Effects of Food Intake on the Pharmacokinetic Properties of Dalcetrapib: Findings From Three Phase I, Single-Dose Crossover Studies in Healthy Volunteers

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ABSTRACT

Background: Preclinical studies have reported that the relative bioavailability of dalcetrapib, a modulator of cholesteryl ester transfer protein (CETP) inhibitor activity, was ~60% higher when administered in the fed state compared with the fasting state.

Objective: This article reports on 3 studies conducted to assess the effects of food intake, timing of administration with respect to meals, and meal size and content on the relative bioavailability of dalcetrapib in healthy male subjects.

Methods: Three Phase I studies were performed in healthy subjects: (1) a 2-period crossover study of a single dose of dalcetrapib 900 mg administered in the fed and fasting states (fed versus fasting study [1999]); (2) a 3-period crossover study of a single dose of dalcetrapib 600 mg administered after a light morning meal, a standard evening meal, and a light evening meal (meal timing/size study [2005]); and (3) a 4-period crossover study of a single dose of dalcetrapib 600 mg administered 30 minutes after a high-fat meal or a standard evening meal, and 30 minutes before or 3 hours after the latter (high-fat meal study [2007]). Blood samples for pharmacokinetic analyses (AUC_{0-36} or $AUC_{0-\infty}$, C_{max}) were collected up to 36, 144, and 96 hours after study drug administration in the fed versus fasting, meal timing/size, and high-fat meal studies, respectively. CETP activity was measured using a radioisotopic method in the fed versus fasting study and a fluorometric method in the meal timing/size and high-fat meal studies. Tolerability was assessed using monitoring of adverse events, laboratory parameters, vital signs, and ECG.

Results: Six men were enrolled in the fed versus fasting study (mean age, 37 years; mean body mass index [BMI], 23.6 kg/m^2). Dalcetrapib exposure was increased by 64% (AUC_{0-36}) and 126% (C_{max}) after administration in the fed state. Eighteen men were enrolled in the analysis of the effects of meal timing and size on the properties of dalcetrapib (mean age, 30.5 years; mean BMI, 25.1 kg/m^2). When dalcetrapib was administered after a light morning or a light evening meal, comparable values were found for mean dalcetrapib $AUC_{0-\infty}$ (7400 and 7860 ng · h/mL, respectively) and C_{max} (589 and 552 ng/mL), whereas administration after a standard evening meal was associated with increased $AUC_{0-\infty}$ (14.3%–14.7%) and C_{max} (25.5%–35.3%). Forty-nine men were included in the analysis in the high-fat meal study (mean age, 32.3 years; mean BMI, 23.9 kg/m^2). Compared with administration after a standard evening meal, administration after a high-fat evening meal was associated with increased $AUC_{0-\infty}$ (34.9%) and C_{max} (43.7%). Between-treatment differences in exposure within each study also were reflected in apparent differences in CETP activity. All treatments were generally well tolerated.

Conclusions: Dalcetrapib exposure was increased in the fed state and, to a lesser extent, was dependent on the size and fat content of the meal. Exposure was independent of dosing time. Dalcetrapib was generally well tolerated. (*Clin Ther.* 2011;33:754–765) © 2011 Elsevier HS Journals, Inc. All rights reserved.

Key words: AUC, CETP, dalcetrapib, fasting, fed, HDL-C.

INTRODUCTION

Many factors contribute to increased cardiovascular risk including disturbances of LDL-C or HDL-C con-

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centrations. Despite aggressive LDL-C lowering with statins, a large proportion of patients at high cardiovascular risk continue to experience new or additional cardiovascular events.[1–3] HDL-C is an independent, inverse predictor of cardiovascular disease (CVD) risk,[4,5] and low baseline HDL-C concentrations remain predictive of major cardiovascular events, even in patients receiving aggressive statin therapy.[1] The limited efficacy and tolerability of available HDL-C–raising agents[6] has prompted a search for novel strategies. Genetic and epidemiologic studies that have reported associations between cholesteryl ester transfer protein (CETP) activity and HDL-C concentration and CVD risk have suggested that targeting CETP activity may be a potential strategy for increasing HDL-C concentrations and reducing the risk for cardiovascular events.[7–12]

Dalcetrapib, an agent that targets CETP activity and that is in development for the prevention of cardiovascular events, has been reported to be associated with increased HDL-C concentrations (by ~30%).[13–16] Pharmacokinetic studies have reported that dalcetrapib had neither clinically relevant effects on the major cytochrome P450 isoforms[17] nor significant interactions with statins.[18,19] Because dalcetrapib is highly lipophilic and poorly soluble, increased exposure might be expected when the drug is administered with food.[20]

This article reports on 3 single-center studies that evaluated the effects of food intake, timing of administration with respect to meals, and meal size and content on the relative bioavailability and CETP activity of dalcetrapib in healthy male subjects.

SUBJECTS AND METHODS

Study Subjects

Volunteers were eligible if they were male and considered healthy according to standard screening assessments, and if aged 18 to 45 years with a body mass index (BMI) of 19 to 27 kg/m^2 (fed versus fasting study) or aged between 18 and 65 years with a BMI of 18 to 32 kg/m^2 (meal timing/size and high-fat meal studies).

Major exclusion criteria were the use of other medications and/or vitamins and supplements; history of major disease or infections; clinically relevant abnormal laboratory results, including persistent or unexplained elevations in liver enzymes or serology test results positive for HIV-1 or -2 and/or hepatitis B and/or C virus; a clinically relevant history of drug or alcohol misuse or abuse (or, in the meal timing/size and high-fat meal studies, a positive drug urine or alcohol breath test at screening); significant (>450–500 mL), recent (up to 3 months before screening) blood loss or donation (meal timing/size and high-fat meal studies) or significant (>1000–1200 mL) blood loss or donation in the preceding 12 months (fed versus fasting study); and/or participation in a clinical study with an investigational drug within the preceding 3 to 4 months. Subjects with any disease or condition that, in the opinion of the investigator, might have caused them undue risk or interfered with the pharmacokinetic assessments or the subjects' ability to complete the study also were excluded. Subjects who smoked (>5 cigarettes, 3 tobacco pipes, or 3 cigars per day), followed a special diet, or were unwilling to use barrier contraception during and for 2 months after the end of the study (meal timing/size study); those with a mean alcohol intake >28 units/wk (fed versus fasting study; *unit* defined as 285 mL of beer, 25 mL of spirits, or 125 mL of wine) or ≥21 units/wk (high-fat meal study); and those under judicial supervision or guardianship or curatorship (high-fat meal study) also were excluded. Additionally, in the fed versus fasting study, subjects with a history of multiple drug or clinically significant drug allergies (with the exception of inactive hayfever), including a known allergy to the study drug and/or to medications chemically related to the study drug, and those with a supine resting systolic/diastolic blood pressure <100/<50 or >150/>90 mm Hg or a heart rate <40 or >90 beats/min were excluded.

Study Design

The fed versus fasting study (1999) was conducted by Japan Tobacco International SA, Tokyo, Japan, at the Clinical Research Unit, Covance Inc., Leeds, United Kingdom. The meal timing/size (2005) and high-fat meal (2007) studies were conducted at the Clinical Pharmacology Unit, F. Hoffmann-La Roche Ltd., Strasbourg, France. All 3 studies were conducted in accordance with the principles of the Declaration of Helsinki[21] and the Good Clinical Practice guideline.[22] Each subject provided written informed consent. All of the study protocols were approved by independent ethics committees (fed versus fasting, Covance Clinical Research Unit Independent Review Board; meal timing/size, Comité Consultatif de Protection des Personnes se prêtant à la Recherche Biomédicale d'Alsace