, altered absorption of nutrients, chronic diarrheal states, or chronic enteropathies; chronic liver or kidney disease; inadequately controlled hypertension (sitting blood pressure $> 160/90$ mmHg); myocardial infarction within 2 months before screening; history of excessive alcohol consumption; serum creatinine levels ≥ 1.5 mg/dl for men and ≥ 1.4 mg/dl for women; aspartate aminotransferase or alanine aminotransferase elevated more than 1.8 times the normal level; hemoglobin < 11 g/dl, or any hemoglobin variant. Patients were not allowed concomitant therapy with glucocorticoids, other investigational drugs (during the study or within 30 days before screening), medications to lower serum lipids or blood pressure (unless they had been receiving a stable dose for ≥ 28 days before screening), or medications that might significantly alter gastrointestinal motility or absorption. Women of childbearing age who were pregnant, who were unable or unwilling to use effective birth control measures, or who were nursing a child during the study were also excluded. Eligibility was further determined based on glycemic control: baseline

HbA_{1c} needed to be within the range of 7–11% (normal range, 4.0–6.0). A major goal of the study was to keep dosages of insulin constant during the baseline period and throughout the duration of the study, although reductions in the insulin dosage were allowed if they were necessary to treat or prevent hypoglycemia.

Of the 195 patients randomized to double-blind therapy, 97 patients were randomized to placebo and insulin therapy, and 98 patients were randomized to acarbose and insulin therapy. Safety analyses were performed on the entire cohort, except for two individuals who were randomized to acarbose but who took no study medication and one individual who was randomized to placebo and in whom no postbaseline evaluations were obtained. Validity of patients for efficacy analysis was determined on the basis of their having at least one valid visit on or after 8 weeks of treatment with study medication. Patients were considered invalid for the following reasons: the patient's background insulin regimen was not the same as the baseline regimen, the end-of-treatment visit was > 10 days after the stop date of the study medication, the patient began or modified chronic glucocorticoid treatment, or the patient was dispensed incorrect study medication at the previous visit. A total of 72 and 73 patients in the acarbose and placebo arms, respectively, were valid for the efficacy analysis; the most common reason for patient invalidity was a change in insulin dosage.

The primary efficacy criterion was the change from baseline in HbA_{1c} at double-blind end point, which was defined as the last valid visit after at least 8 weeks of double-blind treatment. Secondary efficacy criteria included changes in postprandial glucose and triglycerides, changes in fasting plasma glucose, and changes in fasting triglyceride and cholesterol. Total area under the curve (AUC) from 0 to 120 min for glucose and triglycerides was computed using the trapezoidal rule. Changes in HbA_{1c} and other parameters of metabolic control at intermediate points of treatment were also considered in evaluating efficacy of treatment. The proportion of patients who responded to treatment after 8–24 weeks of double-blind treatment was determined. A patient was considered a responder at a particular visit if the reduction from baseline in HbA_{1c} was $\geq 0.7\%$.

All patients were stabilized on diet and insulin therapy for at least 8 weeks before screening. Patients were encouraged to eat

a diet appropriate for people with diabetes, with at least 50% of calories derived from carbohydrates (15). There was a 2-week lead-in period (single-blind placebo treatment phase; weeks -2 to 0) during which baseline assessments were obtained. After randomization at week 0, patients were evaluated at outpatient visits on weeks 4, 8, 12, 18, and 24. Fasting plasma glucose and HbA_{1c} were obtained at each postbaseline visit. At weeks -2 , 0, 4, 12, and 24, a standardized meal challenge was performed to assess postprandial hyperglycemia. For the meal test, patients consumed two cans (total, 16 oz) of Ensure With Fiber (total, 520 calories; 54% of calories from carbohydrates), and blood samples were obtained at 0, 60, 90, and 120 min for later measurements of plasma glucose and triglyceride in a central laboratory. At 30 min before ingesting the test meal, patients injected their usual morning doses of insulin. With the first swallow of each meal, patients took the prescribed dose of study medication. A complete laboratory evaluation (hematology, chemistry profile, and urinalysis) was performed at screening, randomization, and all post-baseline visits.

Acarbose and placebo medication were prescribed according to a defined titration schedule. After randomization, for the first 4 weeks of double-blind treatment, patients were instructed to take 25 mg t.i.d. At the end of week 4, all patients were instructed to increase the dose of study medication to 50 mg t.i.d. and to continue this dosage through week 12. Any patient unable to tolerate 50 mg t.i.d. of study medication was discontinued from the protocol. At week 12, a standardized breakfast meal challenge was performed, and if the 1-h postprandial capillary blood glucose exceeded 160 mg/dl, the dosage of the study medication was increased to 100 mg t.i.d.; otherwise, the previous dosage of 50 mg t.i.d. was continued. If a patient was unable to tolerate the study medication dosage of 100 mg t.i.d., then a downward titration to 50 mg could be made, but if a patient could no longer tolerate 50 mg t.i.d. of the study medication, their participation in the study was discontinued. Throughout the trial, dosages of insulin were to be kept constant except for reductions needed to prevent hypoglycemia.

All significance studies were performed as two-tailed tests at an α -level of 0.05. The efficacy variables were analyzed using two-way analysis of variance; center and treat-

Table 1—Baseline demographic and disease characteristics

Characteristic	Valid for safety		Valid for efficacy	
	Placebo	Acarbose	Placebo	Acarbose
n	96	96	73	72
Age (years)	61.2	61.5	60.8	61.8
Sex (M/F) (%)	49/51	59/41	48/52	63/37
Body weight (kg)	88.0	90.1	88.8	91.4
BMI (kg/m ²)	31.1	31.5	31.1	31.0
Duration of diabetes (years)	12.5	12.4	12.3	12.5
Caucasian (%)	86	88	86	92
Black (%)	9	8	11	7
Hispanic (%)	3	3	1	1
Other (%)	1	1	1	0

Data are means unless otherwise indicated.

ment effects were included in the model. Fisher's exact test was used for the analyses of adverse events and laboratory abnormalities, except when fewer than one-quarter of the cells had expected counts of <5, in which case the χ^2 test was used for computational ease. Triglycerides and normalized urinary albumin excretion were analyzed on the log scale because of departures from normality. Because of this transformation, the results presented are geometric means (i.e., means on the antilog scale).

RESULTS— In the placebo- and acarbose-treated groups, there were 73 and 72 patients valid for efficacy analyses, which represented 75 and 73% of the patients randomized to each treatment arm, respectively. For patients valid for efficacy, the mean duration of known type 2 diabetes was ~12 years, with a mean patient age of 61 years (Table 1). Most of the patients were obese; mean BMI was 31 kg/m². These characteristics were similar in both treatment groups. The acarbose-treated group was 63% male and 92% Caucasian, and the placebo-treated group was 48% male and 86% Caucasian; these differences were not statistically significant. The disease characteristics of the cohort available for efficacy analyses did not differ from the group of patients used for safety analyses, as shown in Table 1. The baseline efficacy variables for the treatment groups are outlined in Table 2. Mean HbA_{1c} at baseline was 8.7%, indicating fair-to-poor glycemic control. The mean daily dose of insulin was 60 U.

Among patients who were valid for efficacy and received placebo and insulin, HbA_{1c} increased by 0.11% above baseline, whereas among patients randomized to acarbose and insulin, there was a mean

decrease in HbA_{1c} of 0.58%; thus, the placebo-subtracted treatment effect of acarbose added to insulin therapy was a mean decrease in HbA_{1c} of 0.69%. This difference in HbA_{1c} between groups was highly significant ($P = 0.0001$) and was apparent not only at the end of the trial but also at intermediate assessments (weeks 4, 8, 12, 18, and 24; $P \leq 0.0018$), as demonstrated in Fig. 1. Among the larger cohort examined by intent-to-treat analysis, acarbose therapy had a very similar and favorable effect on HbA_{1c}: at end point, the 93 placebo-treated patients exhibited a mean increase in HbA_{1c} of 0.12%, whereas the 95 acarbose-treated patients exhibited a mean decrease in HbA_{1c} of 0.51%, for a placebo-

subtracted mean decrease of 0.63%, which was statistically significant ($P < 0.0001$).

Of patients valid for efficacy at end point, a significantly greater proportion were from the acarbose group than from the placebo group (42 vs. 23%, respectively; $P = 0.012$), with HbA_{1c} reductions from baseline of $\geq 0.7\%$.

Acarbose-treated patients had a mean insulin dosage of 62.0 U/day, and placebo-treated patients had a mean insulin dosage of 60.2 U/day. A principal goal of the study was to keep insulin doses constant throughout, and visits that followed changes in insulin dosages were judged invalid for the efficacy analyses. In the placebo-treated group, 77 of 96 patients maintained precisely the same dosages of insulin throughout the study as did 78 of 96 acarbose-treated patients. Among the placebo-treated patients, 8% had increases and 12% had decreases in the daily insulin dosage. In comparison, among the acarbose-treated patients, 7% had increases and 12% had decreases in the daily insulin dosage. Thus, insulin changes were comparable between the treatment groups.

The addition of acarbose to previous insulin therapy produced a slight but non-significant reduction in fasting plasma glucose compared with placebo ($P = 0.4221$). Acarbose did significantly lower postprandial hyperglycemia compared with placebo, and this effect was evident at 60 min ($P = 0.0178$), 90 min ($P = 0.0004$), and 120 min

Table 2—Baseline efficacy variables for all valid patients

Variable	Placebo	Acarbose
HbA _{1c} (%)	8.69	8.77
Daily insulin dose (U)	60.2	62.0
Fasting plasma glucose	197.5	194.3
60-min plasma glucose	279.2	277.8
90-min plasma glucose	301.6	303.2
120-min plasma glucose	305.3	305.7
Plasma glucose AUC (mg · min · dl ⁻¹)	32,379.9	31,932.5
Fasting triglycerides*	137.0	148.4
60-min triglycerides*	159.2	170.7
90-min triglycerides*	181.3	183.1
120-min triglycerides*	183.1	194.4
Triglyceride AUC (mg · min · dl ⁻¹)*	20,130.7	20,333.0
Total cholesterol	200.7	193.0
HDL cholesterol	46.1	41.3†
LDL cholesterol	125.0	118.8
Normalized urinary albumin (mg/day)*	18.4	23.1
Normalized urinary glucose (g/day)	15.9	16.3

Data are means and are expressed in milligrams per deciliter unless otherwise indicated. *Geometric least squares mean; †significantly different from placebo.

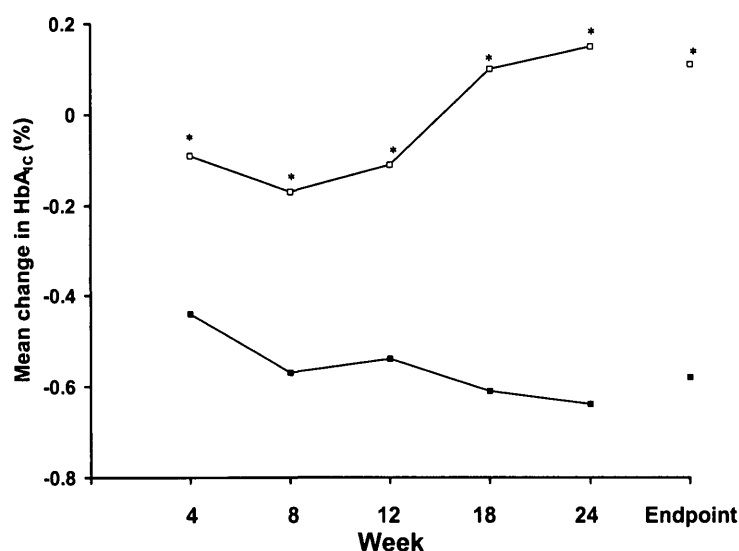


Figure 1—Mean change from baseline in HbA_{1c} in patients receiving acarbose (■) or placebo (□) at 4, 8, 12, 18, and 24 weeks of treatment and at double-blind end point. *Significantly different from acarbose.

($P = 0.0001$) after standardized meal challenges, as shown in Fig. 2. In acarbose-treated patients, the postprandial AUC for plasma glucose was reduced by $-3,964 \text{ mg} \cdot \text{min} \cdot \text{dl}^{-1}$, compared with a modest upward drift of $860 \text{ mg} \cdot \text{min} \cdot \text{dl}^{-1}$ in patients receiving placebo; the difference between groups was significant ($P = 0.0074$) (Table 3). Regarding the prandial increment of plasma glucose (i.e., the increase above fasting plasma glucose), acarbose treatment reduced prandial AUC by 36% compared with baseline studies, whereas in the placebo-treatment arm, the reduction was 3%.

Acarbose treatment also had a favorable effect on postprandial serum triglyceride levels. The combination of acarbose and insulin significantly blunted postprandial triglyceride at 90 min ($P = 0.0050$) and 120 min ($P = 0.0133$) after meal ingestion.

Of the 97 patients randomized to placebo, 23 (24%) prematurely discontinued the study, as did 34 (35%) of 98 patients randomized to acarbose treatment. Among the placebo-treated patients, adverse events and protocol violations accounted for most of the premature discontinuations. Of those 23 patients, 6 discontinued because of adverse events. Among the 34 patients who withdrew prematurely from acarbose treatment, 19 did so because of adverse events, the most common of which were gastrointestinal. Chief among these was flatulence (13 patients); a lower incidence of diarrhea (5

patients) and abdominal discomfort (5 patients) was reported. Among the entire cohort, digestive complaints of any type were reported by 39 (41%) of the patients taking placebo, and by 74 (77%) of the patients taking acarbose. Flatulence was reported by 25 (26%) of the patients taking placebo and by 68 (71%) of the patients taking acarbose (Table 4). For both of these events, the differences between acarbose and placebo were statistically significant. The acarbose-treated patients tended to

have more complaints of diarrhea (25% compared with 15% of patients taking placebo), but this difference was not statistically significant. In the placebo and acarbose treatment arms, 22 and 29 patients, respectively, reported symptoms of hypoglycemia, and this difference was not significant. A documented case of serious hypoglycemia occurred in one acarbose-treated patient. There were no statistically significant differences between treatment groups in the incidence of liver transaminase elevations, and no patient experienced treatment-emergent transaminase elevations greater than 1.8 times the upper limit of normal.

CONCLUSIONS— Type 2 diabetes is a progressive disease, characterized by a slow but steady deterioration of β -cell function (16), and many patients with this disorder eventually require treatment with exogenous insulin. The impairment in β -cell function is particularly evident as diminished early-phase insulin secretion after meal ingestion. It is well recognized that attaining good metabolic control with insulin therapy in patients with type 2 diabetes can be difficult, or at least that it often requires large doses of insulin (17). This difficulty has been an impetus to explore the effectiveness of combining oral agents with insulin therapy (18). The current study was undertaken to evaluate the safety and efficacy of adding the α -glucosidase inhibitor acarbose to the regimen of

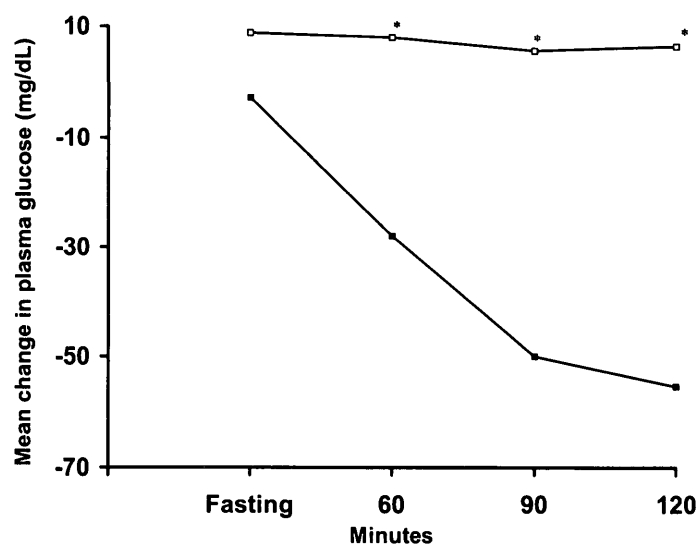


Figure 2—Mean change from baseline in fasting and postprandial plasma glucose levels in patients receiving acarbose (■) or placebo (□) at double-blind end point. *Significantly different from acarbose.

Table 3—Changes from baseline in efficacy variables for all valid patients

Variable	Placebo	Acarbose	P values
HbA _{1c} (%)	0.11	-0.58†	0.0001
Fasting plasma glucose	8.87	-2.84	0.4221
60-min plasma glucose	8.03	-27.99†	0.0178
90-min plasma glucose	5.68	-49.95†	0.0004
120-min plasma glucose	6.51	-55.32†	0.0001
Plasma glucose AUC (mg · min · dl ⁻¹)	859.69	-3,964.2†	0.0074
Fasting triglycerides*	0.99	0.90	0.0546
60-min triglycerides*	0.99	0.90	0.0617
90-min triglycerides*	0.96	0.83†	0.0050
120-min triglycerides*	0.96	0.82†	0.0133
Triglycerides AUC*	0.97	0.86†	0.0223
Total cholesterol	-2.98	-0.43	0.4460
HDL cholesterol	-0.44	-1.24	0.4341
LDL cholesterol	-2.43	6.83†	0.0018
Normalized urinary albumin*	1.23	1.13	0.5113
Normalized urinary glucose (g/day)	6.21	-5.41†	0.0074

Data are means and are expressed in milligrams per deciliter unless otherwise indicated. *Geometric least squares mean of the ratio of the end-point value to the baseline value; †significantly different from placebo.

patients with type 2 diabetes who were already receiving treatment with exogenous insulin injection. The combination of insulin with an α -glucosidase inhibitor, such as acarbose, is a logical approach because acarbose would target prandial hyperglycemia. This approach would be complementary to the effects of exogenous insulin therapy because the pharmacokinetics of human insulin absorption in patients with type 2 diabetes do not recapitulate the normal dynamics of early prandial insulin secretion (19).

In the current study, the addition of acarbose, given in a double-blind placebo-controlled design, reduced HbA_{1c} by 0.69% compared with the placebo-treated patients. This positive outcome is clearly attributable to the addition of acarbose because the study design entailed maintaining constant dosages of exogenous insulin. The addition of acarbose to a previous regimen of insulin did not significantly affect fasting plasma

glucose but did substantially lower prandial hyperglycemia, which is entirely consistent with the drug's known mechanism of action (6). There have been prior clinical trials to evaluate the combined use of acarbose and insulin in the treatment of type 1 and type 2 diabetes (7,10,20). In both trials of combined use of acarbose and insulin therapy in type 2 diabetes (7,10), less improvement in HbA_{1c} was obtained than in the present trial, but insulin dosages were not necessarily kept stable (as they were in the current study), and indeed, more patients assigned to acarbose in those trials had reductions in insulin dosages than did placebo-treated patients. In addition to clarifying the glycemic improvement that can be obtained through the addition of acarbose to insulin treatment in type 2 diabetes, the current study also indicates that efficacy can be achieved without the need to alter previous dosages of insulin in >80% of patients with fair-to-poor glycemic control. There was a low incidence of hypoglycemia, which is consistent with the tendency of acarbose to attenuate postprandial excursions rather than to produce further reductions in the fasting levels of plasma glucose.

In the current trial, acarbose therapy was found to be safe, although not without side effects. Most patients treated with acarbose developed gastrointestinal side effects, chiefly flatulence, and to a lesser extent, diarrhea and abdominal discomfort. It should be noted, however, that there was a relatively high background of gastrointesti-

nal complaints, because ~40% of placebo-treated patients experienced symptoms of a similar nature. It is significant that during the 26-week trial, nearly equal numbers of acarbose- and placebo-treated subjects completed the study.

In summary, the current study indicates that the addition of acarbose to insulin therapy can be a safe and effective method of improving glycemic control in insulin-treated patients with type 2 diabetes, thereby helping to achieve the important goal of reducing the complications of hyperglycemia (21,22).

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Table 4—Incidence of selected adverse events

Adverse event	Placebo	Acarbose
Flu syndrome	3/96 (3)	11/96 (11)*
Flatulence	25/96 (26)	68/96 (71)*
Diarrhea	14/96 (15)	24/96 (25)
Abdominal pain	5/96 (5)	7/96 (7)

Data are proportions (%). *Significantly different from placebo.

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