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Efficacy and safety of ABT-335 (fenofibric acid) in combination with rosuvastatin in patients with mixed dyslipidemia: A phase 3 study

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ABSTRACT

Objective: To evaluate a new formulation of fenofibric acid (ABT-335) co-administered with 2 doses of rosuvastatin in patients with mixed dyslipidemia.
Methods: In a phase 3, multicenter, randomized, double-blind, active-controlled study, a total of 1445 patients with LDL-C ≥ 130 mg/dL, TG ≥ 150 mg/dL, and HDL-C < 40 mg/dL (<50 mg/dL for women) were randomized to either ABT-335 (135 mg), rosuvastatin (10, 20, or 40 mg), or ABT-335 + rosuvastatin 10 or 20 mg, and treated for 12 weeks. The primary efficacy comparisons were mean percent change in HDL-C and TG (ABT-335 + rosuvastatin vs. corresponding dose of rosuvastatin), and LDL-C (ABT-335 + rosuvastatin vs. ABT-335).
Results: Combination therapy with ABT-335 + rosuvastatin 10 mg resulted in significantly ($p < 0.001$) greater improvements in HDL-C (20.3% vs. 8.5%) and TG (−47.1% vs. −24.4%) compared to rosuvastatin 10 mg; and LDL-C (−37.2% vs. −6.5%) compared to ABT-335. Similarly, significantly ($p < 0.001$) greater improvements were observed with ABT-335 + rosuvastatin 20 mg in HDL-C (19.0% vs. 10.3%) and TG (−42.9% vs. −25.6%) compared to rosuvastatin 20 mg; and LDL-C (−38.8% vs. −6.5%) compared to ABT-335 monotherapy. Greater improvements in multiple secondary endpoints were noted with combination therapy compared to prespecified monotherapies. Both combination therapy doses were generally well tolerated, with a safety profile consistent with ABT-335 and rosuvastatin monotherapies. No rhabdomyolysis or unexpected hepatic, renal, or muscle safety signals were identified.
Conclusion: In patients with mixed dyslipidemia, combination therapy with ABT-335 + rosuvastatin resulted in more effective control of multiple lipid parameters than either monotherapy alone, with a safety profile similar to both monotherapies. This combination may be an appropriate therapeutic option to treat mixed dyslipidemia.

1. Introduction

Mixed dyslipidemia, also referred to as atherogenic dyslipidemia [1], is highly prevalent in the US [2] and is characterized by elevated triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C). In addition to elevated LDL-C, both low HDL-C and elevated TG are increasingly being recognized as independent risk factors for coronary heart disease (CHD) [3–6], and the presence of all 3 lipid abnormalities is associated with higher risk for CHD than elevated LDL-C alone [2]. Initial treatment options suggested by the National Cholesterol Education Program, Adult Treatment Panel III include lifestyle changes and LDL-C-lowering therapy with statins [1]. However, in patients with mixed dyslipidemia, statin monotherapy is often insufficient to normalize multiple lipid parameters.

When fibrates, which activate peroxisome proliferators-activated receptor alpha (PPARα), are combined with statins, they offer the potential for greater lipid control in patients with mixed dyslipidemia and results of several short-term studies in diverse patient populations support that premise [7–10]. However, no currently available fibrate has a labeled indication for combination with a statin, due primarily to a paucity of large, randomized, controlled clinical trials with comprehensive databases to formulate

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evidence-based decisions. The study described herein is part of a large comprehensive clinical program that attempts to provide this needed lipid efficacy and safety data on fibrate and statin combination therapy. In addition, the ongoing ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, which is evaluating the effects of the combination of simvastatin and fenofibrate vs. simvastatin alone on cardiovascular outcomes in patients with type 2 diabetes mellitus will provide substantial safety information concerning this combination [11].

Given that the FDA- required prescribing information for both statins and fibrates recommend that clinicians avoid the use of this combination unless the benefit of additional improvements in lipid levels are likely to outweigh the potential for increased risk of adverse events, the clinical trial demonstration that a fibrate can be used safely and effectively in combination with statins would provide a reassuring treatment option for patients with mixed dyslipidemia.

Of the currently available fibrates, fenofibrate has a relatively low potential for interaction with statins based on pharmacokinetic drug interaction studies as well as the observed lower rates of rhabdomyolysis with the combination of fenofibrate and statins compared with gemfibrozil and statins [12]. Fenofibrate is an ester of fenofibric acid and requires enzymatic cleavage to form fenofibric acid, the active metabolite. ABT-335 is a newly developed choline salt of fenofibric acid, and is more hydrophilic than fenofibrate. ABT-335 does not require first pass hepatic metabolism to become active, as it dissociates to the free fenofibric acid within the gastrointestinal tract, which is rapidly absorbed throughout the gastrointestinal tract. The clinical trial described here evaluates the combination of ABT-335 and 2 different doses of rosuvastatin on multiple lipid parameters in patients with mixed dyslipidemia over a treatment period of 12 weeks.

2. Methods

2.1. Patients and study sites

Men and non-pregnant women ≥18 years of age with mixed dyslipidemia, defined as fasting TG ≥150 mg/dL, HDL-C <40 mg/dL for men or <50 mg/dL for women, and LDL-C ≥130 mg/dL, who signed informed consent were included in this study. The primary exclusion criteria included evidence of unstable cardiovascular disease or other significant medical conditions (e.g., type 1 diabetes mellitus), Asian ancestry, and significantly abnormal laboratory analyses of liver, renal, muscle, or thyroid function. Patients with controlled type 2 diabetes mellitus (HbA1c ≤8.5%) and stable CHD could participate. The full inclusion and exclusion criteria and study design are described separately [13]. The first patient received the first dose of study drug on 21 March 2006 and the last patient completed dosing on 14 December 2006.

Two hundred twenty-four (224) sites in the US (including Puerto Rico) and Canada screened patients and 205 sites randomized patients. The protocol was approved by the appropriate ethics committees and institutional review boards at each participating institution, and the study was conducted under the guidelines established by Good Clinical Practice and the International Conference on Harmonization.

2.2. Treatment groups and study design

At baseline, eligible patients were randomized in a double-blind 2:2:2:2:2:1 ratio to ABT-335 (135 mg) + rosuvastatin 10 mg, ABT-335 + rosuvastatin 20 mg, or monotherapy with ABT-335, rosuvastatin 10, 20, or 40 mg. The rosuvastatin 40 mg monotherapy treatment group enrolled half as many patients as the other treatment groups and was not used in formal statistical comparisons, but served as a clinically relevant reference for assessment of efficacy and safety. Randomization was stratified by diabetic status (diabetic or non-diabetic) and screening TG level (≤250 or >250 mg/dL). The site, subject, and sponsor personnel remained blinded to the lipid/lipoprotein values obtained after the baseline visit.

The total duration of the study was 22 weeks, including a 6-week screening/lipid medication washout period, a 12-week treatment period, and a 30-day safety evaluation. At least 42 days before the baseline visit, patients were screened and instructed to discontinue use of excluded medications, including any lipid-lowering medication, and agreed to adhere to the American Heart Association (AHA) diet [14]. Approximately 1 week before the baseline visit, fasting serum lipid profiles were obtained and study eligibility was determined (all laboratory samples were processed by Covance Central Laboratory Services, Indianapolis, IN).

Patients were instructed to take all study medication at approximately the same time of day, with or without food. At the baseline, interim, and final visits, ≥12-h fasting blood samples were taken for the following laboratory measurements: LDL-C (directly measured), HDL-C, TG, non-HDL-C, VLDL-C, total cholesterol (TC), high sensitivity C-reactive protein (hsCRP), and apolipoprotein B (apoB). Routine hematology and clinical chemistry measurements were also performed. Adverse events (AEs) were assessed and recorded at each visit.

2.3. Primary and secondary efficacy endpoints

Statistical comparisons were performed separately for each dose of combination therapy. The primary efficacy endpoint was a composite of the mean percent changes from baseline to final values in HDL-C, TG, and LDL-C levels. The prespecified statistical comparisons for changes in HDL-C and TG were between ABT-335 + rosuvastatin 10 or 20 mg vs. rosuvastatin 10 or 20 mg monotherapy, respectively. The prespecified comparison for change in LDL-C was between ABT-335 + rosuvastatin 10 or 20 mg vs. ABT-335 monotherapy. The secondary endpoints were tested in a fixed sequence, separately for each combination therapy group that resulted in statistically significantly greater improvements for all 3 primary endpoints. The initial comparison was for non-HDL-C, comparing ABT-335 + rosuvastatin vs. ABT-335 monotherapy. The order of the remaining comparisons was non-HDL-C, VLDL-C, TC, apoB, and hsCRP, and each evaluated ABT-335 + rosuvastatin 10 or 20 mg compared to rosuvastatin 10 or 20 mg monotherapy, respectively.

2.4. Sample size determination and statistical methods

The planned total study sample size of 1254 patients assumed a 10% loss to follow-up rate and was based on the primary efficacy endpoints [8]. The sample size provided >99% power to detect, relative to monotherapy, 17% and 43% decreases in TG and LDL-C, respectively, and 92% power to detect, relative to monotherapy, a 5% increase in HDL-C. Standard deviations of 30%, 15%, and 15% for TG, LDL-C, and HDL-C, respectively, were assumed. The overall power to show a significantly greater effect for both combination doses was 85%.

For the primary and secondary efficacy variables, the percent changes were compared between the combination therapy groups and each corresponding monotherapy group using contrast statements within an analysis of covariance (ANCOVA) with the baseline lipid value (lipid parameter corresponding to the outcome variable being modeled) as a covariate and with effects for treatment group, diabetic status, screening TG level, and the interaction of diabetic status by screening TG level. For a particular dose of