



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: Niacin ER/Simvastatin (ABT-118)	Volume:	
Name of Active Ingredient: Niacin ER and simvastatin	Page:	
Title of Study: SUPREME: A 12-week, Open-label, Multicenter Study to Compare the Lipid Effects of Niacin ER and Simvastatin (NS) to Atorvastatin in Subjects With Hyperlipidemia or Mixed Dyslipidemia		
Coordinating Investigator: Anthony N. Vo, MD		
Study Sites: Multicenter; the study was conducted at 40 sites in the US.		
Publications: None		
Studied Period (Years): First Subject First Visit: 17 April 2007 First Subject First Dose: 10 May 2007 Last Subject Last Dose: 20 February 2008	Phase of Development: 3B	
Objectives: The primary objective of this study was to evaluate whether niacin extended release/simvastatin (NER/S) tablets, when compared with atorvastatin, had superior high-density lipoprotein cholesterol (HDL-C)-elevating effects at Week 12 in subjects with primary type II hyperlipidemia or mixed dyslipidemia who were currently off lipid-modifying therapy. The secondary objectives of this study were the following: <ul style="list-style-type: none">To compare the percent change from baseline to Week 8 in HDL-C, and from baseline to Weeks 8 and 12 in non-HDL-C, low-density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), LDL-C:HDL-C ratio, Total-C:HDL-C ratio, triglycerides (TG), and lipoprotein a [Lp(a)] between NER/S and atorvastatin.To compare the proportions of subjects with LDL-C < 100 mg/dL, LDL-C < 130 mg/dL, HDL-C ≥ 40 mg/dL, HDL-C ≥ 60 mg/dL, and Total-C:HDL-C ratio < 4.5 mg/dL at Week 12, between NER/S and atorvastatin.		



Methodology:

This Phase 3B, prospective, randomized, open-label, blinded endpoint (PROBE), multicenter, 12-week study compared the safety and efficacy of NER/S compared with atorvastatin in subjects with primary type II hyperlipidemia or mixed dyslipidemia. The study consisted of a 4- to 5-week screening period, which was used to allow subjects on lipid-modifying agents to return to their baseline lipid levels and to evaluate subject eligibility for randomization, and a 12-week treatment period. NER/S was administered once daily at a dose of 1000/40 mg for the first 4 weeks and 2000/40 mg for the last 8 weeks. Atorvastatin was administered once daily at a dose of 40 mg for 12 weeks. Subject visits occurred at Weeks 8 and 12, at which time samples for lipid determinations were obtained and flushing diary data were reviewed. Because NER/S or atorvastatin may have substantially altered subjects' lipid profiles, study site personnel and the sponsor were blinded to all lipid results after randomization and for the remainder of the study.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 180 subjects were planned for enrollment.

Enrolled: A total of 199 subjects were randomized and 193 subjects were treated (N = 114 NER/S; N = 79 atorvastatin).

Diagnosis and Main Criteria for Inclusion:

Male and female subjects ≥ 21 years of age with primary type II hyperlipidemia or mixed dyslipidemia who met the following lipid criteria at the end of the Screening Period: mean HDL-C < 40 mg/dL for men or < 50 mg/dL for women (with variability $< 15\%$ from 2 consecutive blood draws); mean LDL-C ≥ 130 mg/dL but < 250 mg/dL (with variability $< 15\%$ from 2 consecutive blood draws); and TG < 350 mg/dL. In addition, subjects must have been reasonably compliant with the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) therapeutic lifestyle changes (TLC) diet, as judged by study site personnel, for a minimum of 4 weeks prior to randomization, and willing to comply with the diet for the duration of the study. Subjects who were taking lipid-modifying medications had to be willing to withdraw from these medications for the duration of the study.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

NER/S 1000/40 mg (two 500/20 mg tablets) once daily, orally

Bulk Lot No.: 144S019

Finishing Lot No.: PC100653/144S019

NER/S 2000/40 mg (two 1000/20 mg tablets) once daily, orally

Bulk Lot No.: 164S019

Finishing Lot No.: PC100653/164S019

Duration of Treatment: 12 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Atorvastatin 40 mg (one 40 mg tablet) once daily, orally

Bulk Lot No.: 0346066, 0393096

Finishing Lot No.: PC100653/0346066, PC100653/0393096



Criteria for Evaluation

Efficacy:

The primary efficacy variable was the percent change in HDL-C from baseline to Week 12.

The secondary efficacy variables were the percent change from baseline to Week 8 in HDL-C, and the percent change from baseline to Weeks 8 and 12 in non-HDL-C, LDL-C, Total-C, LDL-C:HDL-C ratio, Total-C:HDL-C ratio, TG, and Lp(a).

Additional efficacy variables were the proportions of subjects who met criteria of LDL-C < 100 mg/dL, LDL-C < 130 mg/dL, HDL-C \geq 40 mg/dL, HDL-C \geq 60 mg/dL, and Total-C:HDL-C ratio < 4.5 mg/dL.

Safety:

Safety assessments included routine serum chemistry and hematology parameters, physical examinations, pregnancy tests, vital signs, adverse events, and flushing information.

Statistical Methods

Efficacy:

The primary hypothesis was that the mean percent change in HDL-C from baseline to Week 12 in the NER/S treatment group would be superior to that of the atorvastatin treatment group. A mixed-effects model for repeated measures was fitted to percent change in HDL-C for estimating and testing treatment effects. The mixed-effects model included week as the repeated effect, subject as the random effect, and fixed effects terms for treatment group within week and baseline measurements within week. An unstructured variance covariance model was assumed to account for the within-subject correlation over time. The primary objective was achieved if the treatment difference in HDL-C percent change for NER/S minus atorvastatin at Week 12 was significantly greater than zero ($P < 0.05$).

For the secondary endpoints of non-HDL-C and LDL-C, the objective was to demonstrate that the treatment response to NER/S was noninferior to that of atorvastatin. Similar mixed-effects models were used to compute a two-sided 95% confidence interval (CI) for the mean difference between NER/S and atorvastatin. Noninferiority was concluded if the upper bound of the 95% CI of the between-group difference in the percent change in non-HDL-C or LDL-C from baseline to Week 12 was \leq 6%.

All other continuous secondary efficacy endpoints were each compared between treatment groups in separate mixed-effects models.

The proportions of subjects with LDL-C < 100 mg/dL, LDL-C < 130 mg/dL, HDL-C \geq 40 mg/dL, HDL-C \geq 60 mg/dL, and Total-C:HDL-C ratio < 4.5 mg/dL at Week 12 were summarized by treatment group using frequencies and percentages.

Safety:

Adverse events were summarized by MedDRA system organ class and preferred term and tabulated by treatment group with frequencies and percentages. The incidence of serious adverse events, adverse events leading to discontinuation, and the incidence of flushing (overall and by severity) were summarized.

All hematology and chemistry parameters were summarized by treatment group and week using means (of observed and change values), standard deviations, median, minimum, and maximum. Shift tables were produced for selected chemistry and hematology parameters. Vital signs were summarized and physical examination results and positive pregnancy tests were listed.



Summary/Conclusions

Efficacy Results:

For the primary efficacy comparison of percent change in HDL-C from baseline to Week 12, NER/S was statistically significantly superior to atorvastatin when administered once daily for 12 weeks in adult subjects with primary type II hyperlipidemia or mixed dyslipidemia. Results of supportive analyses that accounted for missing data were generally consistent with results of the primary analysis.

For the secondary efficacy endpoints, treatment with NER/S, compared with atorvastatin, resulted in similar LDL-C- and non-HDL-C lowering effects at Week 12. Statistical criteria for the noninferiority of NER/S compared with atorvastatin were not met because the result variability was greater than the assumed 15% and the treatment difference was greater than -1.5%. Treatment with NER/S resulted in greater TG- and LP(a)-lowering effects at Week 12 and a greater predicted percent reduction in cardiovascular disease risk at Week 12.

Among subjects who were not at NCEP ATP III lipid goals or targets at baseline, similar proportions of subjects in the NER/S and atorvastatin treatment groups met the targets of LDL-C < 130 mg/dL, LDL-C < 100 mg/dL, and Total-C:HDL-C ratio < 4.5 at Week 12. A greater proportion of subjects in the NER/S treatment group, compared with the atorvastatin treatment group, met the targets of HDL-C \geq 40 mg/dL and HDL-C \geq 60 mg/dL, and the combined goals and targets of HDL-C \geq 40 mg/dL, LDL-C and non-HDL-C meeting NCEP/ATP III goals, and TG < 150 mg/dL or HDL C \geq 60 mg/dL, LDL-C and non-HDL-C meeting NCEP/ATP III goals, and TG < 150 mg/dL.

Safety Results:

NER/S was generally well tolerated in subjects with primary type II hyperlipidemia or mixed dyslipidemia. The incidence of treatment-emergent adverse events was 85.1% in the NER/S treatment group and 45.6% in the atorvastatin treatment group. The treatment-emergent adverse events with the highest incidence (reported by \geq 5 subjects in either treatment group) were flushing, vomiting, diarrhea, nausea, headache, pruritus, and constipation, of which flushing, vomiting, nausea, and pruritus were more common in the NER/S treatment group than the atorvastatin treatment group.

In the NER/S treatment group, 54/97 (55.7%) subjects who experienced an adverse event had events that were mild or moderate in severity. In the atorvastatin treatment group, 33/36 (91.7%) subjects who experienced an adverse event had events that were mild or moderate in severity. A higher proportion of subjects experiencing severe adverse events was observed in the NER/S treatment group (43/97, 44.3%), compared with the atorvastatin treatment group (2/36, 5.6%), mainly because of the higher incidence of severe flushing events in the NER/S treatment group.

Adverse events considered at least possibly drug-related were reported by 75.4% of subjects in the NER/S treatment group and 19.0% of subjects in the atorvastatin treatment group, a difference that was statistically significant and due mostly to the proportion of subjects in the NER/S treatment group (67.5%) who experienced drug-related flushing. Other drug-related adverse events reported by at least 2% of subjects in either treatment group were vomiting, pruritus, nausea, headache, diarrhea, and myalgia.



Safety Results (Continued):

No subject died during the conduct of the study. Three subjects experienced treatment emergent serious adverse events, which included events of chest pain, reported by 1 subject in each treatment group, and coronary artery disease, reported by 1 subject in the NER/S treatment group. The event of chest pain in the NER/S-treated subject was considered possibly drug-related by the investigator. This event occurred in a [REDACTED] female who was hospitalized with atypical chest pain. Laboratory tests for serial troponins were negative. On the day of hospital discharge (5 days after admission), a myocardial perfusion scan and stress test were performed and were reported to be normal. The event was considered to be resolved at that time and the subject completed the study. redacted information

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Twenty-seven subjects experienced treatment-emergent adverse events that led to discontinuation from the study: 24 subjects (21.1%) in the NER/S treatment group and 3 subjects (3.8%) in the atorvastatin treatment group. The most common adverse event leading to discontinuation was flushing (14 subjects) in the NER/S treatment group and myalgia (3 subjects) in the atorvastatin treatment group.

Because niacin is known to cause flushing, this event was assessed in detail in the current study. The incidence of flushing in the NER/S treatment group was highest during the first 4 weeks of study drug treatment (53%) and declined thereafter (45% during Weeks 5-8 and 30% during Weeks 9-12).

Fifty-seven percent of NER/S-treated subjects who experienced flushing during the first 4 weeks and completed the study no longer experienced flushing during the last 4 weeks of the study. Flushing events reported by NER/S-treated subjects were mostly mild or moderate in severity and the rate of discontinuation in the NER/S treatment group because of the adverse event of flushing was 12.3%.

No clinically concerning trends in hematology, clinical chemistry, or vital sign values were observed.

Conclusions:

The efficacy of NER/S with regard to multiple lipid risk factors associated with coronary heart disease, together with its favorable safety profile, support the use of a combination product containing niacin and simvastatin (NER/S) over a statin alone (atorvastatin) for the treatment of patients with primary type II hyperlipidemia or mixed dyslipidemia.