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Efficacy and safety of the cholesteryl ester transfer protein inhibitor anacetrapib in Japanese patients with heterozygous familial hypercholesterolemia

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ABSTRACT

Background and aims: This multicenter, randomized, double-blind, placebo-controlled study assessed the lipid-modifying efficacy/safety profile of anacetrapib 100 mg added to ongoing statin ± other lipid-modifying therapies (LMT) in Japanese patients with heterozygous familial hypercholesterolemia (HeFH).
Methods: Patients 18–80 years with a genotype-confirmed/clinical diagnosis of HeFH who were on a stable dose of statin ± other LMT for ≥6 weeks and with an LDL-C concentration ≥100 mg/dL were randomized to anacetrapib 100 mg (n = 34) or placebo (n = 34) for 12 weeks, followed by a 12-week off-drug reversal phase. The primary endpoints were percent change from baseline in LDL-C (beta-quantification method [BQ]) and safety/tolerability.
Results: At Week 12, treatment with anacetrapib reduced LDL-C (BQ) compared to placebo and resulting in a between-group difference of 29.8% (95% CI: −38.6 to −21.0; $p < 0.001$) favoring anacetrapib. Anacetrapib also reduced non-HDL-C (23. 6%; $p < 0.001$), ApoB (14.1%; $p < 0.001$) and Lp(a) (48.7%; $p < 0.001$), and increased HDL-C (110.0%; $p < 0.001$) and ApoA1 (48.2%; $p < 0.001$) versus placebo. Anacetrapib 100 mg added to ongoing therapy with statin ± other LMT for 12 weeks was generally well-tolerated. There were no differences between the groups in the proportion of patients who discontinued drug due to an adverse event or abnormalities in liver enzymes, creatinine kinase, blood pressure, electrolytes or adjudicated cardiovascular events.
Conclusions: In Japanese patients with HeFH, treatment with anacetrapib 100 mg for 12 weeks resulted in substantial reductions in LDL-C and increases in HDL-C and was well tolerated.
(ClinicalTrials.gov NCT01824238)

1. Introduction

Familial Hypercholesterolemia (FH) is a genetic disorder of lipoprotein metabolism, characterized by high LDL cholesterol (LDL-C) levels and premature cardiovascular (CV) disease [1]. Inheritance follows a predominantly autosomal dominant or co-dominant pattern (i.e., either biallelic mutations in one gene or two different mutations in the same or different candidate genes), with more severe clinical symptoms and nearly twice the cholesterol

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levels in homozygotes versus heterozygotes (HeFH) [2,3]. The specific mutations underlying this disease include genes encoding the LDL receptor (*LDLR;* most common mutation), apolipoprotein (Apo) B (*APOB*), proprotein convertase subtilisin/kexin type 9 (*PCSK9*) and low-density lipoprotein receptor adaptor protein (*LDLRAP*) [1,4–6].

The goal of treatment in FH patients is to adequately reduce LDL-C levels through lifestyle/diet intervention and/or pharmacologic therapy depending on the patient's overall CV risk [7–9]. Treatment guidelines emphasize the use of aggressive cholesterol-lowering strategies in FH patients [2,9–14]. Statins remain the cornerstone of treatment [15–18]; however, other lipid-lowering drugs may be used concurrently because monotherapy fails to adequately reduce LDL-C in a large proportion of FH patients [8,12,19]. Issues with statin intolerance sometime necessitates use of other lipid-lowering drugs. Since current treatments for FH are often suboptimal, there remains a compelling unmet medical need for agents that aggressively lower LDL-C [8,20].

Cholesteryl ester transfer protein (CETP) is a plasma protein that mediates the heteroexchange of cholesteryl esters and triglycerides (TG) between high density lipoproteins (HDL) and atherogenic Apo B-containing lipoproteins, especially very low density lipoprotein (VLDL) [21]. Reduction in CETP activity resulting from genetic mutations or pharmacologic inhibition is associated with decreased levels of Apo B-containing particles (including LDL) and increased levels of HDL-C. A prior report documented a low incidence of coronary heart disease in a group of Japanese patients lacking CETP [22]; however, there is widely conflicting evidence on the prevalence of CV disease in CETP-deficient subjects [23,24]. Three large outcomes trials of CETP inhibitors failed to demonstrate clinical efficacy. One study showed an excess of CV events and death following toracetrapib treatment, likely attributable to off-target effects on aldosterone, blood pressure (BP) and serum electrolytes [25]. Two other trials were terminated early because of lack of clinical efficacy at their interim analyses in the absence of any safety signals; one trial employed the less potent lipid-modifying CETP inhibitor, dalcetrapib, while the other employed the more potent lipid-modifying CETP inhibitor, evacetrapib [26]. Taken together, the lack of clinical benefit seen in these prior studies raises the question of whether CETP inhibitors represent a viable treatment in patients with dyslipidemia [27].

A fourth CETP inhibitor, anacetrapib, is an orally active, potent, selective CETP inhibitor currently in Phase 3 clinical development in the ongoing REVEAL study (NCT01252953). REVEAL will assess the potential impact of this agent on CV outcomes in 30,000-patients with dyslipidemia. In dose-ranging studies conducted in both Japanese and non-Japanese patients, the maximum LDL-C and HDL-C-altering effects of anacetrapib reached a plateau at the 100 mg dose thus establishing it as the clinical dose [28,29]. A 1.5-year safety study conducted in 1623 statin-treated patients at high risk of coronary artery disease reported substantial reductions in LDL-C (36%) with an overall favorable safety profile versus placebo, with no associated effects on BP, aldosterone levels, serum electrolytes or increased CV risk [30]. Moreover, a recent worldwide study conducted in HeFH patients receiving optimal lipid-lowering therapy reported substantial LDL-C reductions of ~40% following concomitant treatment with anacetrapib 100 mg/day for 52 weeks [31]. The large incremental reduction in LDL-C seen in that study holds promise for HeFH patients who are unable to achieve LDL-C goals despite the use of maximal lipid-lowering therapy.

This study assessed the safety and efficacy of anacetrapib 100 mg administered orally once-daily in Japanese patients with HeFH who had LDL-C concentrations of 100 mg/dL or higher despite optimal lipid-lowering therapy.

2. Materials and methods

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of 12-weeks in duration (Merck & Co., Inc., MK-0859 Protocol number 050; registered on ClinicalTrials.gov NCT01824238; Supplementary Fig. 1). After screening and a 2-week, single-blind, placebo run-in period, 68 eligible patients were randomly allocated in equal proportions to treatment with anacetrapib 100 mg (n = 34) or placebo (n = 34) for 12 weeks followed by a post-study follow-up visit occurring 12 weeks after the last dose of study drug/reversal phase (early discontinuation or completion of study drug phase). All patients who discontinued were contacted at their intended Week 24 visit date to assess for serious CV adverse events and all-cause death.

This study was conducted at 16 sites in Japan between February 13, 2013 and May 16, 2014. All participants provided written informed consent before the initiation of study procedures. The study protocol was approved by the appropriate institutional review boards. This study was conducted in accordance with Good Clinical Practice Guidelines, the Declaration of Helsinki as well as other statutes and regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

Eligible patients included adult men and women, 18–80 years of age, with a genotype-confirmed or clinical diagnosis of HeFH. Details of the diagnosis criteria can be found in a published report of a similarly designed study [31]. Eligible patients had to be on an stable dose of a statin and could also be taking one or more other LMTs for ≥6 weeks prior to the screening visit with an LDL-C >100 mg/dL. Patients were required to remain on their regimen of statin ± other LMT throughout the study.

The primary efficacy endpoint was percent change from baseline in plasma levels of LDL-C at Week 12 (measured by the β-quantification [BQ] method) [32]. The secondary efficacy endpoints included percent change from baseline in HDL-C (key secondary endpoint), non-HDL-C, Apo B, Apo A1 and lipoprotein (a) [Lp (a)] at Week 12 following treatment with anacetrapib 100 mg versus placebo. Exploratory endpoints of interest included total cholesterol (TC), triglycerides (TG), Apo E, VLDL-C, VLDL-TG, LDL-C estimated by Friedewald's method, LDL-C (Direct), CETP activity and CETP concentration and the proportion of patients reaching LDL-C goal <100 mg/dL at Week 12.

The safety and tolerability of anacetrapib were assessed through the following pre-specified safety parameters: physical examinations, vital signs, BP, adverse events (AEs), and routine hematology, chemistry and urinalysis surveillance. Laboratory safety measurements included alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), and electrolytes (potassium, sodium, chloride and bicarbonate). Serious CV AEs and all-cause deaths occurring during the treatment phase and the protocol-specified off-drug reversal phase were adjudicated by an independent adjudication committee.

Laboratory and other measurements, except for Lp(a), CETP concentration, CETP activity and plasma anacetrapib concentrations, were performed by SRL Inc. (Tokyo, Japan). Lipid efficacy measurements were analyzed by PPD Global Central Laboratories, Singapore. Plasma CETP concentration was analyzed by PPD Global Central Laboratories, USA. Lp(a) was analyzed by Northwest Lipid Research Laboratories (Seattle, WA, USA). CETP activity was analyzed by Tandem Labs Biotechnology Services A LabCorp Company (New Jersey, USA). Comprehensive genetic analyses were performed at Academic Medical Center, Amsterdam, The Netherlands. Plasma cholesterol and TG were quantified by a standardized enzymatic assay. LDL-C was measured using β-quantification ([BQ] primary endpoint), and Friedewald method