Comparison of Effects of Ezetimibe/Simvastatin Versus Simvastatin Versus Atorvastatin in Reducing C-Reactive Protein and Low-Density Lipoprotein Cholesterol Levels

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The lowering effects of ezetimibe/simvastatin combination therapy on low-density lipoprotein (LDL) cholesterol and high-sensitivity C-reactive protein (CRP) were compared with those of simvastatin or atorvastatin monotherapy in a large cohort of patients with primary hypercholesterolemia. To compare ezetimibe/simvastatin with simvastatin, data were combined from 3 identical, prospective 12-week trials in which patients were randomized to receive placebo; ezetimibe 10 mg; ezetimibe 10 mg added to simvastatin 10, 20, 40, or 80 mg; or simvastatin 10, 20, 40, or 80 mg. To compare ezetimibe/simvastatin with atorvastatin, data were analyzed from a phase III double-blind, active-controlled study in which patients were randomized equally to receive ezetimibe/simvastatin 10/10, 10/20, 10/40, or 10/80 mg or atorvastatin 10, 20, 40, or 80 mg for 6 weeks. When averaged across doses, ezetimibe/simvastatin produced significantly greater reductions compared with simvastatin alone in LDL cholesterol (52.5\% vs 38.0\%, respectively) and CRP levels (31.0\% vs 14.3\%, respectively). At each individual simvastatin dose, co-administration with ezetimibe produced significant further CRP reductions versus simvastatin alone. Ezetimibe/simvastatin was significantly more effective at lowering LDL cholesterol than atorvastatin when pooled across doses (53.4\% vs 45.3\%, respectively) and in each milligram-equivalent dose comparison. Reductions in CRP of similar magnitude were observed with ezetimibe/simvastatin and atorvastatin when averaged across doses and at each milligram-equivalent statin dose comparison. In conclusion, the lipid-modulating and anti-inflammatory effects of ezetimibe/simvastatin provide additional benefits not realized by statin monotherapy alone. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99:1706–1713)

Ezetimibe is a novel agent that potently inhibits the intestinal absorption of cholesterol from dietary and biliary sources by blocking the Niemann-Pick C1–Like 1 protein for cholesterol transport across the intestinal wall without affecting the absorption of bile acids, fatty acids, fat-soluble vitamins, or triglycerides (TGs).\textsuperscript{1–6} Unlike 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (i.e., statins), the metabolic effects of ezetimibe appear to be limited to the liver and intestine; the target of ezetimibe (the sterol transporter Niemann-Pick C1–Like 1 protein) has little or no distribution outside the intestines and/or portal system.\textsuperscript{2,4} Previous studies have shown that, in addition to the favorable effects on lipid levels, combined therapy with ezetimibe plus a statin produced significant reductions in C-reactive protein (CRP) relative to statin monotherapy. To more fully explore this observation, we conducted the present analysis to compare the anti-inflammatory and lipid-modifying effects of ezetimibe/simvastatin therapy with those of simvastatin and atorvastatin monotherapy across the marketed doses in a large number of patients with hypercholesterolemia.

### Methods

**Design of pooled simvastatin factorial studies:** Results were analyzed from 3 similar phase III randomized, multicenter, double-blind, placebo-controlled, 10-arm, parallel-group studies designed to evaluate the efficacy and safety profile of ezetimibe/simvastatin relative to ezetimibe and simvastatin monotherapy. The design of the 3 studies has been previously reported.\textsuperscript{7–9} After a 4-week single-blind...
placebo lead-in period, patients with primary hypercholesterolemia (plasma low-density lipoprotein [LDL] cholesterol concentration of ≥145 to ≤250 mg/dl and TG levels ≤350 mg/dl) were randomized in equal numbers to 1 of 10 daily treatments for 12 weeks: ezetimibe/simvastatin 10/10, 10/20, 10/40, or 10/80 mg; simvastatin 10, 20, 40, or 80 mg; ezetimibe 10 mg; or placebo. Individual tablets of ezetimibe and simvastatin were co-administered in 2 of the studies7,8 and a single co-granulated tablet (ezetimibe/simvastatin) was administered in the third.9 Bioequivalence between co-administered ezetimibe and simvastatin and the single co-granulated ezetimibe/simvastatin tablet was demonstrated in a previous study.10 Patients were required to have alanine aminotransferase and aspartate aminotransferase levels ≤2 times the upper limit of normal (ULN) with no active liver disease and creatine kinase levels ≤1.5 times the ULN. Patients with uncontrollable or unstable cardiac, endocrine, hepatic, renal, or metabolic conditions or who were taking nonstatin lipid-lowering drugs, immunosuppressants, corticosteroids, or potent cytochrome P-450 3A4 inhibitors were ineligible to participate. All lipid-altering drugs were discontinued for 6 weeks (for statins) or 8 weeks (for fibrates) before randomization. Patients were instructed to maintain a cholesterol-lowering diet throughout the duration of the trial. Blood samples were collected at weeks −4 and −2 for an assay of qualifying parameters and at weeks 0 (i.e., baseline), 2, 4, 8, and 12 for assay of lipid efficacy variables. Plasma concentrations of CRP were measured at baseline and end point (or the last available lipid determination in patients who discontinued study treatment prematurely).

**Design of atorvastatin factorial study:** The atorvastatin factorial study was a phase III, multicenter, double-blind, randomized, active-controlled, 8-arm parallel-group study designed to evaluate the efficacy and safety profiles of ezetimibe/simvastatin and atorvastatin monotherapy. The study design has been reported previously.11 After a 4-week single-blind placebo run-in period, patients with primary hypercholesterolemia who were not at their LDL cholesterol goal as defined by the Third Report of the National Cholesterol Education Program Adult Treatment Panel guidelines were randomized in equal numbers to 8 treatment arms: ezetimibe/simvastatin at doses of 10/10, 10/20, 10/40, or 10/80 mg or atorvastatin monotherapy at doses of 10, 20, 40, or 80 mg for 6 weeks. Patients were eligible for enrollment if they met prespecified criteria with regard to coronary heart disease (CHD) or CHD risk and/or LDL cholesterol levels. Other criteria included fasting serum TG level ≤350 mg/dl; alanine aminotransferase, aspartate aminotransferase, or creatinine kinase level ≤1.5 times ULN; serum creatinine level ≤1.5 mg/dl; and hemoglobin A1c <9.0% in patients with diabetes. Randomization was stratified according to LDL cholesterol levels at visit 2: ≥130 and <160 mg/dl, ≥160 and <190 mg/dl, and ≥190 mg/dl. Patients discontinued fibrate therapy 9 weeks before the start of the study and all other lipid-lowering therapy 7 weeks before the start of the study. Patients were instructed to maintain a cholesterol-lowering diet throughout the duration of the trial. Blood specimens were collected at weeks −4, −1, and 1, day 1; and week 6 or at discontinuation.

All study protocols were reviewed and approved by the appropriate institutional review boards or independent ethics committees. Patients provided written informed consent before initiation of any study procedure.

**Laboratory methods:** In each study, lipid levels were analyzed from fasting plasma samples at Medical Research Laboratories International (Highland Heights, Kentucky) as described previously.7 LDL cholesterol concentrations (in milligrams per deciliter) were calculated according to the Friedewald equation: LDL cholesterol = total cholesterol – high-density lipoprotein (HDL) cholesterol – (TG/5).12 Assays of CRP were performed in a post hoc manner on
archived plasma samples stored during the study at \(-70^\circ\)C and then batch-processed together in a treatment-blinded fashion. CRP was measured by high-sensitivity immunonephelometry (Dade Behring, Deerfield, Illinois), as previously described.\textsuperscript{13}

**Statistical analysis:** Analyses of LDL cholesterol and CRP were performed on a modified intent-to-treat population, which included all randomized patients who had valid baseline and end point measurements for LDL cholesterol and CRP. Analysis of variance (ANOVA) models were used to obtain the within-treatment estimates and between-treatment comparisons for LDL cholesterol and CRP. For the LDL cholesterol analyses, the ANOVA model included terms for study and treatment (10 treatment groups) in the pooled simvastatin factorial studies and terms for treatment (8 treatment groups) and LDL cholesterol stratum at visit 2 in the atorvastatin factorial study. Because the distribution of CRP measurements follows a log-normal distribution, logarithms of the ratios of end point to baseline values (i.e., log-ratio) were modeled through ANOVA. The geometric mean percentage changes from baseline in CRP levels were calculated based on back-transformation via exponentiation of the model-based least-squared means obtained from the ANOVA model with the terms for treatment (i.e., dose combinations), baseline CRP, baseline LDL cholesterol, and baseline HDL. Various Spearman’s correlation coefficients were calculated within each treatment group to study the relations between LDL cholesterol and CRP parameters.

The geometric mean percentage change from baseline in CRP (±SE) was examined for various patient subgroups. The ANOVA model for the subgroup analyses included terms for treatment, baseline CRP, baseline LDL cholesterol, baseline HDL, subgroup, and treatment-by-subgroup interaction.

The percentage of patients in whom defined single and dual LDL cholesterol levels (<70 and <100 mg/dl) and CRP levels (<1 and <2 mg/L) were achieved, without regard to patients’ baseline CHD risk, were examined across the individual and pooled treatment groups. The differences between the pooled groups were tested for significance with Fisher’s exact test. A model-based analysis was also performed using logistic regression for the achievement of single and dual LDL cholesterol/CRP levels with terms for treatment, baseline CRP, baseline LDL cholesterol, and baseline HDL cholesterol levels. For both analyses, between-group comparisons for ezetimibe/simvastatin versus statin monotherapy were performed for only the pooled treatment groups to control experiment-wise error rate.
Results

Demographics: Paired baseline and post-treatment CRP measurements were available for 2,541 patients in the cohort from the pooled simvastatin factorial studies and 1,832 patients from the atorvastatin factorial study. The treatment groups were generally well balanced in terms of patient demographics, baseline CRP levels, and baseline lipid parameters within and between studies, with the exception that patients in the atorvastatin factorial study had slightly higher median TG levels compared with patients in the simvastatin factorial studies (Table 1). In addition, there were larger proportions of patients with diabetes and metabolic syndrome in the atorvastatin factorial study than in the simvastatin factorial studies (Table 1).

Effects on LDL cholesterol in pooled simvastatin factorial studies: After 12 weeks of treatment, ezetimibe monotherapy was significantly more effective at reducing LDL cholesterol compared with placebo ($-18.3\%$ vs $-0.5\%$, respectively; $p < 0.001$). Averaged across all doses, pooled ezetimibe/simvastatin produced significantly greater mean percentage reductions from baseline in LDL cholesterol compared with pooled simvastatin monotherapy ($-52.5\%$ vs $-38.0\%$, respectively; $p < 0.001$; Figure 1). At each dose tested, ezetimibe/simvastatin was significantly more effective at lowering LDL cholesterol than pooled atorvastatin ($-53.4\%$ vs $-45.3\%$, respectively; $p < 0.001$; Figure 2). At each dose tested, the LDL cholesterol reductions achieved with ezetimibe/simvastatin were significantly greater compared with each milligram-equivalent dose of atorvastatin monotherapy ($p < 0.001$ for all comparisons; Figure 2).

Effects on CRP in pooled simvastatin factorial studies: In the fitted model predicting log ratio of CRP as a measure of CRP change, the terms for treatment, baseline CRP, and baseline LDL cholesterol were significant ($p < 0.0001$, $p < 0.0001$, and $p = 0.0146$, respectively), whereas baseline HDL was not a significant predictor ($p = 0.4833$). Median baseline CRP values were similar across individual treatment groups. Relative to placebo, treatment with ezetimibe 10 mg for 12 weeks did not produce significant reductions from baseline in CRP (Figure 3). When averaged across all doses, ezetimibe/simvastatin demonstrated significantly greater reductions in CRP compared with simvastatin ($p < 0.001$; Figure 3). The geometric mean percentage reductions from baseline in CRP were $31.0\%$ for pooled ezetimibe/simvastatin and $14.3\%$ for pooled simvastatin, leading to an incremental reduction of $16.7\%$ (95% confidence interval 11.7% to 21.7%) in favor of ezetimibe/simvastatin therapy (Figure 3). A nonparametric analysis yielded similar results; the median percentage reductions from baseline in CRP were $33.3\%$ for ezetimibe/simvastatin and $15.4\%$ for simvastatin averaged across doses.

The CRP-lowering effects of ezetimibe/simvastatin and simvastatin were compared across each of the simvastatin doses tested. Significantly greater geometric mean percent-
age reductions in CRP were achieved with ezetimibe/simvastatin compared with each corresponding dose of simvastatin monotherapy (p < 0.01 for ezetimibe/simvastatin 10/10 vs simvastatin 10 mg, ezetimibe/simvastatin 10/20 vs simvastatin 20 mg, ezetimibe/simvastatin 10/40 vs simvastatin 40 mg, and ezetimibe/simvastatin 10/80 vs simvastatin 80 mg; Figure 3).

The relation between simvastatin and ezetimibe/simvastatin dose and CRP response was examined in this pooled analysis through pairwise comparisons (Figure 3). The reductions in CRP associated with placebo, ezetimibe 10 mg, and simvastatin 10 mg were not significantly different from zero (p > 0.10 for each between-group comparison). Additionally, simvastatin 10 mg did not produce significant reductions from baseline in CRP relative to placebo (−4.0% vs 7.4%, respectively; p = 0.0859) or ezetimibe alone (−4.0% vs −2.8%, respectively; p = 0.8406). Relative to simvastatin 10 mg, significantly greater reductions in CRP were observed with simvastatin 20 mg (−4.0% vs −16.2%, respectively; p < 0.05), 40 mg (−4.0% vs −17.3%, respectively; p < 0.05), and 80 mg (−4.0% vs −18.4%, respectively; p < 0.05). However, there were no significant differences in CRP-lowering response among simvastatin 20, 40, and 80 mg (p > 0.05 for each between-group comparison). For ezetimibe/simvastatin at every dose level, significant reductions in CRP were observed relative to zero, placebo, and ezetimibe alone (p < 0.006 for each between-group comparison). The geometric mean percentage reduction in CRP associated with ezetimibe/simvastatin 10/10 mg was significantly lower than those of ezetimibe/simvastatin 10/20 mg (−19.0% vs −30.3%, respectively; p < 0.05), 10/40 mg (−19.0% vs −35.0, respectively; p < 0.001), and 10/80 mg (−19.0% vs −37.8%, respectively; p < 0.0001). However, there were no significant differences in CRP-lowering response among ezetimibe/simvastatin 10/20, 10/40, and 10/80 mg (p > 0.05 for each between-group comparison).

The enhanced CRP-lowering efficacy of ezetimibe/simvastatin was consistent across patient subgroups based on age (<65 vs ≥65 years), gender, race (Caucasian versus non-Caucasian), body mass index (BMI; <30 vs ≥30 kg/m²), and baseline presence of diabetes, CHD, and metabolic syndrome status (Figure 4). Median percentage changes in CRP varied across baseline CRP levels, with the greatest reductions observed in the patients with the highest baseline CRP levels (Figure 5). However, the trend in CRP response was similar to that observed in the entire cohort, with ezetimibe/simvastatin being more effective in reducing CRP than simvastatin or ezetimibe alone.

Spearman’s correlation coefficients for placebo, ezetimibe 10 mg, simvastatin, and ezetimibe/simvastatin demonstrated minimal associations (most coefficients <0.2) between baseline LDL cholesterol and percentage change in CRP, percentage change in LDL cholesterol and percentage change in CRP, per-
fore, although ezetimibe/simvastatin and atorvastatin produced
through pairwise comparisons. However, the geometric mean
atorvastatin dose and CRP response could not be examined
significant, the relation between ezetimibe/simvastatin and
across doses and at each milligram-equivalent statin dose
that reductions in CRP of similar magnitude were observed
the treatment groups was not performed. This finding indicated
in the fitted model was not significant, pairwise testing among
atorvastatin averaged across doses and 26.7% for ezetimibe/
percentage reductions from baseline in CRP were 26.5% for
were observed in a nonparametric analysis; the median per-
Effects on CRP in atorvastatin factorial study: In the
fitted model, predicting log ratio of CRP, the term for
Baseline CRP was significant (p <0.0001), whereas the
terms for treatment, baseline LDL cholesterol, and baseline
HDL cholesterol were not significant (p = 0.20, p = 0.62,
and p = 0.22, respectively). Median baseline CRP values
were similar across the individual treatment groups. After 6
weeks of treatment, the geometric mean percentage reduc-
tions from baseline in CRP were 25.1% for pooled
atorvastatin and 24.8% for pooled atorvastatin, resulting in
a between-group difference of 0.3% (95% confidence interval,
−5.14 to 5.82; Figure 6). Similar results were observed in a
nonparametric analysis; the median percentage reductions from
baseline in CRP were 26.5% for atorvastatin averaged across
doses and 26.7% for ezetimibe/simvastatin averaged across
doses. Because the treatment term in the fitted model was not
significant, pairwise testing among the treatment groups was not performed. This finding indicated that
reductions in CRP of similar magnitude were observed with
atorvastatin and atorvastatin when averaged across doses and at each milligram-equivalent statin dose
comparison.

Because the treatment term in the fitted model was not
significant, the relation between ezetimibe/simvastatin and
atorvastatin dose and CRP response could not be examined
through pairwise comparisons. However, the geometric mean
percentage reductions from baseline CRP levels observed with
atorvastatin 10, 20, 40, and 80 mg and ezetimibe/simvastatin
10/10, 10/20, 10/40, and 10/80 mg were significantly different
than zero (p <0.0001 for each comparison; Figure 6). There-
fore, although ezetimibe/simvastatin and atorvastatin produced
significant reductions in CRP, there were no differences in the
CRP-lowering response across the individual ezetimibe/sim-
vastatin and atorvastatin doses.

The similar CRP-lowering efficacy of ezetimibe/simva-
tatin and atorvastatin was consistent among subgroups
based on age (<65 vs ≥65 years), gender, race (Caucasian
vs non-Caucasian), BMI (<30 vs ≥30 kg/m²), and baseline
presence of diabetes, CHD, and metabolic syndrome status
(data not shown). Median percentage changes in CRP varied
across baseline CRP levels, with the greatest reductions
observed in the patients with the highest baseline CRP
levels (Figure 7). However, the trend in CRP response was
similar to that observed in the entire cohort, with ezetimibe/
simvastatin and atorvastatin producing reductions in CRP of
similar magnitude.

Spearman’s correlation coefficients for the individual
ezetimibe/simvastatin and atorvastatin groups demonstrated
minimal association (most coefficients <0.2) between
baseline LDL cholesterol and percentage change in
CRP; percentage change in LDL cholesterol and percentage
change in CRP; percentage change in LDL cholesterol
and change in CRP; and change in LDL cholesterol
and change in CRP (Table 2, online only).

Attainment of single and dual LDL and CRP levels in
pooled simvastatin factorial studies: Predefined LDL,
CRP, and dual LDL cholesterol/CRP levels were achieved in
a significantly greater proportion of patients treated with
pooled ezetimibe/simvastatin than with pooled simvastatin
monotherapy (p <0.05 for CRP <2 mg/L, p <0.001 for all
other comparisons; Table 3). In general, a trend toward
greater LDL cholesterol, CRP, and dual LDL
cholesterol/CRP goal attainment was observed across the
individual ezetimibe/simvastatin and

### Table 3

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<th>Treatment</th>
<th>LDL Cholesterol</th>
<th>CRP</th>
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p Values are based on the Fisher’s exact test.
Between-treatment group comparisons were only performed on pooled simvastatin and pooled ezetimibe/simvastatin groups to minimize multiplicity errors.

* Expressed as number of patients achieving level/number of patients above level at baseline. For inclusion in the dual LDL cholesterol/CRP analysis, patients had to be above the stated LDL cholesterol and/or CRP level at baseline and have baseline and post-treatment CRP measurements.
1 One-sided p value <0.001 versus simvastatin monotherapy.
2 One-sided p value <0.050 versus corresponding dose of simvastatin monotherapy.
simvastatin doses. Similar results were obtained from the model-based analysis as well (data not shown).

**Attainment of single and dual LDL and CRP levels in atorvastatin factorial study:** When averaged across doses, predefined LDL cholesterol and dual LDL cholesterol/CRP levels were achieved in a significantly greater proportion of patients treated with ezetimibe/simvastatin than with atorvastatin monotherapy (p < 0.002 for all comparisons; Table 4). The percentage of patients in whom CRP levels <1 and <2 mg/L were achieved were similar between pooled ezetimibe/simvastatin and pooled atorvastatin groups. In general, a trend toward greater LDL cholesterol and dual LDL cholesterol/CRP goal attainment was observed across the individual ezetimibe/simvastatin and atorvastatin doses. However, a similar proportion of patients had CRP levels <1 and <2 mg/L across these dose groups. Similar results were obtained from the model-based analyses as well (data not shown).

**Discussion**

The present analysis showed that, when averaged across the dose range and at each milligram-equivalent statin dose, ezetimibe/simvastatin produced significantly greater reductions in LDL cholesterol relative to simvastatin and atorvastatin monotherapy in patients with hypercholesterolemia. The superior LDL cholesterol–lowering efficacy of ezetimibe/simvastatin was consistently observed within all prespecified patient subgroups, including age, gender, race, and BMI, and was independent of baseline presence of diabetes, CHD, and metabolic syndrome. In addition, ezetimibe/simvastatin produced significantly greater CRP reductions relative to simvastatin monotherapy and similar CRP reductions compared with atorvastatin monotherapy.

The precise mechanism by which statins reduce CRP levels is not understood, but is poorly correlated with statin effects on LDL cholesterol or other individual lipid parameters in some reports, suggesting a direct effect on inflammation in peripheral tissues or on liver metabolism. Ezetimibe provides additional insight into this mechanism, as its direct effects are believed to be limited to inhibition of cholesterol absorption (with consequent LDL cholesterol lowering) and potential direct effects on liver metabolism. The latter may be important because the liver is the primary source of CRP synthesis. Significant CRP reductions were not observed with ezetimibe monotherapy but rather when ezetimibe and simvastatin were co-administered; thus, ezetimibe appears to potentiate the CRP-lowering effect of simvastatin despite the low likelihood of direct effects of ezetimibe at peripheral sites. There were significant reductions in CRP with simvastatin 20 mg (16.2%) and atorvastatin 10 mg (18.1%), with respective LDL cholesterol reductions of 34% and 36%. One possible interpretation is that there is a threshold effect, meaning one needs an LDL cholesterol reduction of ≥30% to achieve a reduction in CRP. However, in the present study, there was a lack of evidence of strong correlations between baseline LDL cholesterol level and percentage change in CRP, percentage change in LDL cholesterol and percentage change in CRP, percentage change in LDL cholesterol and change in CRP, change in LDL cholesterol and change in CRP, and baseline LDL cholesterol and baseline CRP. Therefore, one possible explanation is that ezetimibe may potentiate the effects of statins on hepatic production of CRP after a threshold of LDL cholesterol reduction is reached. This would not necessarily imply a reduction in inflammation in the arterial system; therefore, the inference that a reduction in CRP indicates a reduction in cardiovascular disease risk would require verification in trials with clinical end points.

**Acknowledgment:** We thank Hongwei Wang, PhD, and Jianxin Lin, MS, from Merck & Co., Inc., for computational assistance.


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<td>0.00</td>
<td>0.99</td>
<td>0.02</td>
<td>0.73</td>
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<tr>
<td>Atorvastatin 20 mg</td>
<td>0.04</td>
<td>0.57</td>
<td>0.08</td>
<td>0.25</td>
</tr>
<tr>
<td>Atorvastatin 40 mg</td>
<td>0.07</td>
<td>0.27</td>
<td>-0.03</td>
<td>0.64</td>
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<td>Atorvastatin 80 mg</td>
<td>0.05</td>
<td>0.46</td>
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<td>0.05</td>
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<tr>
<td>Ezetimibe/simvastatin 10/10 mg</td>
<td>-0.04</td>
<td>0.55</td>
<td>-0.02</td>
<td>0.79</td>
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<tr>
<td>Ezetimibe/simvastatin 10/20 mg</td>
<td>-0.12</td>
<td>0.08</td>
<td>0.11</td>
<td>0.09</td>
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<tr>
<td>Ezetimibe/simvastatin 10/40 mg</td>
<td>-0.02</td>
<td>0.77</td>
<td>0.16</td>
<td>0.02</td>
</tr>
<tr>
<td>Ezetimibe/simvastatin 10/80 mg</td>
<td>0.16</td>
<td>0.02</td>
<td>0.14</td>
<td>0.04</td>
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