

**Colesevelam HCl Improves Glycemic Control and Reduces LDL-Cholesterol in Patients with Type 2 Diabetes Inadequately Controlled on Sulfonylurea-Based Therapy**

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*Running title:* Colesevelam Improves Glucose and Lipid Levels

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**Objective:** Hyperglycemia is a risk factor for microvascular complications and may increase the risk of cardiovascular disease in patients with type 2 diabetes. This study tested the LDL-cholesterol-lowering agent colesevelam HCl (colesevelam) as a potential novel treatment for improving glycemic control in patients with type 2 diabetes on sulfonylurea-based therapy.

**Research Design and Methods:** A 26-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter study was carried out between August 2004 and August 2006 to evaluate the efficacy and safety of colesevelam for reducing A1C in adults with type 2 diabetes whose glycemic control was inadequate (A1C 7.5%–9.5%) with existing sulfonylurea monotherapy or sulfonylurea in combination with additional oral antidiabetic agents. In total, 461 patients were randomized (230 [colesevelam 3.75 g/day] and 231 [placebo]). The primary efficacy measurement was mean placebo-corrected change in A1C from baseline to Week 26 in the intent-to-treat population (last observation carried forward).

**Results:** The LS mean change in A1C from baseline to Week 26 was -0.32% in the colesevelam group and +0.23% in the placebo group, resulting in a treatment difference of -0.54% ( $P<0.001$ ). The LS mean percent change in LDL-cholesterol from baseline to Week 26 was -16.1% in the colesevelam group and +0.6% in the placebo group, resulting in a treatment difference of -16.7% ( $P<0.001$ ). Furthermore, significant reductions in fasting plasma glucose, fructosamine, total cholesterol, non-HDL-cholesterol, and apolipoprotein B were demonstrated in the colesevelam group relative to placebo at Week 26.

**Conclusions:** Colesevelam improved glycemic control and reduced LDL-cholesterol levels in patients with type 2 diabetes receiving sulfonylurea-based therapy.

Trial Registration: Trial NCT00147758, U.S National Institutes of Health clinical trials registry (<http://www.clinicaltrials.gov>).

**H**yperglycemia is a risk factor for microvascular complications in patients with type 2 diabetes,(1) and landmark clinical studies have documented that improved glycemic control results in decreased development and progression of the microvascular complications of type 2 diabetes.(2,3,4,5) The American Diabetes Association (ADA) recommends a glycosylated hemoglobin (A1C) target of <7.0%,(6) the level at which clinical trials have demonstrated fewer long-term microvascular complications.(7) Although the impact of hyperglycemia on macrovascular complications is unknown, individuals with type 2 diabetes have a 2–4 fold higher risk for initial coronary events and more importantly, those developing coronary heart disease have a relatively poor prognosis for recurrent coronary heart disease events and coronary death.(8,9) In addition to hyperglycemia, dyslipidemia and hypertension also contribute to the risk of complications in patients with type 2 diabetes. Therefore, treatment regimens for type 2 diabetes should aim to address multiple clinical features of this disease.

Effective lipid management reduces macrovascular disease and mortality in individuals with type 2 diabetes, particularly in those who have had prior cardiovascular events.(10,11,12) However, in a study by Kennedy and colleagues, the ADA goal of LDL-cholesterol (LDL-C) <100 mg/dL [2.6 mmol/L] was achieved by only 49% of patients with type 2 diabetes, and only 16% achieved LDL-C <70 mg/dL [1.8 mmol/L], the optional goal for very-high-risk individuals.(13) Individuals with type 2 diabetes may exhibit a characteristic dyslipidemia that includes elevated triglyceride (TG) levels, decreased HDL-cholesterol (HDL-C) levels, and small, dense

LDL particles, which increases the risk of complications.

Preliminary evidence suggested that altering bile acid metabolism with a bile acid sequestrant in patients with type 2 diabetes has a beneficial effect on glucose control. Colesevelam HCl (Welchol™ [colesevelam]; Daiichi Sankyo, Inc.), a specifically-engineered bile acid sequestrant that significantly lowers LDL-C levels in patients with primary hypercholesterolemia, improved glycemic control in adults with type 2 diabetes based on *post-hoc* analysis of data from a 6-month primary lipid trial.(14) A short-term, double-blind, placebo-controlled pilot study in subjects with type 2 diabetes inadequately controlled with metformin and/or sulfonylurea therapy was conducted; after 12 weeks, colesevelam reduced A1C by -0.50% in the total population ( $P=0.007$  vs placebo) and by -1.0% in those with a baseline A1C  $\geq 8.0\%$  ( $P=0.002$  vs placebo).(15) A subsequent study in which colesevelam was added to insulin-based therapy showed that the addition of colesevelam reduced A1C by 0.5% relative to placebo after 16 weeks.(16) The present study was designed to evaluate the longer-term efficacy of colesevelam for improving glycemic control and the lipid profile in patients with type 2 diabetes not adequately controlled on a stable sulfonylurea-based antidiabetic regimen.

## RESEARCH DESIGN AND METHODS

This 26-week, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 49 sites in the United States and 2 in Mexico. The study protocol was conducted in compliance with Institutional Review Board regulations, Good Clinical Practice Guidelines, and the 4<sup>th</sup> amendment of the Declaration of Helsinki. All individuals provided written informed consent.

This study enrolled adults with type 2 diabetes who were inadequately controlled (A1C 7.5%–9.5%, inclusive) on a stable dose of sulfonylurea alone or in combination with additional oral antidiabetic agents for  $\geq 90$  days. All subjects were advised to follow ADA dietary recommendations.

Subjects were excluded for the following reasons: LDL-C  $< 60$  mg/dL [1.6 mmol/L]; TG  $> 500$  mg/dL [5.7 mmol/L]; BMI  $> 45$  kg/m<sup>2</sup>; uncontrolled hypertension (BP  $> 160/95$  mmHg); history of type 1 diabetes, ketoacidosis, dysphagia, swallowing disorders, or intestinal motility disorders; any serious medical/psychiatric disorder; drug/alcohol abuse within 2 years; hospitalization within 14 days; treatment with colesevelam within 8 weeks; chronic use or recent initiation of insulin; participation in a weight loss program with ongoing weight loss; starting an intensive exercise program within 4 weeks; use of any investigational drug within 30 days of first dose of study medication; or any condition or therapy which might have posed a risk or made participation not in the best interest of the subject.

Oral corticosteroids, cholestyramine, and colestipol were excluded. Oral contraceptives, hormone replacement therapy, thyroid replacement therapy, and lipid-altering drugs (HMG-CoA reductase inhibitors, fibrates, niacin, fish oils, and cholesterol absorption inhibitors) were permitted, provided a stable dose had been maintained for  $\geq 30$  days prior to the initiation of the study and dosage changes were not anticipated.

Subjects were discontinued for hyperglycemia if A1C increased to  $\geq 10.0\%$ , or fasting plasma glucose (FPG) increased to  $> 260$  mg/dL [14.4 mmol/L], and was confirmed within three days. The management, reporting, and actions taken in response to hypoglycemia (FPG  $< 60$  mg/dL) were left to the judgement of the investigators. Discontinuation was considered

only after repeated measurements of hypoglycemia.

Subjects underwent a 1-week screening period and then entered a 2-week single-blind placebo run-in period, during which subjects took 6 placebo tablets/day. Subjects chose their preferred dosing regimen: 3 tablets with the noon and evening meals or 6 tablets with the evening meal. The dosing regimen selected was to be maintained throughout the double-blind treatment period for an individual subject. Following the placebo run-in period, subjects were randomized 1:1 to colesevelam 3.75 g/day (6 tablets: 625 mg/tablet) or matching placebo for 26 weeks of double-blind treatment. Subjects continued taking their pre-study oral antidiabetic medication(s) at the same dose and time as prior to the start of the study.

The primary efficacy parameter was mean change in A1C from baseline to Week 26 in the intent-to-treat (ITT) population with last observation carried forward (LOCF) analysis. Secondary efficacy parameters included: mean change in FPG, fructosamine, and C-peptide; mean change in A1C for the sulfonylurea monotherapy and sulfonylurea combination therapy cohorts; percentage of subjects achieving a reduction in FPG  $\geq 30$  mg/dL or A1C  $\geq 0.7\%$ ; mean change and mean percent change in lipids, lipoproteins, and lipid and lipoprotein ratios; median change and median percent change in high-sensitivity C-reactive protein (hsCRP) and TG. For all secondary efficacy parameters, the change from baseline to Week 26 was calculated using both LOCF and non-LOCF analyses.

All blood samples were obtained under fasting conditions. Tests were performed by a certified laboratory (Medical Research Laboratories International, Highland Heights, KY). Total cholesterol (TC) and TG were measured by enzyme assay. HDL-C was measured by cholesterol oxidase assay of the supernatant from the precipitate of non-HDL

lipoproteins with heparin and manganese chloride. Apolipoprotein (apo) B, apo A-I, and hsCRP were quantitated by immunonephelometry. The method used to calculate LDL-C was based on TG concentration at screening (Friedewald equation for subjects with TG  $\leq$ 400 mg/dL [4.5 mmol/L] and Lipid Research Clinic beta-quantification method for subjects with TG  $>$ 400 mg/dL [4.5 mmol/L] and  $\leq$ 500 mg/dL [5.7 mmol/L]). The method of LDL-C determination used at screening was used throughout the study for an individual subject, regardless of changes in TG.

Safety assessments included treatment-emergent adverse events (AEs), clinical laboratory tests, changes in vital signs, and physical examinations. Compliance with the medication regimen was evaluated by counting unused tablets.

**Statistical Method:** The ITT population was the primary analysis population for all efficacy parameters and included all randomized subjects who took  $\geq$ 1 dose of randomized study medication, and had a baseline and  $\geq$ 1 post-baseline A1C measurement. Analyses of the mean change in A1C from baseline were conducted for two mutually exclusive protocol-defined cohorts: subjects on background sulfonylurea monotherapy, and those on background of sulfonylurea combination therapy. The safety population included all randomized subjects who took  $\geq$ 1 dose of study medication.

This study required 400 randomized subjects and had 86%–95% power to detect a difference of 0.50%–0.80% reduction in mean A1C from baseline between colesevelam and placebo (with a 2-sided type I error at 0.05), assuming a common standard deviation of  $\leq$ 1.5% and a maximum dropout rate of 15%.

Comparisons between the treatment groups in age, weight, height, BMI, A1C, and FPG at baseline were evaluated using a one-way analysis of variance (ANOVA) model with treatment as a factor. Gender and race

were tested using a Fisher's exact/Fisher-Freeman-Halton test. An analysis of covariance (ANCOVA) model with treatment and concomitant antidiabetic medication status as fixed effects and baseline A1C as a covariate was used to evaluate the treatment effect. The normality assumption of the efficacy data was examined prior to conducting the ANCOVA. When a significant departure from normality was observed, a nonparametric equivalent of ANCOVA (rank analysis of covariance) was applied.

The treatment effect in A1C change from baseline with LOCF was estimated and presented as least-squares (LS) mean, standard error of the mean, corresponding 2-tailed 95% CI, and 2-sided *P*-value. Secondary efficacy parameters were compared with the same statistical methodology unless otherwise noted.

Median change and median percent change in hsCRP and TG were analyzed using a nonparametric ANCOVA model. The treatment difference was estimated by the Hodges-Lehmann estimator, and a 2-tailed 95% CI for the treatment difference was obtained using the method of Moses. The glycemic-control response rate was tabulated and compared using Pearson's chi-square test.

## RESULTS

**Subject Disposition and Baseline Characteristics:** The study was conducted between August 2004 and August 2006. A total of 1180 subjects were screened with 493 entering the placebo run-in period. In total, 461 subjects were randomized (230 [colesevelam] and 231 [placebo]), with 307 subjects completing the 26-week study (Figure 1). Baseline demographic characteristics did not differ between the colesevelam and placebo groups at randomization (Table 1).

Sixty-four subjects in the colesevelam group withdrew prior to study completion, relative to 90 in the placebo group. Twenty-

two subjects in the colesevelam group discontinued due to glycemia-related events compared to 46 subjects in the placebo group. Sixteen subjects in the colesevelam group and 39 in the placebo group discontinued due to protocol-specified discontinuation criteria (FPG >260 mg/dL [14.4 mmol/L], A1C  $\geq$ 10.0%, or change in antidiabetic regimen).

Mean compliance was similar during the double-blind treatment period (92.7% [colesevelam group] and 90.8% [placebo group]).

**Efficacy: Glycemic Parameters-** Colesevelam reduced A1C by -0.32%  $\pm$  0.066% while placebo increased A1C by +0.23%  $\pm$  0.065%, resulting in a significant LS mean treatment difference of -0.54%  $\pm$  0.090% at Week 26 LOCF ( $P$ <0.001; Figure 2A; online appendix Table 2 which is available at <http://care.diabetesjournals.org>). Similar treatment effects were observed in the sulfonylurea monotherapy (-0.79%  $\pm$  0.154%;  $P$ <0.001) and sulfonylurea combination therapy cohorts (-0.42%  $\pm$  0.110%;  $P$ <0.001).

A1C was also evaluated by stratifying the total population into two subgroups according to baseline A1C to evaluate the effect of baseline A1C on the response to the addition of colesevelam. In the subgroup with A1C  $\leq$ 8.0% at baseline, the treatment effect for A1C was -0.48%  $\pm$  0.124 ( $P$ =0.0002). A greater A1C treatment effect was observed in the subgroup with A1C >8.0% at baseline (-0.58%  $\pm$  0.128;  $P$ <0.0001).

A significant LS mean treatment difference in FPG was observed by Week 26 LOCF (-13.5 mg/dL  $\pm$  5.14 [0.75 mmol/L  $\pm$  0.29];  $P$ =0.009; online appendix Table 2), with a significant treatment difference observed as early as 6 weeks (-13.7 mg/dL  $\pm$  3.98 [0.76 mmol/L  $\pm$  0.22];  $P$ <0.001).

A significantly greater percentage of subjects in the colesevelam group achieved an A1C reduction  $\geq$ 0.7% compared with the placebo group (35.2% vs 16.5%, respectively;  $P$ <0.001; online appendix Table 3). In

addition, there was a significantly greater number of individuals in the colesevelam group relative to the placebo group who achieved either a reduction in A1C  $\geq$ 0.7% or a reduction in FPG  $\geq$ 30 mg/dL by study end (104 [47.5%] vs 70 [32.1%], respectively;  $P$ =0.001; online appendix Table 3).

A significant LS mean treatment difference in fructosamine was reported at Week 26 LOCF (-21.4  $\mu$ mol/L  $\pm$  4.59;  $P$ <0.001).

There was no significant LS mean treatment difference in C-peptide at Week 26 LOCF (-0.17 ng/mL  $\pm$  0.101;  $P$ =0.102).

**Lipid Parameters:** Significant LS mean percent treatment differences in LDL-C, non-HDL-C, TG, TC, apo A-I, and apo B were observed after 26 weeks of treatment with colesevelam relative to placebo ( $P$ <0.001 for all; Figure 2B). The LS mean percent change in LDL-cholesterol from baseline to Week 26 (LOCF) was -16.1% in the colesevelam group and +0.6% in the placebo group, resulting in a treatment difference of -16.7% ( $P$ <0.001). In addition, a significant mean percent reduction in non-HDL-C, TC, and apo B concentrations occurred in the colesevelam group relative to the placebo group at Week 26 LOCF, while a significant mean percent increase in apo A-I concentration occurred with colesevelam relative to placebo. Although mean HDL-C increased from baseline by Week 26 in both the colesevelam and placebo groups (0.5% vs 0.3%, respectively), there was no significant treatment difference by Week 26 LOCF (+0.1%;  $P$ =0.916). Median TG levels increased with colesevelam relative to placebo treatment (19.5% vs 1.0%), resulting in a significant LS mean percent treatment difference at Week 26 (+17.7%;  $P$ <0.001).

Significant LS mean treatment differences between the colesevelam and placebo groups were reported in the ratio of TC/HDL-C (-0.24  $\pm$  0.08), LDL-C/HDL-C (-0.43  $\pm$  0.05), non-HDL-C/HDL-C (-0.24  $\pm$

0.08), and apo B/apo A-I ( $-0.08 \pm 0.01$ ) at Week 26 LOCF ( $P \leq 0.003$  for all).

**Inflammatory markers:** There was a LS median treatment difference of marginal significance in hsCRP by Week 26 LOCF ( $-0.40 \text{ mg/L} \pm 4.50$ ;  $P=0.063$ ).

**Safety:** Colesevelam was generally safe and well tolerated in subjects with type 2 diabetes when added to sulfonylurea-based therapy. In total, 145 subjects in the colesevelam group and 126 in the placebo group experienced an AE during this study (online appendix Table 4). The most frequently reported AEs with colesevelam were constipation, upper respiratory tract infection and urinary tract infection, while upper respiratory tract infection, headache, and nasopharyngitis were more common with placebo. Forty-seven subjects in the colesevelam group and 21 in the placebo group experienced a drug-related AE, with constipation being the most common drug-related AE in both groups (6.1% vs 2.6%, respectively). Most AEs were mild-to-moderate in severity, although 9 subjects in the colesevelam group and 7 in the placebo group experienced a severe AE. Three severe AEs were judged to be drug-related (2 in the colesevelam group and 1 in the placebo group). Eighteen subjects in the colesevelam group and 9 in the placebo group withdrew due to an AE, mostly gastrointestinal AEs. Twelve subjects in the colesevelam and 4 in the placebo group withdrew due to a drug-related AE. There were 8 serious AEs (SAEs) in the colesevelam group and 11 in the placebo group; however none were drug-related.

Six subjects in the colesevelam group experienced hypoglycemia relative to 2 subjects in the placebo group. None of these hypoglycemic episodes were considered severe and no subject in either group discontinued due to hypoglycemia. Mean changes in safety laboratory parameters and vital signs were similar between the groups

during the randomized treatment period. No weight gain was noted in either group; mean weight change was  $-0.01 \text{ kg}$  in the colesevelam group and  $-0.4 \text{ kg}$  in the placebo group.

## CONCLUSIONS

This study investigated the glucose-lowering effect of colesevelam in patients with type 2 diabetes, when added to an existing regimen of sulfonylurea, alone or in combination with additional oral antidiabetic agents. Colesevelam resulted in a significant mean A1C reduction ( $-0.54\%$ ) by Week 26 in the total population, with the sulfonylurea monotherapy and sulfonylurea combination therapy cohorts reporting a significant reduction at Week 26 as well ( $-0.79\%$  and  $-0.42\%$ , respectively). While the magnitude of A1C reduction may appear modest, it is similar to the observed effect from another study in which a new antidiabetic agent was combined with a sulfonylurea in patients with advanced type 2 diabetes.(17) Importantly, individuals with declining beta cell function would be expected to be heavily represented in this population.(18)

The lower dropout rate with colesevelam (27.8%) compared with placebo (39.0%) was likely related to treatment failure, as many patients discontinued in the placebo group due to meeting protocol-specified discontinuation criteria, attesting to the efficacy of colesevelam. Furthermore, colesevelam produced significant reductions in LDL-C, TC, non-HDL-C, and apo B by Week 26, supporting its use as a novel treatment for improving glycemic control with added lipid benefits for patients with type 2 diabetes.

There was a rise in TG levels in patients receiving colesevelam in this study ( $+17.7\%$ ;  $P < 0.001$  vs placebo). This is a known and expected phenomenon with bile acid sequestrants. Although hypertriglyceridemia is a cardiovascular

disease risk factor, the effect of elevated TG levels in patients on existing statin therapy, or in the context of a reduction in LDL-C, remains to be determined. Current studies are addressing the contribution of TG levels on cardiovascular outcomes.(19,20) Importantly, the rise in TG with colesevelam was accompanied by a reduction in LDL-C (-16.7%) and apo B (-6.7%) and an increase in apo A-I concentration (+3.8%;  $P < 0.001$  vs placebo for LDL-C, apo B, and apo A-I). Hence, the overall effect of colesevelam on circulating lipid levels may be interpreted as reassuring.

The exact mechanism(s) through which colesevelam demonstrates its effect on glycemic control is unknown. Potential explanations include: 1) bile acid sequestrants act in the gastrointestinal tract, reducing the amount of glucose absorbed and/or altering the time course of glucose absorption;(21) and/or 2) bile acid sequestrants bind bile acids, thus disrupting the enterohepatic pathway of bile metabolism, which has indirect effects on glucose metabolism.(22) It is known that bile acids are endogenous ligands of the farnesoid X receptor (FXR), a member of the nuclear receptor superfamily of ligand-activated transcription factors,(23) which play an important role in bile acid, cholesterol, and glucose metabolism. There is a complex interplay between FXR and additional nuclear receptors, including the liver X receptor, hepatocyte nuclear factor 4 alpha receptor, and the fibroblast growth factor 19 receptor. Little is currently known about how bile acids affect these pathways, particularly in patients with type 2 diabetes whose glucose regulation is impaired. Further research is needed to determine the mechanism underlying the glucose-lowering effect of colesevelam.

It is increasingly recognized that controlling hyperglycemia and cholesterol levels may afford better outcomes in patients with type 2 diabetes.(24) In spite of this,

approximately two-thirds of individuals with type 2 diabetes fail to achieve the ADA-recommended goal of A1C  $< 7.0\%$  and almost 75% do not achieve the LDL-C goal of  $< 100$  mg/dL. Thus, new treatment regimens that can improve both glycemic control and lipid management in individuals with type 2 diabetes would be clinically beneficial. This study showed that colesevelam significantly reduced A1C and LDL-C concentration in patients with type 2 diabetes when added to a sulfonylurea-based therapy. Colesevelam therapy was safe and well tolerated in this study. No patient reported a severe episode of hypoglycemia and none discontinued due to hypoglycemia. Furthermore, colesevelam did not result in weight gain.

The positive effects of colesevelam in patients with type 2 diabetes reported in this study suggest that the bile acid sequestrant colesevelam may represent a novel therapeutic add-on strategy for improving multiple metabolic parameters in patients with type 2 diabetes.

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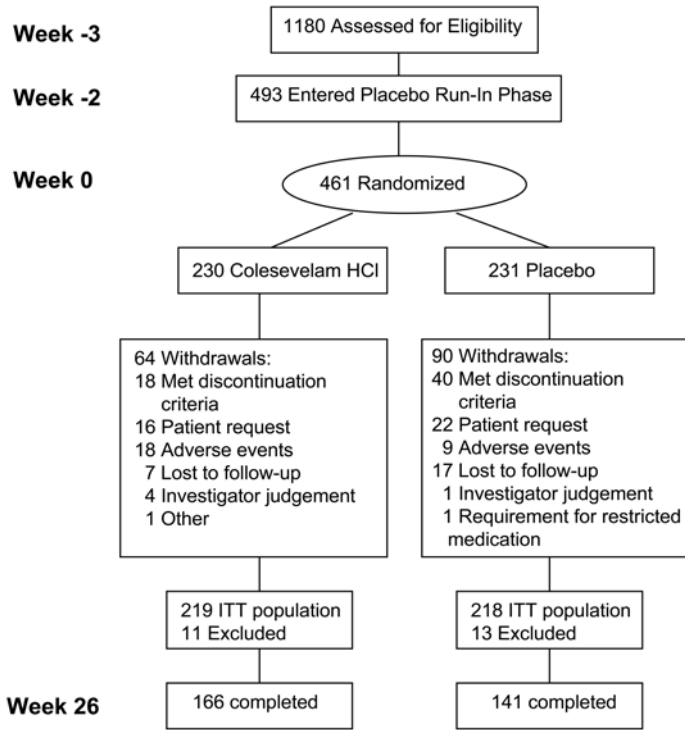
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**Table 1.** Demographic characteristics (randomized population).

	<b>Colesevelam HCl (N = 230)</b>	<b>Placebo (N = 231)</b>
<b>Mean age, years ± SD</b>	56.6 ± 10.3	57.0 ± 10.3
	<i>P</i> =0.670	
<b>Gender, n (%)</b>		
Male	128 (55.7)	122 (52.8)
Female	102 (44.3)	109 (47.2)
	<i>P</i> =0.575	
<b>Race, n (%)</b>		
Caucasian	135 (58.7)	128 (55.4)
Hispanic	66 (28.7)	59 (25.5)
Black	23 (10.0)	34 (14.7)
Asian	4 (1.7)	7 (3.0)
Other	2 (0.9)	3 (1.3)
	<i>P</i> =0.438	
<b>Mean weight, kg ± SD</b>	95.0 ± 22.6	92.5 ± 20.2
	<i>P</i> =0.197	
<b>Mean BMI, kg/m<sup>2</sup> ± SD</b>	33.1 ± 5.95	32.5 ± 5.64
	<i>P</i> =0.225	
<b>Mean A1C, % ± SD</b>	8.2 ± 0.68	8.3 ± 0.72
	<i>P</i> =0.054	
<b>Mean FPG, mg/dL ± SD</b>	176.6 ± 46.5	181.0 ± 50.4
	<i>P</i> =0.323	
<b>Concomitant antidiabetic medication status, n (%)</b>		
Sulfonylurea monotherapy	75 (32.6)	81 (35.1)
<i>Glibenclamide</i>	39 (52.0)	44 (54.3)
<i>Glipizide</i>	24 (32.0)	25 (30.9)
<i>Glimepiride</i>	10 (13.3)	12 (14.8)
<i>Tolbutamide</i>	1 (1.3)	0
<i>Gliclazide</i>	1 (1.3)	0
Sulfonylurea combination therapy	154 (67.0)	150 (64.9)
<b>Concomitant antidiabetic medications in the sulfonylurea combination therapy group, n (%)<sup>†</sup></b>		
Sulfonamides, urea derivatives	120 (77.9)	122 (81.3)
<i>Glipizide</i>	62 (40.3)	50 (33.3)
<i>Glibenclamide</i>	37 (24.0)	50 (33.3)
<i>Glimepiride</i>	21 (13.6)	21 (14.0)
<i>Tolazamide</i>	1 (0.6)	2 (1.3)
Biguanides	104 (67.5)	105 (70.0)
Thiazolidinediones	40 (26.0)	40 (26.7)
Biguanide/sulfonamide fixed-dose combinations	33 (21.4)	27 (18.0)
α-glucosidase inhibitors	0	1 (0.7)
Other antidiabetic agents*	13 (8.4)	10 (6.7)

\* Other antidiabetic agents included fixed-dose rosiglitazone/metformin, fixed-dose glipizide/metformin, nateglinide, and repaglinide; <sup>†</sup> Some subjects took >1 oral antidiabetic agent in combination with background sulfonylurea therapy and thus, the total number of concomitant oral antidiabetic agents in the columns exceed the N values in the colesevelam HCl and placebo headings; A1C = glycosylated hemoglobin; FPG = fasting plasma glucose.



**Figure 1.** Subject disposition.

**Figure 2 (A)** Mean change in A1C (%) from baseline to Week 6, 12, 18 and 26 (LOCF) in the ITT population. \* $P < 0.001$  vs placebo. **(B)** Mean percent change in lipid and apolipoprotein parameters from baseline to Week 26 (LOCF) in the ITT population. \* $P < 0.001$  vs placebo; †TG reported as median rather than mean.

