



2.0 Synopsis

Abbott Laboratories	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: Niaspan	Volume:	
Name of Active Ingredient: Niacin extended-release	Page:	
Title of Study: A Randomized, Double-Blind, Parallel, Multicenter Placebo-Controlled Prospective Study to Evaluate the Functionality of the Flushing ASsessment Tool (FAST) in Subjects Administered Niaspan [®] Plus Acetylsalicylic Acid (ASA), Niaspan [®] Plus ASA Placebo or Niaspan [®] Placebo Plus ASA Placebo Daily for Six Weeks		
Coordinating Investigator: [REDACTED] MD redacted information 14Nov2014		
Study Sites: 41 sites in the United States		
Publications: 1 manuscript		
Studied Period (Years): First Subject First Visit: 18 February 2008 Last Subject Last Visit: 09 June 2008	Phase of Development: 3	
Objectives: To evaluate the psychometric characteristics of the FAST. Secondary objectives were to assess the efficacy, tolerability, and safety of niacin extended-release (NER) and ASA administration.		
Methodology: Randomized, placebo-controlled, double-blind, parallel group, multicenter, prospective, study to evaluate the FAST in a dyslipidemia population. Subject received NER (starting at 500 mg and titrating to 2000 mg) or NER placebo and ASA 325 mg or ASA placebo once daily for 6 weeks. Subjects were randomized in equal proportions to 1 of 3 treatment groups: NER plus ASA (NER/ASA); NER plus ASA placebo (NER/Pbo); or NER placebo plus ASA placebo (Pbo/Pbo).		
Number of Subjects (Planned and Analyzed): 246 subjects planned for enrollment, 276 randomized, 269 analyzed		
Diagnosis and Main Criteria for Inclusion: Male and female subjects ≥ 18 years of age who had not previously been treated with NER (or niacin-containing products) and who were either not currently taking ASA or were willing to refrain from use of ASA/nonsteroidal anti-inflammatory drugs (other than a prophylactic aspirin dose ≤ 100 mg at least 10 hours prior to their bedtime study drug dose) for the duration of the study. Subjects were to have a fasting laboratory LDL-C value < 250 mg/dL at the Screening Visit and one of the following: HDL-C < 40 mg/dL for males or < 50 mg/dL for females, or TG ≥ 150 and ≤ 400 mg/dL, or LDL-C ≥ 70 mg/dL if subject had history of coronary heart disease (CHD) or CHD risk equivalents, or ≥ 100 mg/dL if subject had 2 risk factors, or ≥ 160 mg/dL if subject had 0 to 1 risk factor.		



Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:			
Study Drug	Strength and Dosage		Manufacturer
	Form	Lot Number	
NER	500 mg tablet	[REDACTED]	[REDACTED]
NER	1000 mg tablet	[REDACTED]	[REDACTED]
ASA	325 mg tablet	[REDACTED]	[REDACTED]
Duration of Treatment: 6 weeks of treatment with NER plus ASA, NER plus ASA placebo, or NER placebo plus ASA placebo.			
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:			
Study Drug	Strength and Dosage		Manufacturer
	Form	Lot Number	
NER placebo	500 mg tablet	[REDACTED]	[REDACTED]
NER placebo	1000 mg tablet	[REDACTED]	[REDACTED]
ASA placebo	325 mg tablet	[REDACTED]	[REDACTED]
Criteria for Evaluation			
<p>Efficacy: The primary objective was to evaluate the psychometric characteristics of the FAST. This was performed by evaluating the test-retest reliability, construct validity, and responsiveness of the FAST, primarily by evaluating the weekly mean and maximum severity of flushing events as compared to other questions within the FAST and other subject- and clinician-reported outcomes.</p> <p>The secondary objectives were as follows: 1) maximum severity of flushing events subjects experienced during Week 1 (initiation of NER) categorized as none/mild, moderate, severe, or very severe using the FAST; 2) mean/median maximum severity of flushing events analyzed as a numeric variable using the FAST; 3) mean/median severity of flushing events analyzed as a numeric variable using the FAST; 4) mean/median number of days per week with moderate or greater flushing; 5) percentage of subjects with flushing (by severity); 6) total number of flushing episodes by severity; 7) mean/median number of flushing events (all, and by severity) per subject per week; 8) duration of flushing events; 9) days to the first most severe flushing episode; 10) days to the last flushing episode; 11) correlation of flushing severity with discontinuations, troublesomeness, activities of daily living, and sleep indices; 12) mean/median percent change and mean/median absolute change from Baseline in lipid parameters; 13) frequencies and percentages of subjects reaching National Cholesterol Education Program Adult Treatment Panel III (ATP III) lipid goals and targets at Day 43; 14) discontinuation rates due to flushing and adverse events; 15) time to discontinuation due to flushing and adverse events; 16) treatment satisfaction questionnaire comparisons between groups; 17) subject-rated and physician-rated overall treatment effect (OTE) comparisons between groups; 18) RAND-36 emotional well-being scale comparisons between groups; and 19) correlation of NER compliance to mean/median flushing scores.</p> <p>Safety: Safety assessments included routine serum chemistry and hematology parameters, physical examinations, pregnancy tests, vital signs, adverse events, and flushing information.</p>			

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Statistical Methods

Efficacy: Evaluation of the FAST was based on 3 primary data analyses: (1) test-retest reliability based on the intraclass correlation coefficient (ICC); (2) construct validity based on Spearman rank-order correlation coefficients; and (3) responsiveness based on effect sizes. The weekly mean and maximum severity of flushing events as measured in the FAST were the primary variables evaluated in each of the 3 data analyses mentioned above. Descriptive statistics, including frequency and distribution of responses, measures of central tendency, and floor and ceiling effects were calculated for dichotomous and categorical items on the FAST.

The percentage of subjects with flushing events, the percentage of subjects that withdrew from treatment due to flushing, and the percentage of subjects reaching NCEP ATP III lipid goals and targets were compared among the treatment groups using Fisher's exact test. The percentage of subjects with mild, moderate, severe, or very severe flushing was compared among the treatment groups using the Cochran-Mantel-Haenszel test. The mean severity of flushing, mean duration of flushing, and the number of days with flushing events were summarized for each treatment group. The percent change from Baseline to each visit in lipid parameters was compared among the treatment groups using an analysis of covariance, with treatment as main effect and baseline values as covariate. Correlations between the severity of flushing and discontinuations and the sleep, activities of daily living, and overall troublesomeness scales were assessed using regression analyses.

The time to discontinuation due to a flushing event was defined as the number of days from randomization to the date of the last dose of randomized study drug for the subjects who discontinued study drug due to a flushing event. Subjects who did not discontinue study drug due to a flushing event were censored on the date of their last dose of study drug. Treatment group comparisons were performed using the log rank test and the distributions of time to discontinuation are presented using Kaplan-Meier methodology.

The RAND-36 emotional well-being scale collected at Day 1 and Day 43, and the treatment satisfaction questionnaire administered at Days 15 and 43, were summarized. Frequencies and descriptive information for physician and subject ratings of treatment effect using the OTE and clinician-based ratings of improvement at Days 8, 15, and 43 were summarized.

Safety: All randomized subjects who received at least one dose of study drug were assessed for safety. Treatment-emergent adverse events were defined as those events that began after initiation of randomized study drug and not more than 30 days after the last dose of randomized study drug. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 11.0), tabulated by system organ class (SOC) and MedDRA preferred term, and summarized by severity and relationship to study drug. For laboratory data, mean change from Baseline to Final Visit was analyzed using a one-way analysis of variance. Laboratory data collected more than 30 days after the last dose of study drug were included in the change from baseline analyses. Laboratory results of particular interest (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and creatine phosphokinase [CPK]) were summarized.



Summary/Conclusions

Efficacy Results: The results of this study suggest that the FAST has good test-retest reliability, construct validity, and responsiveness, particularly for the mean and maximum flushing severity scores.

Test-retest Reliability

The test-retest reliability, or stability, of FAST scores from Day 8 to Day 15 was evaluated in subjects who had stable symptoms during this interval (on the basis of subject-rated and physician-rated OTE responses at Day 15). The ICC for the mean flushing severity score was 0.75 and the ICC for the maximum flushing severity score was 0.40. Test-retest reliability was also demonstrated for the individual symptom scores (redness, warmth, tingling, and itching) and the overall troublesomeness of flushing, sleep interference, and impact on daily activities scores.

Construct Validity

Construct validity of the FAST was assessed by evaluating the relationship between individual FAST items and between FAST items and the RAND-36 emotional well-being scale, subject- and physician-rated OTE scales, and the treatment satisfaction questionnaire. Cross-sectional construct validity (relationships between items at one point in time) and longitudinal construct validity (relationships between changes in items over time) were evaluated.

Cross-sectional Construct Validity: Week 1 scores for mean and maximum flushing severity were significantly correlated with Week 1 scores for the 4 individual flushing symptoms (redness, warmth, tingling, and itching), overall troublesomeness, sleep interference, impact on daily activities, number of flushing episodes per week, duration of flushing events, percentage of days with severe flushing events, and percentage of days with flushing events. Statistically significant correlations between FAST item scores and RAND-36 emotional well-being scores at Day 1, subjects' dissatisfaction associated with flushing, as assessed by the treatment satisfaction questionnaire on Day 15, and subjects' treatment satisfaction associated with NER, as assessed on Day 15 and Day 43, were also observed.

Longitudinal Construct Validity: Changes in FAST scores were computed by subtracting values for earlier time points from later time points and were compared to the RAND-36 emotional well-being scale, subject- and physician-rated OTE scales, and the treatment satisfaction questionnaire across different study phases. RAND-36 emotional well-being scores at the end of the study were generally not statistically significantly correlated with change in FAST scores. Subject and physician ratings of the overall treatment effect at Day 43 and subjects' dissatisfaction associated with flushing and treatment satisfaction associated with NER as assessed on Day 43 were significantly correlated with most FAST item change scores.

Responsiveness

Responsiveness analyses were performed to determine how effectively the FAST was able to detect change among individuals who were known to have changed clinically in their flushing symptoms over a defined period of time. Changes in FAST scores from Baseline to Day 43 were compared in responders (flushing symptoms had improved between Baseline and Day 43) and nonresponders (flushing symptoms did not change or worsened between Baseline and Day 43). The mean flushing severity score improved 0.51 points from Day 1 to 43 in responders and worsened 0.15 points in nonresponders and the mean maximum flushing severity score improved 1.85 points in responders and improved 0.18 points in nonresponders, differences that were statistically significant. Statistically significant differences were also observed for changes in scores for redness, warmth, and tingling.



Secondary Endpoints: Flushing and Lipids

Coadministration of ASA with NER mitigated several aspects of subjects' flushing experiences, as indicated by the following results: a 20% relative reduction in maximum flushing severity during Week 1; relative reductions in the maximum severity of redness (43%), tingling (52%), and itching (40%) during Week 1; a 59% relative reduction at Week 6 in the mean maximum severity of flushing events; an 83% relative reduction at Week 6 in the mean number of days per subject per week with moderate or greater flushing; a 43% relative reduction at Week 6 in the percentage of subjects who experienced flushing, and an 86% relative reduction at Week 6 in the percentage of subjects with a maximum flushing severity of moderate or greater. Improvements in other aspects of subjects' flushing experiences were also observed.

Subjects who received NER (NER/ASA and NER/Pbo treatment groups) showed greater improvements in all lipid parameters compared with subjects who received NER placebo (Pbo/Pbo treatment group) and coadministration of ASA did not have a negative impact on NER effectiveness in this regard. Similarly, the percentages of subjects reaching NCEP ATP III lipid goals and targets at Day 43 were greater in subjects receiving NER compared with NER placebo and no differences between the NER/ASA and NER/Pbo treatment groups were noted.

Safety Results:

NER plus ASA was well tolerated in adult subjects with dyslipidemia. The overall incidence of treatment-emergent adverse events was 81.3%, 90.0%, and 71.1% in the NER/ASA, NER/Pbo, and Pbo/Pbo treatment groups, respectively. The most frequently reported ($\geq 5\%$ of subjects in any treatment group) treatment-emergent adverse events were flushing, diarrhea, and headache. A statistically significantly greater percentage of subjects in the NER/Pbo treatment group (86.7%, $P < 0.001$), but not the NER/ASA treatment group (74.7%), experienced an adverse event of flushing compared with the Pbo/Pbo treatment group (62.2%). All other events occurred at similar incidences among treatment groups.

The incidence of gastrointestinal disorders was similar among treatment groups but was higher in female subjects, compared with male subjects, in the NER/ASA treatment group (14.3% of females versus 4.1% of males) and NER/Pbo treatment group (19.5% of females versus 6.1% of males) and similar in the Pbo/Pbo treatment group (11.9% of females versus 10.4% of males). A total of 6 female subjects and 2 male subjects discontinued due to gastrointestinal adverse events.

No deaths were reported. Four subjects experienced treatment-emergent serious adverse events: 1 subject in the NER/ASA treatment group (non-cardiac chest pain); 1 subject in the NER/Pbo treatment group (myocardial infarction); and 2 subjects in the Pbo/Pbo treatment group (nephrolithiasis and right renal cyst in 1 subject and adenomatous polyposis coli in 1 subject). Only the event of non-cardiac chest pain was considered by the investigator to be possibly related to study drug.

Twenty-six subjects experienced treatment-emergent adverse events that led to discontinuation, most of which were considered by the investigator to be at least possibly related to study drug: 11 subjects (12.1%) in the NER/ASA treatment group; 8 subjects (8.9%) in the NER/Pbo treatment group; and 7 subjects (7.8%) in the Pbo/Pbo treatment group. Of these 26 subjects, 8 subjects discontinued at least in part due to gastrointestinal adverse events and 10 subjects discontinued at least in part due to flushing.



Safety Results (Continued):

Mean changes from Baseline to the Final Visit in most hematology and serum chemistry values were small, generally similar across treatment groups, and not clinically relevant. Mean decreases in platelet count and mean increases in AST and ALT were observed in the NER/ASA and NER/Pbo treatment groups. No adverse events were associated with decreases in platelet count and 1 subject each in the NER/ASA and NER/Pbo treatment groups reported adverse events associated with increases in AST and ALT. Mean increases in glucose and HbA1c% were observed in all treatment groups and were greatest in the Niaspan/Pbo treatment group; ASA mitigated this response such that increases in the Niaspan/ASA group were not statistically significantly different from increases in the Pbo/Pbo treatment group.

Two subjects had 5 instances of abnormalities in laboratory parameters of particular interest. One subject in the NER/ASA treatment group had elevated ALT $> 5 \times$ ULN on 1 occasion and elevated AST $> 5 \times$ ULN on 2 consecutive occasions. No adverse events were reported. One subject in the NER/Pbo treatment group had elevated ALT $> 5 \times$ ULN on 1 occasion and elevated AST $> 5 \times$ ULN on 1 occasion. Adverse events of elevated ALT lab value and elevated AST lab value were reported. No subject had elevated CPK $> 5 \times$ ULN on 2 consecutive occasions or $> 10 \times$ ULN on a single occasion.

No clinically meaningful changes from Baseline to the Final Visit in urinalysis or vital signs values were observed.

Conclusions: Overall, results from this study indicate that the FAST has the appropriate psychometric qualities to assess flushing in clinical trials and that coadministration of ASA improves several aspects of subjects' overall flushing experience in response to NER, without increased incidence of adverse events.