

# Assessment of potential pharmacokinetic interactions of ezetimibe/simvastatin and extended-release niacin tablets in healthy subjects

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## Abstract

**Background** Efforts to lower plasma lipid levels sometimes require multiple agents with different mechanisms of action to achieve results specified by national treatment guidelines.

**Methods** This was an open-label, randomized, three-period, multiple-dose crossover study that assessed the potential for pharmacokinetic interaction between extended-release niacin and ezetimibe/simvastatin and their major metabolites. Eighteen adults received three randomized treatments: (A) extended-release (ER) niacin 1000 mg/day for 2 days, followed by 2000 mg/day for 5 days; (B) ezetimibe/simvastatin 10 mg/20 mg/day; (C) coadministration of Treatments A and B. Treatments were given once a day after a low fat breakfast for a total of 7 days, with a 7-day inter-dose period.

**Results** There were small (mean  $\leq 35\%$ ) increases in drug exposure for all analytes after coadministration of ER niacin and ezetimibe/simvastatin 10 mg/20 mg. The least-square mean between treatment  $C_{\max}$  (maximum plasma concentration) ratios ( $\times 100$ ) were 97, 98, and 109% for ezetimibe,

simvastatin and niacin, respectively. The corresponding ratios for total ezetimibe, simvastatin acid, and nicotinic acid were 99, 118, and 110%. The  $AUC_{(0-24)}$  (area under the plasma concentration–time curve from time zero to 24 h after dosing) ratios for ezetimibe, simvastatin, and niacin were 109, 120, and 122%, respectively, and the corresponding ratios for total ezetimibe, simvastatin acid, and nicotinic acid were 126, 135 and 119%.

**Conclusion** There is a small pharmacokinetic drug interaction between ER niacin and ezetimibe/simvastatin and although this is not considered to be clinically significant, the concomitant use of these drugs should be appropriately monitored, especially during the niacin titration period.

**Keywords** Ezetimibe · Simvastatin · Extended-release niacin · Pharmacokinetics

## Introduction

The use of multiple drugs for the treatment of dyslipidemia has been discussed and proposed in the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines as possibly needed to achieve lipid targets in patients with multiple lipoprotein anomalies associated with hyperlipidemia who have not responded to dietary and lifestyle modifications and to monotherapy with or without adjunct lipid-altering agents. [1–3] The use of combination therapy presents the possibility that there may be changes in the pharmacokinetics (PK) of any one of the drugs and/or their metabolites during such therapy. The combination of ezetimibe/simvastatin is a recommended treatment for reducing low-density lipoprotein cholesterol (LDL-C) when statins in combination with diet and life

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style changes do not achieve the desired lipid targets. There is a general recognition that even with relatively high doses of statins, patients with mixed hyperlipidemia do not achieve all of the lipid altering targets suggested in the guidelines. In particular, because of the relatively high levels of triglycerides, the relatively low level of high-density lipoprotein-C, and the increases in the small dense LDL particles, high-dose niacin therapy in combination with other lipid-lowering therapy may be an option to help achieve all lipid targets. Therefore, therapy with the combination of ezetimibe/simvastatin added to high-dose extended-release (ER) niacin therapy is a potential option for positive alteration of all major lipoprotein fractions. Several clinical studies examining the clinical efficacy of the combination of simvastatin with ER niacin at a simvastatin dose of 20 [4] or 40 mg/day [5] have been recently published. The fixed dose combination of simvastatin with ER niacin has also been approved and the results of the supporting clinical study published [6]. The clinical effectiveness of ezetimibe/simvastatin 10 mg/20 mg a day administered with ER niacin titrated to 2 g/day has also been examined in type IIa and IIb hyperlipidemic patients [7]. However, there is very little published information on plasma concentrations and the PK parameters describing the use of niacin with statins or other lipid-lowering agents.

There is no a priori reason to expect a PK drug interaction between simvastatin or ezetimibe and niacin due to the different metabolic clearance mechanisms of these drugs, and these drugs have not been shown to be inhibitors of common clearance pathways. Ezetimibe is primarily cleared via glucuronidation with subsequent biliary excretion. Simvastatin is a lactone that is readily hydrolyzed in vivo to the corresponding  $\beta$ -hydroxyacid, a potent HMG-CoA reductase inhibitor, which is extensively metabolized via cytochrome P450, particularly CYP3A4, and glucuronidation and drug interactions between simvastatin and inhibitors of these clearance pathways are well documented in the clinical literature. Niacin undergoes extensive first-pass metabolism which is species- and dose-rate specific and does not appear to involve CYP3A4 enzymes but rather glycine conjugation and other pathways. [8]. Despite the different clearance pathways, an interaction was observed between niacin and simvastatin in a single-dose trial, where concomitant niacin increased the exposure to simvastatin acid by approximately 135–165% depending on whether the area under the curve values were limited to 24 h or to the last measured value, respectively [9]. In view of this data, a PK interaction study between ezetimibe/simvastatin and ER niacin was warranted since, similar to the simvastatin–niacin interaction, there may be other transport or clearance mechanisms involved which may lead to a PK interaction between niacin and ezetimibe. Thus, the purpose of this study was to evaluate the potential

for an interaction with the coadministration of ER niacin and ezetimibe/simvastatin in a clinically relevant multiple-dose setting. The PK of the major metabolites of each of the drugs were also measured to assure that the metabolites, as potential components of an interaction, are considered in the assessment of any potential interaction.

## Methods

### Study design

This was a single-center randomized, open-label, three-period, three-treatment multiple-dose crossover study that was conducted in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice Guidelines, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. The study protocol (S/P 4955) was approved by the Compass Institutional Review board of Mesa, Arizona, USA. All participants of the study provided written informed consent prior to any study-related activities. The clinical phase of protocol was conducted between May 2007 and July 2007. The trial was registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT00652431).

### Subjects

Subjects of either sex and of any race between the ages of 18 and 55 years with a body mass index between 19 and 32 kg/m<sup>2</sup> inclusive were eligible for the study. Eighteen subjects, with approximately equal numbers of male and female subjects, were enrolled to ensure that a minimum of 12 subjects completed the study.

### Study plan

After a subject screening and selection period of up to 21 days, eligible subjects were admitted to the study center on the evening of Day -1 for baseline assessment to confirm continued eligibility to participate in the study. Eligible subjects were assigned allocation (subject) numbers in the order that they were deemed eligible. Beginning on Day 1 of each period of the crossover, randomized subjects received one of the following three treatment sequences: (A) ER niacin 1000 mg (1 × 1000 mg NIASPAN tablet) once-daily in the morning on Days 1–2, followed by ER niacin 2000 mg (2 × 1000 mg tablets) once-daily in the morning on Days 3–7 for a total of 7 days of treatment; (B) ezetimibe/simvastatin [VYTORIN 10/20 mg (1 × 10/20 mg tablet containing ezetimibe 10 mg and simvastatin 20 mg)] once-daily in the morning for 7 days; (C) ER niacin 1000 mg (1 × 1000 mg tablet) once-daily in the morning on

Days 1–2, followed by ER niacin 2000 mg ( $2 \times 1000$  mg tablets) once-daily in the morning on Days 3–7+ezetimibe/simvastatin 10/20 mg ( $1 \times 10/20$  mg tablet containing ezetimibe 10 mg and simvastatin 20 mg) once-daily in the morning for 7 days. All study treatments were administered between approximately 8:00 and 9:00 a.m. with 240 mL of noncarbonated water within 5 min of completing a standardized low-fat breakfast consumed over a 20-min period. Subjects were confined to the study center for the duration of treatment in each period of the crossover. Dosing of all medications was supervised, and swallowing of each dose was verified by inspection. The subjects were discharged on Day 8 of each period after completion of all study-related procedures. There were at least 7 days between treatment periods. Safety laboratory assessments were performed throughout the study. Vital signs, adverse events, and concomitant medications were recorded throughout the study.

#### *Dose justification*

The recommended maintenance dose of ezetimibe/simvastatin ranges from 10/10 mg/day through 10/80 mg/day, administered as a single dose in the evening (to optimize the efficacy of simvastatin), with or without food [10]. The recommended maintenance dose of ER niacin is 1000–2000 mg to be taken once daily at bedtime (qhs), after a low-fat snack in order to maximize bioavailability and reduce the incidence and severity of side effects (flushing, dizziness, headache, gastrointestinal complaints) [11]. This once-nightly dosing regimen also improves the diurnal free fatty acid and triglyceride profile.

The dose of ezetimibe/simvastatin used in this interaction study was 10/20 mg per day, and the dose of ER niacin used was 2000 mg per day, which are the maximum daily doses of simvastatin and ER niacin recommended in the ER niacin package insert [12]. As this dose of ER niacin may not be initially well tolerated, a lower dose (1000 mg once-daily) was administered during an initial 2-day titration period. According to the product label, ER niacin should be initiated at 500 mg once-daily taken at bedtime, and the dosage should not be increased by more than 500 mg in any 4-week period to a maximum of 2000 mg at bedtime in order to reduce the incidence and severity of side effects and provide adequate time to observe a full therapeutic response [12]. In order to further improve ER niacin tolerability and reduce PK variability, the treatments were administered following a meal (low-fat breakfast), which is consistent with ER niacin labeling. Since this was a PK study, treatments were administered in the morning for logistic and optimal PK sampling considerations rather than in the evening/bedtime which would have been optimal from a therapeutic perspective. Given the primary objective

and the high inter-subject variability in the PK of the drugs being evaluated, this study was designed as a randomized three-way crossover in order to minimize systematic bias and PK variability. Multiple doses of the treatments were administered to achieve steady state conditions to allow adequate time for inhibition of any drug-metabolizing enzymes or other clearance mechanisms which may be involved in a potential interaction. Considering that ezetimibe has the longest apparent PK half-life (approx. 22 h) of any of the analytes [13], a washout period of 7 days between treatments was deemed adequate.

#### *Sample size*

In an earlier study, the inter-subject variability for niacin was estimated to range between 40 and 60%. Assuming that the variability in this study would be the same, the study with at least 12 subjects was to detect about a 30–45% difference in derived PK parameters for niacin between Treatments C (ER niacin + ezetimibe/simvastatin) and A (ER niacin only) with 80% power and a 90% confidence interval (CI). The intra-subject variability for ezetimibe, total ezetimibe, simvastatin, and simvastatin acid are estimated to be 34, 30, 42, and 35%, respectively. Assuming that the variability remained the same, the study with at least 12 subjects would detect about a 36, 31, 44, and 37% difference in derived PK parameters for ezetimibe, total ezetimibe, simvastatin, and simvastatin acid between Treatments C (ER niacin + ezetimibe/simvastatin) and B (ezetimibe/simvastatin only) with 80% power and a 90% CI, respectively. All treatment-by-period interaction tests were performed at the significance level of 0.1. A pre-specified two-fold increase in exposure to any of the analytes was considered to be potentially of clinical relevance.

#### *Safety*

The overall safety and tolerability evaluation included all safety data, physical exams and subject-reported experiences, and specified clinical laboratory tests, i.e., serum alanine and aspartate transaminases (ALT, AST, respectively), creatine kinase (CK), urinalysis, electrocardiograms (ECGs), adverse events, and vital signs.

#### *Analytical procedures*

Ezetimibe, total ezetimibe (includes ezetimibe glucuronide), simvastatin, simvastatin acid, and niacin and nicotinic acid were analyzed in heparin-treated blood plasma which had been stored frozen at  $-80^{\circ}\text{C}$  using validated, extraction and liquid chromatography–tandem mass spectrometry methods specific for each analyte (PPD Inc, Richmond,

VA). A corresponding deuterated internal standard in the case of simvastatin/simvastatin acid and niacin/nicotinuric acid or  $^{13}\text{C}$ -labeled ezetimibe/total ezetimibe was used for each analyte. No interference was found between the analytes within an assay for the parent and metabolite pairs or from the plasma for all analytes and potentially interfering plasma components. There was essentially no conversion of metabolite to parent or parent to metabolite in the case of simvastatin during the assay process.

The lower limit of quantitation (LLOQ) for each analyte was defined as the standard sample value for which the coefficient of variation was  $\leq 20\%$  or the lowest standard falling below this limit. The reproducibility across the standard curve, run in duplicate, for the range of point values and the between-day reproducibility (as percentage coefficient of variance, CV%) are presented in Table 1 for all the analytes.

### Pharmacokinetics

The plasma concentration–time curve developed for Day 7 for ezetimibe, total ezetimibe, simvastatin, simvastatin acid, niacin, and nicotinuric acid was examined for the highest post-dose value, which was the  $C_{\max}$  value, and its time of occurrence was the  $T_{\max}$  value. Plasma samples for the drug assay were drawn on Day 1 (predose blank sample) and predose (0 h) and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h post-dose on Day 7. The  $\text{AUC}_{(0-24)}$  (area under the plasma concentration–time curve from time zero to 24 h after dosing) was determined by computerized methods for each analyte across the same interval. In cases where the final quantifiable value occurred before the 24-h value, the AUC value to the last time available was calculated as an  $\text{AUC}_{(tf)}$  without extrapolation to 24 h. Both AUC values were evaluated statistically to determine if similar conclusions could be derived from either value.

### Statistical methods

**Pharmacokinetics** Plasma concentrations and PK parameters for ezetimibe, total ezetimibe, simvastatin, simvastatin

acid, niacin, and nicotinuric acid after multiple doses were listed and summarized by treatment using descriptive statistics. To assess the effect of ezetimibe/simvastatin on niacin and nicotinuric acid from ER niacin, the log-transformed AUC and  $C_{\max}$  for niacin and nicotinuric acid (NUA) after multiple doses (Day 7) in treatments A (ER niacin only) and C (ER niacin + ezetimibe/simvastatin) were analyzed using an analysis of variance (ANOVA) model extracting the effects due to treatment, period, and subject (sequence effect was not tested due to very small sample size per sequence). The relative bioavailability (geometric mean ratio, GMR) along with the 90% CI was provided for Treatment C (ER niacin + ezetimibe/simvastatin) versus A (ER niacin only). Similarly, to assess the effect of ER niacin on ezetimibe/simvastatin, the Day-7 log-transformed AUC and  $C_{\max}$  for ezetimibe, total ezetimibe, simvastatin, and simvastatin acid in Treatment B (ezetimibe/simvastatin only) and C (ER niacin + ezetimibe/simvastatin) were analyzed using an ANOVA model extracting the effects due to treatment, period, and subject. The relative bioavailability (GMR) along with the 90% CI were calculated for Treatment C (ER niacin + ezetimibe/simvastatin) versus B (ezetimibe/simvastatin only).

**Safety** Adverse events, ECGs (PR, QSR, QT, and QTc intervals, and ventricular rate), vital signs, and results for urinalysis and clinical laboratory tests were listed for each subject and tabulated by treatment. These were summarized using descriptive statistics only because of the limited number of subjects.

## Results

### Subjects and demographic and baseline characteristics

A total of 18 adult subjects (11 men, 7 women) between the ages of 19 and 52 years, inclusive, (mean 34.1 years) received study medication. Of the 18 subjects, 13 (72%) were white, two (11%) were Asian, two (11%) were native Hawaiian or

**Table 1** Analytical quality information for the analysis of ezetimibe, total ezetimibe, simvastatin, simvastatin acid, niacin, and nicotinuric acid by liquid chromatography–tandem mass spectrography methods

LLOQ, Lower limit of quantitation; QA, quality assurance

<sup>a</sup> Coefficient of variation as a percentage

Analyte	LLOQ (ng/mL)	Standard reproducibility <sup>a</sup>		QA reproducibility <sup>a</sup>	
		Low	High	Low	High
Ezetimibe	0.2	5.50	3.97	8.86	3.51
Total ezetimibe	1.0	6.03	4.69	6.25	5.54
Simvastatin	0.1	3.50	0.80	2.19	1.07
Simvastatin acid	0.1	3.75	1.74	5.70	3.50
Niacin	5.0	2.75	1.48	2.62	2.10
Nicotinuric acid	5.0	2.62	2.10	3.95	2.36

other Pacific islanders, and one (6%) was black/African American. The mean body mass index (BMI) was 24.12 kg/m<sup>2</sup>. The characteristics of the 13 subjects (9 men, 4 women) who completed the treatment phase were similar to the demographics of the starting group: mean age was 36 years (range 25–52 years) and the mean BMI was 24.59 kg/m<sup>2</sup>; 11 (85%) of the 13 subjects were white, one (8%) was Asian, and one (8%) was black/African American.

#### Pharmacokinetics/statistics

Fifteen subjects completed treatment with ezetimibe/simvastatin and with ER niacin + ezetimibe/simvastatin; 13 subjects completed treatment with ER niacin and with ER niacin + ezetimibe/simvastatin. Statistical analyses and comparisons are based on data from 15 subjects for ezetimibe, total ezetimibe, simvastatin, and simvastatin acid, and from 13 subjects for niacin and nicotinuric acid. There were no period effects observed for any of the six analytes. The conclusions drawn from the results for AUC<sub>(t<sub>f</sub>)</sub> did not differ from those based on the AUC<sub>(0–24)</sub>

**Ezetimibe and total ezetimibe** Niacin administered as ER niacin tablets (2000 mg/day with food) did not affect the PK of ezetimibe administered as ezetimibe/simvastatin 10/20 mg once-daily. The 90% CI for C<sub>max</sub> and AUC were within 80–125% bioequivalence acceptance criteria (Table 2, Fig. 1). Concomitant ER niacin had no effect on total ezetimibe C<sub>max</sub>, but it did increase the mean AUC by 26%. The 90% CI for C<sub>max</sub> and AUC of total ezetimibe were 87–113% and 110–144%, respectively.

While it must be kept in mind that there only 15 subjects in this comparison, Fig. 1 clearly shows that the plasma

concentration–time curve for total ezetimibe shifted to the longer time intervals with little change in initial absorption phase during the first few hours and that there were no significant changes in C<sub>max</sub>. Since ezetimibe and the ezetimibe metabolite ezetimibe glucuronide undergo cycles of enterohepatic circulation, the later accumulation of total ezetimibe in the presence of niacin may indicate either that there was improved absorption from the gut or that there was impairment in the excretion via the liver after absorption. It was noted that one subject (Subject 103) had the greatest change, while 9–11 of the subjects demonstrated smaller increases in C<sub>max</sub> and AUC values when niacin was added.

**Simvastatin and simvastatin acid** Niacin administered as ER niacin tablets (2000 mg/day with food) had no effect on the C<sub>max</sub> of simvastatin administered as ezetimibe/simvastatin 10/20 mg once-daily. The treatment ratio estimate (ER niacin + ezetimibe/simvastatin/ezetimibe/simvastatin alone) and the 90% CI for simvastatin C<sub>max</sub> were 98 and 85–112%, respectively (Table 3, Fig. 2). The treatment ratio estimate and 90% CI for simvastatin AUC<sub>(0–24 h)</sub> were 120 and 103–140%, respectively. The effect of niacin on the simvastatin AUC varied among subjects, and this effect was not considered to clinically significant as it was within the bounds of the prespecified limits. The 90% CI were 86–163% for the simvastatin acid C<sub>max</sub> and 97–188% for the simvastatin acid AUC<sub>(0–24 h)</sub>. There was high inter- and intra-subject variability in the PK of simvastatin acid, with an inter-subject variability of 97–99% in the C<sub>max</sub> and 99–101% in the AUC<sub>(0–24 h)</sub> and an intra-subject variability of 49 and 51% in the C<sub>max</sub> and AUC<sub>(0–24 h)</sub>, respectively.

**Table 2** Comparison of the ezetimibe and total ezetimibe C<sub>max</sub> and AUC values following treatment with extended-release niacin + ezetimibe/simvastatin (Treatment C) versus ezetimibe/simvastatin (Treatment B) in healthy subjects

Parameter	LS mean (N=15) <sup>a, b</sup>		Comparison <sup>a</sup>		
	Ezetimibe/simvastatin	ER niacin + ezetimibe/simvastatin	Ratio (%)	90% CI	Range of Ratios
<b>Ezetimibe</b>					
C <sub>max</sub> (ng/mL)	5.91 (0.28)	5.76 (0.63)	97	80–119	(80–260)
AUC <sub>(0–24 h)</sub> (ng•h/mL) <sup>c</sup>	83.2 (0.32)	90.6 (0.44)	109	98–122	(80–190)
<b>Total ezetimibe</b>					
C <sub>max</sub> (ng/mL)	71.8 (0.35)	71.2 (0.35)	99	87–113	(50–190)
AUC <sub>(0–24 h)</sub> (ng•h/mL) <sup>c</sup>	671 (0.30)	845 (0.35)	126	110–144	(70–210)

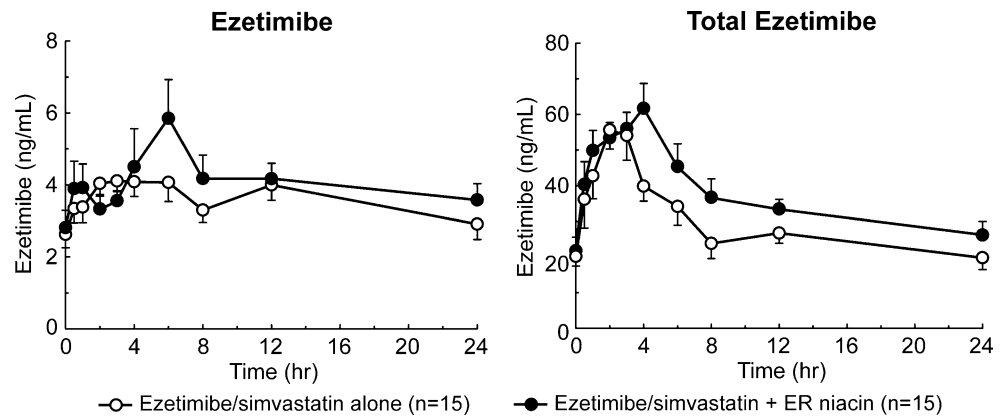
AUC<sub>(0–24 h)</sub>, Area under the plasma concentration–time curve from time zero to 24 h after dosing; CI, confidence interval; C<sub>max</sub>, maximum observed plasma concentration; LS, least squares, ER, extended release

<sup>a</sup> Model-based (least squares) mean. ANOVA (analysis of variance) was used to extract the effects due to treatment, period, and subject. Values in parenthesis for the LS mean are the coefficient of variation (CV)

<sup>b</sup> Three subjects were excluded from the analysis due to early withdrawal from study

<sup>c</sup> AUC<sub>(0–24 h)</sub> value equaled the AUC from time 0 to the time of the final quantifiable sample (AUC<sub>(t<sub>f</sub>)</sub>) because the time of the final quantifiable sample was 24 h for all subjects

**Fig. 1** Mean ( $\pm$  standard error, SE) plasma concentrations of ezetimibe and total ezetimibe following multiple-dose oral extended-release (ER) niacin coadministered with ezetimibe/simvastatin (Treatment C) vs. ezetimibe/simvastatin administered alone (Treatment B) in healthy subjects



Again, keeping in mind that there were only 15 subjects in this comparison, Fig. 2, it is apparent that the plasma concentration–time curve for simvastatin peaked earlier and was slightly shifted to the longer time intervals and that there were no significant changes in  $C_{max}$ . The initial levels of simvastatin acid were similar between treatments; however, the peak and the later phase remained higher in the presence of niacin, possibly indicating a decreased simvastatin acid clearance. It was noted that one subject (Subject 103) had the greatest changes, while 9–11 of the subjects demonstrated smaller increases in  $C_{max}$ , and nine subjects demonstrated increased AUC values when niacin was added.

**Niacin and nicotinuric acid** Ezetimibe/simvastatin 10/20 mg once-daily had no apparent effect on the PK of niacin and nicotinuric acid administered as ER niacin tablets (2000 mg/day with food). The 90% CI for niacin  $C_{max}$  and  $AUC_{(0-24\ h)}$  were 64–186% and 72–205%, respectively (Table 4, Fig. 3). There was high inter- and intra-subject variability in the PK of niacin. The inter-

subject variability was 108–130% for  $C_{max}$  and 123–147% for AUC; the intra-subject variability was 74 and 72% in  $C_{max}$  and AUC, respectively. The 90% CI for nicotinuric acid  $C_{max}$  and  $AUC_{(0-24\ h)}$  were 99–122% and 99–143%, respectively. Of these, the  $C_{max}$  values for niacin and nicotinuric acid were not significantly different between the treatments. However, the upper 90% CI were on the order of 186% for niacin and only 122% for nicotinuric acid.

Both AUC values for niacin were not significantly different, but the range of the 90% CI was very large as was the range of values (Table 4). This observation is primarily due to the small number of subjects in the study and the moderate to high degree of variability in the niacin and nicotinuric acid PK parameters.

#### Safety

A total of 17 (94%) of the 18 subjects reported at least one treatment-emergent adverse event during the study: 56% (9/16) while receiving ezetimibe/simvastatin alone, 82% (14/17)

**Table 3** Statistical comparison of simvastatin and simvastatin acid  $C_{max}$  and the AUC values following treatment with ER niacin + ezetimibe/simvastatin (Treatment C) versus ezetimibe/simvastatin (Treatment B) in healthy subjects

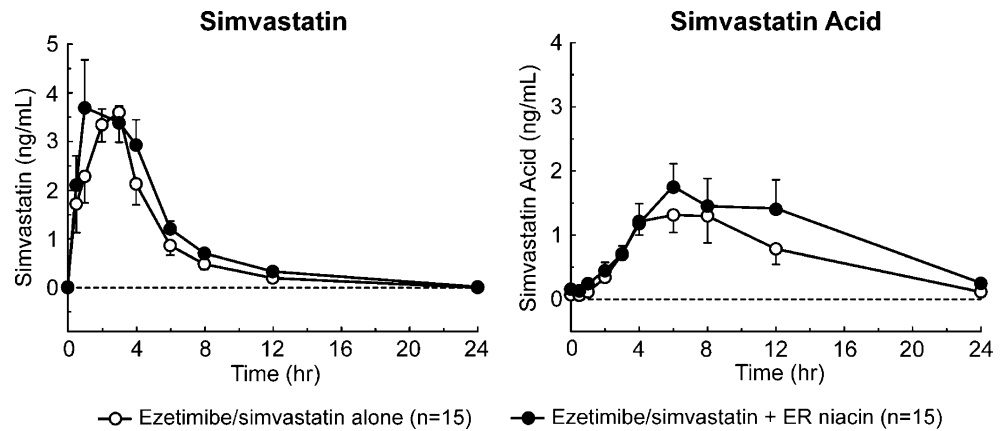
Parameter	LS mean (N=15) <sup>a, b</sup>		Comparison <sup>a</sup>		
	Ezetimibe/simvastatin	ER niacin + ezetimibe/simvastatin	Ratio (%)	90% CI	Range of Ratios
<b>Simvastatin</b>					
$C_{max}$ (ng/mL)	4.77 (0.15)	4.66 (0.61)	98	85–112	(50–150)
$AUC_{(tf)}$ (ng•h/mL)	15.7 (0.32)	18.6 (0.44)	119	103–137	(80–170)
$AUC_{(0-24\ h)}$ (ng•h/mL)	16.8 (0.33)	20.2 (0.45)	120	103–140	(90–200)
<b>Simvastatin acid</b>					
$C_{max}$ (ng/mL)	1.22 (0.99)	1.44 (0.97)	118	86–163	(60–200)
$AUC_{(tf)}$ (ng•h/mL)	9.32 (1.2)	13.7 (1.04)	147	100–216	(30–400)
$AUC_{(0-24\ h)}$ (ng•h/mL)	11.6 (1.01)	15.6 (0.99)	135	97–188	(50–300)

$AUC_{(tf)}$ , Area under the plasma concentration–time curve from time 0 to the time of the final quantifiable sample

<sup>a</sup> Model-based (least squares) mean. ANOVA was used to extract the effects due to treatment, period, and subject. Values in parenthesis for the LS mean are the CV

<sup>b</sup> Three subjects were excluded from the analysis due to early withdrawal from study

**Fig. 2** Mean (SE) plasma concentrations of simvastatin and simvastatin acid following multiple-dose oral with ER niacin coadministered with ezetimibe/simvastatin (Treatment C) versus ezetimibe/simvastatin administered alone (Treatment B) in healthy subjects



while receiving ER niacin alone, and 94% (15/16) while receiving ER niacin + ezetimibe/simvastatin. Overall, the most prevalent adverse events were flushing (89%; 16/18), pruritus (72%; 13/18), and headache (28%; 5/18). Flushing and pruritus occurred while subjects were receiving ER niacin alone or ER niacin + ezetimibe/simvastatin, but not ezetimibe/simvastatin alone. Headache was reported during all treatments. Adverse events reported after the coadministration of ER niacin and ezetimibe/simvastatin were similar in incidence and severity to those reported after the administration of ER niacin alone or ezetimibe/simvastatin alone. There were no deaths or serious adverse events. One subject was withdrawn from the study after 7 days of treatment with ER niacin because of myalgia and moderately increased blood CK (1064 U/L; baseline value 81 U/L) measured 9 days after the last dose. This patient also had clinically significant increases (two-fold) in ALT and AST. All symptoms resolved and laboratory values returned to normal within 17 days of withdrawal of drug treatment. The myalgia and increased creatine phosphokinase (CPK) were considered possibly related to the study treatment. Clinically significant increases

in CK, ALT, and AST occurred in another subject after dosing with ER niacin + ezetimibe/simvastatin. Consistent with sustained-release niacin labeling, mild increases in uric acid occurred in one subject after receiving sustained-release niacin + ezetimibe/simvastatin and in three subjects dosed with sustained-release niacin alone. No other notable changes in blood chemistry, hematological parameters, vital signs, or ECGs occurred.

**Discussion and overall conclusions**

The study was completed with a sufficient number of subjects to meet the PK objectives. Although there are observed mean PK differences between monotherapy and coadministration, the overall variability of the study was relatively high, particularly during ER niacin coadministration. This high variability in conjunction with the small number of subjects and apparently little or no effect on the exposure to the parent drugs makes it difficult to establish cause and effect relationships for the potential interactions.

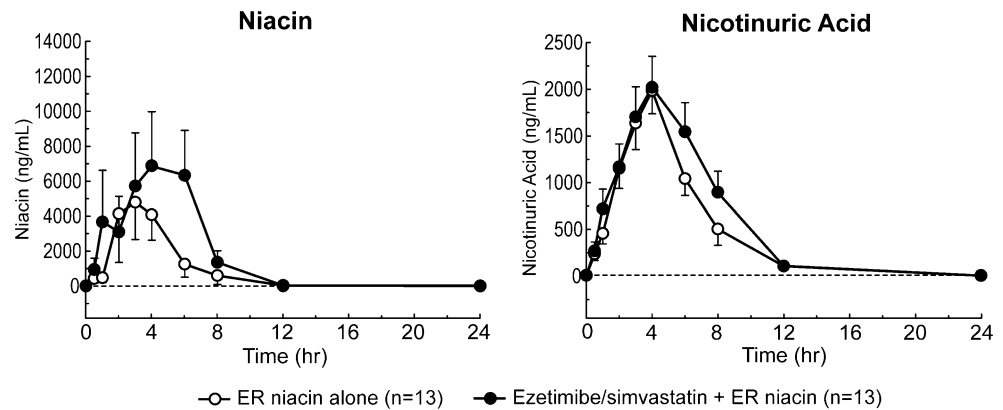
**Table 4** Statistical comparison of niacin and nicotinic acid C<sub>max</sub> and AUC values following treatment with ER niacin with ezetimibe/simvastatin (Treatment C) versus ezetimibe/simvastatin (Treatment B) in healthy subjects

Parameter	LS mean (N=13) <sup>a, b</sup>		Comparison <sup>a</sup>		
	ER niacin	ER niacin + ezetimibe/simvastatin	Ratio (%)	90% CI	Range of Ratios
<b>Niacin</b>					
C <sub>max</sub> (µg/mL)	4.61 (1.30)	5.03 (1.08)	109	64–186	(50–590)
AUC <sub>(0-t)</sub> (µg•h/mL)	11.6 (1.24)	13.8 (1.53)	119	73–195	(15–550)
AUC <sub>(0-24 h)</sub> (µg•hr/mL)	11.9 (1.23)	14.5 (1.47)	122	72–205	(15–780)
<b>Nicotinic acid</b>					
C <sub>max</sub> (µg/mL)	2.05 (0.39)	2.25 (0.40)	110	99–122	(90–170)
AUC <sub>(0-t)</sub> (µg•h/mL)	9.70 (0.38)	11.6 (0.44)	120	98–146	(70–230)
AUC <sub>(0-24 h)</sub> (µg•h/mL)	9.89 (0.37)	11.8 (0.44)	119	99–143	(70–220)

<sup>a</sup> Model-based (least squares) mean. ANOVA was used to extract the effects due to treatment, period, and subject. Values in parenthesis for the LS mean are the CV

<sup>b</sup> Five subjects were excluded from the analysis due to early withdrawal from study

**Fig. 3** Mean ( $\pm$ SE) plasma concentrations of niacin and nicotinuric acid following multiple-dose oral with ER niacin coadministered with ezetimibe/simvastatin (Treatment C) versus ezetimibe/simvastatin administered alone (Treatment B) in healthy subjects



The only reported differences for drug exposure previously reported for dosing of ER niacin and simvastatin are found in the package insert for the combination drug [9]. The mean increase in simvastatin acid was 35 or 65%, depending on whether the AUC was calculated for 24 h or to the final quantifiable time point. The results for the mean increase in AUC of simvastatin acid in this study, at the same comparative doses, were comparable at 35 and 47%, respectively. This study also reports that simvastatin exposure (based on AUC) was increased by a mean of approximately 20% with the upper 90% CI of 140%, which is not that much higher than the 125% limit that is typically established for bioequivalence, considering the small sample size and moderate variability.

With the exception of the  $AUC_{(0-24\text{ h})}$  for niacin, with a mean increase of 22%, all 90% CI in our study were below 200%. Keeping in mind that there were only 13 subjects in this comparison, it is difficult to assess from Fig. 3 what is happening to both niacin and nicotinuric acid. It appears that the plasma concentration–time curve for niacin peaked later and had shifted to the longer time intervals. However, three subjects demonstrated very large increases in  $C_{\max}$ , with the remainder changing only slightly, both increasing and decreasing. This may indicate that there was impairment in the metabolism and/or excretion of niacin in some of the individuals. It was noted that one subject had the greatest changes in all six analytes. For nicotinuric acid, seven subjects showed an increase in  $C_{\max}$  and AUC values, and six showed a decrease; exaggerated increases were observed in three subjects. Again, this higher upper 90% CI bound for niacin is primarily the result of the small sample size and high variability in the PK parameters. The study pre-specified that a mean two-fold (200%) increase in exposure to any of the analytes was to signal that the differences could be possibly of clinical importance.

Overall, the results from this study clearly show that the mean increase in any of the analytes is much smaller ( $\leq 35\%$ ) than a two-fold increase in exposure, and although the upper 90% CI for some analytes (e.g., simvastatin acid and niacin) may be slightly larger than 200%, this is

primarily due to the small number of subjects and the moderate to high degree of variability in these PK parameters.

Discussion of only the mean PK parameters in relationship to the criteria for either bioequivalence or to clinical significance does not give a full evaluation for potential interactions. In general, the subjects participating in our study should reflect the behavior of the drug in an open population of patients. That this study was highly controlled and the dosing times were about 12 h off the typical dosing times should be taken into account. Even with this regimentation, about 20–30% of the subjects displayed large swings in the plasma levels of the drugs and the metabolites. One subject in particular had what could be considered exaggerated changes in drug levels when all of the drugs were dosed together. The values involved, while large in relation to a given mean, were not sufficiently large to meet the criterion for a statistical outlier, and therefore they were kept in the statistical evaluation. There is the potential that individual patients in an open population may display these characteristics and be a risk for a higher drug exposure than expected from the dose level.

The labeling for the dosing of simvastatin and ER niacin are restricted to 10 mg/20 mg of ezetimibe/simvastatin and no more than 2000 mg of ER niacin. There is a very specific dosing regimen for the initial and escalation of the dose of ER niacin over weeks so as to acclimate the patient to the drug and associated side effects, such as flushing. The ER niacin (NIASPAN) label states "Therapy with NIASPAN must be initiated at 500 mg at bedtime in order to reduce the incidence and severity of side effects which may occur during early therapy and should not be increased by more than 500 mg in any four week period" [12]. This study used a rapid dose escalation starting with 1000 mg and increased to 2000 mg by the third day of treatment, with the drug taken in the morning as opposed to the recommended instruction of taking it at bedtime [12]; as a result, almost all subjects experienced side effects. However, in PK terms, there should have been enough time to achieve steady state for all the drugs as the 7 days of dosing



were greater than five-fold the reported half-lives for each of the drugs, although there was no planned PK sampling aimed at confirming that steady state conditions were indeed achieved.

The fact that some subjects have experienced as much as a 200% increase in simvastatin acid exposure would mean that they had in effect an exposure to a 40 mg dose of simvastatin. Although this is an approved dose of simvastatin and is considered safe when used as monotherapy, it could be of potential concern in the presence of coadministered ER niacin and, therefore, careful titration to the maximum recommended dose of ER niacin to minimize potential side effects would be prudent and consistent with product dosing recommendations.

This increased exposure to total ezetimibe (i.e., ezetimibe + ezetimibe glucuronide) is not likely to be clinically relevant as the mean was 26%, with an upper 90% CI of 144% of the monotherapy AUC, and doses of ezetimibe many times higher than the dose used here have been examined during the clinical development of ezetimibe without increased incidence of adverse effects [13].

On the basis of these results, no dose adjustment for ezetimibe/simvastatin should be necessary when ezetimibe/simvastatin 10 mg/20 mg is administered in combination with sustained-release niacin. The same would be true for the ER niacin. These statements would be true if indeed the patient was equal to a subject displaying near mean plasma levels of drug in this study. Given the wide variability in the results for all the drugs when administered together, caution in the form of close monitoring of the patient by blood tests and safety evaluations would be reasonable.

The treatment emergent adverse events that occurred during coadministration were similar in incidence and severity to those reported during the administration of sustained-release niacin alone or ezetimibe/simvastatin alone and to those reported in registration documents, i.e., the package insert. The notable changes from baseline in laboratory parameters after coadministration of sustained-release niacin and ezetimibe/simvastatin were also expected from previous experience with sustained-release niacin or simvastatin administered alone. The adverse events observed are similar in type and degree to those observed in clinical trials testing the efficacy of combinations of ER niacin and either simvastatin [4–6] or ezetimibe/simvastatin [7]. These results, which demonstrate high intra- and inter-subject variability due to high-dose ER niacin, have to be tempered by the fact that the individual medications alone and in combination can increase the risk of myopathy and rhabdomyolysis.

In conclusion, the data suggest that there is a small PK drug interaction between ER niacin and ezetimibe/simvastatin and that although this is not considered to be clinically significant, the concomitant use of these drugs should be

appropriately monitored, especially during the prescribed niacin titration period.

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