2 EFFICACY AND SAFETY OF IMPLITAPIDE (BAY 13-9952), A MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN INHIBITOR, IN PATIENTS WITH PRIMARY HYPERCHOLESTEROLEMIA

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ABSTRACT

Background

The inhibition of the Microsomal Triglyceride Transfer Protein (MTP) is an attractive target in the management of dyslipidemia. First administration of a novel MTP inhibitor, implitapide, to human volunteers yielded promising results. Subsequently, a dose-ranging study, of a double-blind, placebo-controlled and parallel-group design, comparing the efficacy and the safety of 4 doses of implitapide (20, 40, 80 and 160 mg/day) and cerivastatin (0.3 mg/day) in patients with primary hypercholesterolemia, was carried out.

Methods and Results

After a 4-week placebo period, 309 patients with primary hypercholesterolemia (LDL-C ≥ 130 mg/dL and TG <350 mg/dL) were randomized to one of the 6 treatment groups for a period of 4 weeks. Mean % change from baseline to endpoint (last treatment visit or end of trial) in the valid for efficacy population (N=283) for LDL-C ranged from -8.2% at low dose (20 mg) to -55.1% ($p < 0.001$ compared to placebo) on high dose (160 mg), compared to -33.3% for 0.3 mg cerivastatin and -0.2% for placebo. The analysis of response defined by a greater than 15% decrease of LDL-C showed a 31.4% responder rate for implitapide 20 mg, increasing to 67.9%, 97.8%, and 100% in the 40 mg, 80 mg, and 160 mg groups respectively. Mean % change from baseline to endpoint for the other lipid parameters also showed a significant dose-related decrease, ranging from -6.4% with 20 mg to -4.8% with 160 mg for total cholesterol, from -1.8% to -17.9% for HDL-C, from -1.3% to -29% for triglycerides, from -2% to -22.3% for Apo A1, and from -5.7% to -49% for Apo B. Changes in Lp(a) did not follow the same dose-dependent response. The percentage of adverse events (AE) increased with the dose of implitapide with a high incidence of digestive AE (mainly diarrhoea) in the 80 and 160 mg groups. The percentages of patients with elevations in transaminases >3 times the upper limit of normal were 11.8% and 15.4% for AST, 27.4% and 25% for ALT in groups receiving respectively 80 and 160 mg of implitapide. Only minor changes were observed in mean vitamin A values, and vitamin E/LDL-C or vitamin E/ApoA1 ratios did not change significantly. Lung function tests and hepatic ultrasound did not show any relevant clinically significant abnormality, and liver fatty infiltration remained mild and evenly distributed among the 6 treatment groups.

Conclusions

Implitapide 20 to 160 mg led to a dose-dependent decrease in LDL-C from 8 to 55% and in addition a dose-dependent reduction in total cholesterol, ApoB, HDL-C and triglycerides. The tolerability of implitapide in the higher doses, especially 80 mg and 160 mg, is less acceptable than that of lower doses or that of placebo and cerivastatin, mainly in terms of digestive adverse events and incidence of liver function test abnormalities.

INTRODUCTION

Recently published outcome studies have established that lipid-lowering therapy, particularly with statins, is of clear benefit in terms of cardiovascular morbidity and mortality in the primary and secondary prevention of coronary heart disease[1-5]. International and national guidelines have been derived from these findings, and provide cardiologists and physicians with clear recommendations on lifestyle, risk factor, and therapeutic targets for patients with hyperlipidemia[6,7]. These guidelines recommend bile acid sequestrants, nicotinic acid, fibrates and HMG-CoA reductase inhibitors if dietary therapy is not sufficient to reach therapeutic targets. Thus, research has intensely focused on the discovery of novel agents which can also effectively control plasma lipid levels.

Microsomal triglyceride transfer protein (MTP) is an enzyme present in liver and intestinal cells which catalyses the assembly of cholesterol, triglycerides and ApoB to VLDL or chylomicrons, respectively. Hence, the production rate of Apolipoprotein B containing particles is decreased if MTP is inhibited and a marked positive effect can be expected from MTP inhibition on both hypercholesterolemia and hypertriglyceridemia. BAY 13-9952 (implitapide) is a MTP inhibitor. Implitapide potently inhibits secretion of apoB-containing VLDL-like lipoproteins from human hepatoma cell line (HepG2), with an IC value of 1.1nM[8]. Implitapide was also shown to suppress MTP-catalyzed transport of triglycerides[9].

This study is the first to date to present clinical efficacy and safety data in a considerable number of humans, evaluating implitapide in doses ranging from 20 mg to 160 mg once daily, in the treatment of primary hypercholesterolaemia. As this is an early phase II dose-ranging study, the 4 doses of Bay 13-9952 were compared to placebo and to an active comparator, cerivastatin 0.3 mg.

METHODS

Study design

This was a multicenter, multinational, double-blind, randomised, placebo-controlled, pilot dose-ranging, 6-parallel-group comparative study. Four doses of implitapide, 20 mg, 40 mg, 80 mg, and 160 mg once daily, were compared to placebo and to cerivastatin 0.3 mg once daily, during a 4-week treatment period. The study was performed in 25 sites, distributed over Belgium, France, Israel, Netherlands, Norway, Spain and South Africa. The study was carried out according to the guidelines of Good Clinical Practice, and the Declaration of Helsinki, and was approved by all local ethics committees and institutional Review Boards. Written informed consent was obtained from all patients before enrollment into the study.

Study population

Study participants were men and post-menopausal or surgically sterile women, aged 18 to 70 years old. They had to present with primary hypercholesterolemia, defined by fasting LDL-C ≥ 130 mg/dl (or 3.37 mmol/l) and fasting plasma triglycerides < 350 mg/dl (3.99 mmol/l) after at least 4 weeks on AHA step 1 or equivalent diet. Patients were followed 8 to 12 weeks during the run-in period, including 4 weeks placebo, followed by 4 weeks of randomised study treatment and by 2 weeks of post-treatment follow-up. To be eligible for randomisation, the two values of the calculated LDL-C during the run-in

period (week–4 and week –2) had to be ≥ 130 mg/dl, and could not differ from the mean of these two values by more than 12%. Major exclusion criteria were: recent myocardial infarction or cerebrovascular accidents, diabetes mellitus, endocrine disease, known cataract, serum CPK ≥ 3 times the upper limit of normal, hepatic disease or transaminase levels > 1.5 times the upper limit of normal, clinically significant abnormality on hepatic ultrasound or pulmonary function test performed before randomisation, known intolerance to HMG-CoA reductase inhibitors, treatment with immunosuppressants, antiacids, ketoconazole, erythromycin, oral anticoagulants, digoxin, drug or alcohol abuse, compliance under 70% during placebo run-in.

Outcome measures and assessments

All laboratory assessments were assayed in a single central laboratory, Central Research Laboratories Europe, in Belgium. Plasma lipid parameters remained blinded, all other laboratory results were faxed to the investigator.

Evaluation of efficacy

The primary efficacy parameter was the mean percent change from baseline to endpoint (end of trial visit 8 or last visit) of calculated LDL-C, as well as the percentage of patients with a decrease of 15% in calculated LDL-C, at least, between baseline and endpoint. Secondary efficacy measures included percent change from baseline to endpoint of total cholesterol, HDL-cholesterol, triglycerides, apolipoprotein (Apo) A1, Apo B, and Lp(a).

Evaluation of safety

Adverse events were recorded at each visit following open questioning by the investigator. Their relation to study drug and intensity was also assessed by the investigator. Safety laboratory parameters, including hepatic enzymes, creatinine phosphokinase, vitamin E and vitamin A, biochemistry parameters, were performed at each visit. An ultrasound scan of the liver was performed before randomisation, as well as pulmonary function tests. These two examinations were performed again at the end of the 4-week active treatment period.

Statistical analysis

The primary efficacy analysis was percentage change from baseline to endpoint of fasting plasma levels of calculated LDL-C, in four doses of implitapide, compared to placebo and cerivastatin. The primary analysis was performed on the population of patients valid for efficacy (per protocol analysis), defined as all randomised patients receiving double blind study medication without violating major inclusion/exclusion and randomisation criteria, with at least two valid values of plasma LDL-C measured at weeks -4, -2 and 0, and within 12% of the mean, and with at least one valid plasma LDL-C measurement available after at least 14 days treatment post randomisation, and unbroken random codes. All statistical tests were two-tailed and statistical significance was evaluated at the 5% level. The primary efficacy analysis was performed using an ANOVA model with treatment group and country as main effects. Treatment group comparisons were performed for demographic characteristics and baseline lipid values using ANOVA for continuous data or Mantel-Haenzsel Chi square test for categorical data. Treatment group comparability was checked for all parameters. Patients valid for safety were compared between groups for

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