2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-919 (Niaspan®)	**Volume:**	
Name of Active Ingredient: Niacin	**Page:**	
Title of Study: Multicenter, Randomized, Double-Blind, Parallel, Acetylsalicylic Acid (ASA) Run-In Study to Evaluate the EFFECTS of Acetylsalicylic Acid on Niaspan®–Induced Flushing in Subjects With Dyslipidemia (ASA EFFECTS)		
Coordinating Investigator: [redacted] redacted information 14Nov2014		
Study Sites: 47 sites within the United States		
Publications: None		
Studied Period (Years): First Subject First Visit: 01 Feb 2008 Last Subject Last Visit: 21 April 2008	**Phase of Development:** 3	
Objectives: To assess the effect of ASA on niacin-induced flushing collected with an electronic diary (e-diary) in subjects with dyslipidemia. Secondary objectives were to assess the efficacy and safety of Niaspan and ASA administration.		
Methodology: Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study of 5-week duration (1 week run-in period with ASA 325 mg or placebo and 4-week treatment period with Niaspan with ASA 325 mg or Niaspan with placebo).		
Number of Subjects (Planned and Analyzed): 258 planned for run-in period, 240 planned to be enrolled, 277 enrolled, 256 analyzed		

Diagnosis and Main Criteria for Inclusion:

Subjects at least 18 years old with dyslipidemia, defined as low-density lipoprotein cholesterol (LDL-C) of < 250 mg/dL at screening and one of the following: (1) high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL for males and < 50 mg/dL for females, (2) triglycerides ≥ 150 and ≤ 400 mg/dL, or (3) LDL-C ≥ 70 mg/dL if subject has history of coronary heart disease (CHD) or CHD risk equivalent, ≥ 100 mg/dL if subject has 2 or more risk factors, or ≥ 160 mg/dL is subject has 0 to 1 risk factor. CHD history includes myocardial infarction, unstable angina, stable angina, coronary artery procedures, or evidence of clinically significant myocardial ischemia. CHD risk equivalents include other clinical forms of atherosclerotic disease and diabetes. Risk factors include cigarette smoking, hypertension (≥ 140 to 90 mm Hg or on antihypertensive medication), low HDL-C (< 40 mg/dL; HDL-C > 60 mg/dL is a negative risk factor), family history of premature CHD (in first-degree male relative < 55 years or in first-degree female relative < 65 years), age (≥ 45 years for males and > 55 years for females). Potential subjects currently taking a daily regimen of ASA ≤ 100 mg for cardiovascular prophylaxis and who could not commit to adjusting the timing of the dose to allow at least 10 hours between study medication and the daily dose of ASA and those who were taking any other product containing ASA were excluded, as were those who were taking anticoagulants, nonsteroidal anti-inflammatory drugs, and statins or other lipid-modifying drugs. Potential subjects with glycosylated hemoglobin (HbA1c) ≥ 9.0%, those with inadequate renal function, those with peptic ulcer disease or gastrointestinal reflux disease, and those with a vitamin k deficiency or predisposition to bleeding were also excluded.

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

Study Drug	Formulation	Lot Numbers	Manufacturer
Niaspan® 500 mg tablet	Niacin 500 mg extended-release (ER) film-coated tablet	[redacted]	[redacted]
Niaspan® 1000 mg tablet	Niacin 1000 ER film-coated tablet	[redacted]	[redacted]
Aspirin 325 mg (acetylsalicylic acid)	Aspirin 325 mg micro-coated tablet	[redacted]	[redacted]

Duration of Treatment: 1 week of run-in with ASA 325 mg or placebo and 4 weeks of treatment with Niaspan and ASA 325 mg or Niaspan and placebo.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Placebo for ASA 325 mg

Placebo for Niaspan® 500 mg tablet	Placebo tablet to match Niacin 500 mg ER film-coated tablet	[redacted]	[redacted]
Placebo for Niaspan® 1000 mg tablet	Placebo tablet to match Niacin 1000 mg ER film-coated tablet	[redacted]	[redacted]
Placebo for aspirin 325 mg	Placebo for aspirin 325 mg micro-coated tablet	[redacted]	[redacted]

redacted information 14Nov2014

Criteria for Evaluation:

Analyses were designed to compare the following:

(1) Active ASA run-in/active ASA versus ASA placebo run-in/ASA placebo (500 mg and 1000 mg): Arm 1 versus Arm 3, and Arm 4 versus Arm 6, (2) ASA placebo run-in/active ASA versus ASA placebo/ASA placebo (500 mg and 1000 mg): Arm 2 versus Arm 3, and Arm 5 versus Arm 6, (3) Active ASA run-in/active ASA versus placebo ASA run-in/active ASA arm (500 mg and 1000 mg): Arm 1 versus Arm 2, and Arm 4 versus Arm 5; (4) Pooled active ASA versus ASA placebo coadministered (500 mg and 1000 mg): Arms 1 and 2 combined versus Arm 3, and Arms 4 and 5 combined versus Arm 6, (5) Pooled all active ASA versus pooled all ASA placebo: Arms 1, 2, 4, and 5 combined versus Arm 3 and 6 combined.

All efficacy analyses (except changes in lipid parameters) were designed to compare the following treatment groups:

Effect of interest	**Comparison between 2 specified treatment regimens**		**Analysis between specified treatment groups**
Effect of any ASA	Any ASA	*No ASA, only placebo*	Pooled Arms 1, 2, 4, and 5 vs. *pooled Arms 3 and 6*
Effect of any ASA within treatment groups	Any ASA	*No ASA, only placebo*	Pooled Arms 1 and 2 vs. *Arm 3* Pooled Arms 4 and 5 vs. *Arm 6*
Effect of ASA run-in	ASA run-in ASA coadministration	*Placebo run-in* *ASA coadministration*	Arm 1 vs. *Arm 2* Arm 4 vs. *Arm 5*
Effect of initial dose of Niaspan	Initial Niaspan dose of 500 mg	*Initial Niaspan dose of 1000 mg*	Arm 1 vs. *Arm 4* Arm 2 vs. *Arm 5* Arm 3 vs. *Arm 6* Pooled Arms 1 and 2 vs. *pooled Arms 4 and 5*
Effect of ASA coadministration only	Placebo run-in ASA coadministration	*Placebo run-in* *Placebo coadministration*	Arm 2 vs. *Arm 3* Arm 5 vs. *Arm 6*
Effect of ASA run-in and ASA coadministration within treatment groups	ASA run-in ASA coadministration	*Placebo run-in* *Placebo coadministration*	Arm 1 vs. *Arm 3* Arm 4 vs. *Arm 6*

Efficacy: The primary endpoint was the maximum severity of flushing events that subjects experience during Week 1 (initiation of Niaspan) categorized as none/mild, moderate, severe, or very severe using the Flushing Assessment Tool (FAST). Secondary endpoints were (1) mean and median maximum severity of flushing events subjects experience during Week 1, and over the 4 weeks of Niaspan treatment analyzed as numeric variable using the FAST, (2) the mean and median number of days per week with moderate or greater flushing over the 4 weeks of Niaspan treatment, (3) percentage of patients by categorical severity of over the 4 weeks of Niaspan treatment, (4) total number of flushing episodes by severity over the 4 weeks of Niaspan treatment, (5) the mean and median number of flushing events, total and by severity category, per subject per week over the 4 weeks of Niaspan treatment, (6) the duration of flushing events over the 4 weeks of Niaspan treatment, (7) correlation of flushing severity with study discontinuations, with troublesomeness, activities of daily living, and sleep indices over the 4 weeks of Niaspan treatment, (8) the mean and median percent change and absolute change from baseline in lipid parameters, e.g., total cholesterol, HDL-C, non–HDL-C, LDL-C, triglycerides, Lp(a), LDL-C/HDL-C ratio, and hsCRP, at each visit, (9) the percentage of subjects reaching National Cholesterol Education Program (NCEP) lipid goals or targets at the end of 4 weeks of Niaspan treatment, (10) rates of discontinuation due to flushing events or adverse events, and (11) time to discontinuation due to flushing.

Safety: Safety endpoints include the evaluation of adverse events, clinical laboratory parameters (fasting serum chemistries, hematology, HbA_{1c}, prothrombin time, activated partial thromboplastin time, and urinalysis), vital signs, and physical examination results.

Statistical Methods

Efficacy: Severity was captured for the overall flushing event as well as for each symptom of flushing: redness, warmth, itching, and tingling. Subjects assessed the severity of flushing in e-diaries as measured by FAST. The primary endpoint of maximum severity of flushing events subjects experienced during Week 1 (initiation of Niaspan) categorized as none/mild, moderate, severe, or very severe were analyzed using the Cochran-Mantel-Haenszel test to compare treatment arms. The continuous variables for flushing were analyzed to compare treatment groups using an ANOVA model with effect of treatment. The percentage of subjects experiencing flushing by visit and severity were compared among treatment arms using the Fisher exact test. The time to discontinuation due to flushing was to be compared among treatment arms using the log-rank test. The change from baseline to each visit for lipid parameters was analyzed to compare treatment arms using an ANCOVA model, with baseline lipid value (lipid parameter corresponding to the outcome variable being modeled) as a covariate and with effect of treatment. The baseline was defined as the last measurement prior to the first dose of Niaspan. The number and percentage of subjects meeting NCEP ATP III guidelines for LDL-C and non–HDL-C goals at the end of Week 4 were calculated for each treatment arm.

Statistical Methods (Continued):

Safety: Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA®, version 10.1) dictionary, and all events were categorized by primary system organ class (SOC) and preferred term. Serious adverse events were summarized by treatment groups. Treatment-emergent adverse events were summarized for each treatment group. Treatment-emergent adverse events are defined as adverse events with a start date on or after the first dose of study drug (Niaspan). Adverse events starting more than 30 days following discontinuation of study drug were not included in summaries of adverse events. Events were also summarized by severity and relationship to study drug. The change from baseline in clinical laboratory parameters and in vital signs was assessed and summarized by treatment arm to identify all clinically meaningful changes. The baseline was defined as the last measurement prior to first dose of Niaspan. The measurements obtained more than 30 days after the last dose of study drug were excluded from analyses.

Summary/Conclusions

Efficacy Results: Most efficacy analyses were designed to compare the treatment effect of any ASA, the effect of a weeklong ASA run-in before initiating Niaspan therapy, and the effect of the initial Niaspan dose (500 mg versus 1000 mg). Analysis of changes in lipid parameters was designed to compare the treatment effect of the initial Niaspan dose and the effect of ASA use. Most efficacy analyses were performed on data from the modified intent-to-treat population; analysis of changes in lipid parameters was performed with data from study completers, as well as all subjects in the mITT population.

Effect of Any ASA

The primary endpoint, the maximum severity of flushing events during Week 1 of ASA coadministration, was selected to reflect the flushing experience of patients who initiate Niaspan therapy, on the basis of the hypothesis that aspirin can mitigate this transient adverse effect and that this mitigation could be captured in a quantitative fashion. For the primary analysis, administration of any ASA resulted in a 48% relative reduction in the percentage of subjects whose most severe flushing event was of moderate or higher intensity at Week 1. This statistically significant effect was maintained over the 4 weeks of ASA coadministration during a Niaspan dose-escalation regimen. Overall, over the weeks of therapy, the relative reduction in these events with ASA administration was 40%.

These results were corroborated by the mean maximum severity of flushing, based on the flushing score, which was 1.5 at Week 1 and 3.1 overall for subjects who received ASA, and 2.3 at Week 1 and 5.1 overall for subjects who did not receive ASA. The relative reduction in the mean maximum severity score with ASA administration was 35% at Week 1 and 39% overall.

Study drug ASA use also mitigated the incidence of flushing events during Week 1: 43% for subjects who received ASA and 52% for subjects who did not, while the overall incidence was 70% and 85%, respectively. ASA administration resulted in a 17% relative reduction in the incidence of flushing during Week 1 and an 18% relative reduction overall compared with no ASA administration. The mean number of moderate to very severe flushing episodes per subject per week was 0.3 both at Week 1 and overall for subjects who received ASA. For those who received no ASA, the means were 0.6 at Week 1 and 0.8 overall. Relative to no ASA use, ASA administration resulted in a 50% reduction at Week 1 and a 63% reduction overall in the mean number of moderate to very severe flushing episodes.

Effect of ASA Run-in

While the use of ASA coadministration 30 minutes prior to Niaspan to mitigate flushing has been discussed in the literature, the concept of an aspirin run-in period prior to Niaspan dosing has not been well explored. This study examined the effect of a 7-day ASA run-in period on the flushing experience. The most meaningful comparison to determine the effect of ASA run-in was in the groups that received an initial Niaspan dose of 500 mg, the recommended starting dose (Arm 1 versus Arm 2). For the primary endpoint, ASA use during the run-in period resulted in a 29% relative reduction of flushing events during Week 1 of Niaspan for those whose maximum flushing severity was moderate or higher when compared with placebo. Although this difference was not statistically significant, the effect was also observed for the comparable 1000 mg Niaspan groups (Arm 4 versus Arm 5).

Similarly, the relative reduction in the mean maximum severity score with ASA administration during run-in was 23% at Week 1, when intensity was evaluated as a continuous measure.

ASA administration during the weeklong run-in period resulted in a 29% relative reduction in the incidence of flushing during Week 1. The incidence of flushing events during Week 1 was 32% for subjects who received ASA during run-in and 45% for subjects who received placebo. The mean number of moderate to very severe flushing episodes per subject per week was 0.1 at Week 1 for subjects who received ASA and 0.4 for those who received placebo, resulting in a 75% relative reduction at Week 1 in the mean number of moderate to very severe flushing episodes as a consequence of a weeklong run-in period with ASA.

Effect of Initial Niaspan Dose

This study examined the effect of 2 ASA regimens on the flushing experience of subjects taking Niaspan. Although the effect of ASA has been described previously in the literature, this study used 2 different initial doses of Niaspan, 500 mg and 1000 mg, in order to evaluate more fully the benefit of ASA. A meaningful comparison to determine the effect of the initial Niaspan dose was in the groups that received placebo instead of ASA throughout the study (Arm 3 versus Arm 6). For the primary endpoint, subjects who received the lower initial Niaspan dose of 500 mg experienced a statistically significant 46% relative reduction in the maximum severity of flushing events during Week 1 compared with those who received the higher initial Niaspan dose of 1000 mg. For the overall study, the relative reduction in these events with the 500-mg initial dose was 18%.

Consistent with this, the relative reduction in the mean maximum severity score with the lower dose was 38% at Week 1 and 15% overall.

In secondary analyses, the incidence of flushing events during Week 1 was 41% for subjects who received Niaspan 500 mg initially and 63% for subjects who received Niaspan 1000 mg initially, while the overall incidence was 78% and 91%, respectively. The lower initial Niaspan dose resulted in a 35% relative reduction in the incidence of flushing during Week 1 and a 14% relative reduction overall compared with the higher initial Niaspan dose.

The mean number of moderate to very severe flushing episodes per subject per week was 0.4 at Week 1 and 0.6 overall for subjects who received the lower initial Niaspan dose, while the values were 0.9 and 1.0, respectively, for subjects who received the higher initial Niaspan dose. This corresponds to a 56% relative reduction at Week 1 and a 40% relative reduction overall in the mean number of moderate to very severe flushing episodes relative to a higher initial dose of 1000 mg.

Discontinuation Due to Flushing

Among the safety population, ASA use led to fewer discontinuations due to flushing (3 subjects: 1 each in Arm 1, Arm 4, and Arm 5) than no ASA use (8 subjects: 6 subjects in Arm 3 and 2 subjects in Arm 6). Because the number of discontinuations due to flushing was low in this study, further analyses are limited.

Change in Lipid Parameters

Subjects who received the higher initial Niaspan dose of 1000 mg showed greater improvements in lipid parameters than those who received the lower initial Niaspan dose of 500 mg. With an initial dose of 1000 mg Niaspan, final HDL-C mean value was 4.6 mg/dL higher, final LDL-C mean value was 5.0 mg/dL lower, and final triglyceride median value was 12.5 mg/dL lower than with 500 mg Niaspan. ASA coadministration did not negatively affect the effectiveness of Niaspan in improving lipid parameters.

Attainment of NCEP Goals/Targets

Among all subjects, at least 74% of subjects in every treatment arm achieved HDL cholesterol ≥ 40 mg/dL at the end of Week 4. Among subjects who did not meet NCEP goals at baseline, the percentage who achieved HDL cholesterol ≥ 40 mg/dL ranged from 25% in Arm 1 to 67% in Arm 6.

Evaluation of the Flushing Assessment Tool

Among subjects who experienced flushing, the mean maximum flushing severity rating was higher for subjects who discontinued because of flushing than for those who did not: 7.7 versus 4.9. Flushing severity correlated well with discontinuation from the study because of flushing, with the troublesomeness of symptoms and the effect of the symptoms on sleep at every week during the course of the study, and with effect on completion of daily activities for Weeks 1 though 3. These results show that the FAST instrument was useful for measuring effects of flushing on multiple domains of subjects' lives.

Safety Results:

In general, ASA in combination with Niaspan was well tolerated in this study. More adverse events were reported in the groups that received ASA placebo. A higher incidence of musculoskeletal and connective tissue disorders was reported for subjects in Arm 6, who received no ASA, versus those in pooled Arms 4 and 5 (11.4% versus 1.2%, $P = 0.018$). Flushing was the most common adverse event and the incidence of these events was statistically significantly higher among subjects who received ASA placebo (pooled Arms 3 and 6) compared with those who received ASA (pooled Arms 1, 2, 4, and 5) (83.5% versus 68.4%, $P = 0.011$).

The highest incidence of subjects who reported gastrointestinal events were those who received ASA and a starting Niaspan dose of 1000 mg (Arms 4 and 5). All gastrointestinal events were either mild to moderate in severity. Only 5 subjects on ASA-containing regimens, 4 females and 1 male, experienced a gastrointestinal event resulting in discontinuation.

One subject experienced a serious adverse event during the run-in period; the subject died from a road traffic accident. Two subjects experienced serious adverse events during the coadministration period. After 3 weeks of coadministration, 1 subject in Arm 1 experienced a serious event of dyspnea, which the investigator considered not related to study drug. After 4 weeks, 1 subject in Arm 6 experienced an esophageal ulcer, which the investigator considered possibly related to study drug. The subject had received placebo during both the run-in and coadministration periods.

Safety Results (Continued):

There were no clinically meaningful changes in mean or mean percent for laboratory values for hematology and chemistry variables over the course of the study. All 6 treatment groups experienced mean increases from baseline to final value in glucose, but the changes were not clinically relevant. Eleven subjects experienced an adverse event related to elevated glucose. Six of these subjects had diabetes at study entry. The events occurred on Day 1 before Niaspan administration for 3 of the 6 subjects. All but 1 of these subjects had elevated glucose at the final evaluation.

Five subjects experienced changes in ALT, AST, or CPK that were considered potentially clinically meaningful. All were detected after the last dose of study drug and all resolved to within normal limits 2 to 3 weeks later, except for ALT for 1 subject who had no follow-up visit. No subject discontinued because of a laboratory abnormality. No subject experienced an elevation in CPK that was 10 × ULN, and no subject had 2 consecutive elevations in ALT or AST.

There were few statistically significant and no clinically meaningful changes in mean vital sign determinations over the course of the study.

Conclusions: The results of this study confirm that ASA administrated 30 minutes before extended-release Niaspan significantly reduces the maximum severity and incidence of flushing, the most common adverse event associated with niacin therapy. These improvements translated into a reduction in the proportion of subjects who discontinued Niaspan because of flushing or any other reason. Results also suggest that beginning ASA therapy 1 week before the initiation of Niaspan treatment may reduce further the severity of flushing during Niaspan administration. Overall, the results of this study suggest that a clinically meaningful reduction in Niaspan-induced flushing may be achieved with ASA, a well-characterized agent with a long-standing history, administered 30 minutes before Niaspan dosing.