Single-Dose, Randomized Crossover Comparisons of Different-Strength Imatinib Mesylate Formulations in Healthy Korean Male Subjects

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ABSTRACT

Background: Imatinib mesylate is used to treat chronic myeloid leukemia and advanced gastrointestinal stromal tumors.

Objective: The purpose of this study was to compare the pharmacokinetics of 2 different strengths of the imatinib formulation containing 100 mg (reference) and 400 mg (test) to satisfy the regulatory requirement for marketing.

Methods: A single-center, randomized, single-dose, open-label, 2-period, 2-sequence, comparative crossover study with a 14-day washout period was conducted in 30 healthy male volunteers. Plasma samples for the drug analysis were collected up to 72 hours after drug treatment. Participants received either the reference (4 tablets of 100-mg imatinib) or the test (1 tablet of 400-mg imatinib) formulation during the first period and the alternative formulation during the second period. The safety profiles and tolerability of the 2 formulations were also assessed based on physical examinations, laboratory tests, a 12-lead ECG, and vital signs.

Results: Thirty participants were initially enrolled; their mean (SD) age, height, weight, and body mass index were 24.9 (2.0) years (range, 23–30 years), 174 (5) cm (range, 164–185 cm), 69.9 (2.0) kg (range, 54.1–87.4 kg), and 23.0 (2.0) kg/m^2 (range, 18.5–26.9 kg/m^2); 28 healthy participants completed both treatment periods. Two subjects did not complete the study because they withdrew consent for personal reasons. The observed mean (SD) C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ values for the reference formulation were 1792 (357) ng/mL, 28,485 (6274) ng · h/mL, and 29,079 (6371) ng · h/mL, respectively. Corresponding values for the test formulation were 1710 (312) ng/mL, 27,222 (4624) ng · h/mL , and 27,872 (4751) ng · h/mL. The geometric mean ratios (90% CIs) between the 2 formulations at the 400-mg dose of imatinib were 0.9579 (0.9054–1.0136) for C_{max}, 0.9652 (0.9174–1.0155) for AUC_{0-last}, and 0.9679 (0.9203–1.0179) for $AUC_{0-\infty}$, respectively. During the study period, 6 adverse events (3 for the reference and 3 for the test formulation) were reported; all were transient, mild, and resolved completely during the treatment period. There were 4 cases of nausea and 1 case each of dizziness and oropharyngeal pain. Four adverse events were considered related to the study drugs.

Conclusions: The results showed that despite the different strengths of the 2 imatinib formations, the test and reference formulations both met the regulatory criteria for pharmacokinetic equivalence at a dose of imatinib 400 mg in these healthy Korean male subjects. Both imatinib formulations seemed to be generally well tolerated. ClinicalTrials.gov identifier: NCT01270984. (*Clin Ther*. 2013;▮:▮▮▮–▮▮▮)

Key words: imatinib, pharmacokinetic equivalence, pharmacokinetics, bioequivalence.

INTRODUCTION

Protein tyrosine kinase is involved in signal transduction pathways that regulate diverse cellular processes such as growth, differentiation, metabolism, and apoptosis.[1] Deregulated tyrosine kinase activity is associated with the pathogenesis of various cancers,

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including chronic myeloid leukemia (CML) and gastrointestinal stromal tumors, as well as other proliferative diseases.[2]

Imatinib, a phenylaminopyrimidine derivative, is a potent competitive inhibitor of the Bcr-Abl tyrosine kinase. Imatinib competitively inhibits the binding of adenosine triphosphate with the enzyme and thereby inhibits its ability to phosphorylate and activate downstream proteins.[3] Imatinib is well absorbed, with an absolute bioavailability of 98%, and it reaches C_{max} in 2 to 4 hours. Its pharmacokinetic characteristics are linear over a dose of 1000 mg given once daily.[4] Food does not influence the rate or extent of absorption. The $t_{½}$ of imatinib after single-dose administration is ~13 hours, and it is ~95% bound to plasma proteins, mainly to albumins and α_1-acid glycoprotein.[4–6] Cytochrome P450 (CYP) 3A4 and CYP3A5 are the major enzymes responsible for the metabolism of imatinib and other CYP enzymes, including CYP1A2, CYP2D6, CYP2C9, and CYP2C19.[4]

Pharmacokinetics of imatinib may be 1 of the factors that influence its effectiveness clinically. Interestingly, Chinese[7] and Jordanian[8] patients with CML showed higher imatinib trough levels than white CML patients despite the use of a standard dosage regimen.[9] This finding suggests an ethnic variability of imatinib pharmacokinetics, although there is little information regarding ethnic differences in the literature.

The efficacy and tolerability of imatinib 400 mg daily for patients with CML have been reported, and this dosage is suggested as the gold standard pharmacotherapy for this disorder.[10] Imatinib is currently available in Europe and the United States as a 400-mg tablet, but only the 100-mg tablet is available in Korea. The advantages of the 400-mg tablets include convenience for patients, who, in most cases, will need to take only 1 tablet per day (instead of four 100-mg tablets); therefore, this dosage has the potential to improve compliance with long-term treatment.[6,11]

The objective of the present study was to compare the pharmacokinetic characteristics of the new imatinib (ie, test) formulation* containing 400 mg of imatinib per tablet and the conventional formulation containing 100 mg of imatinib† in 4 tablets (ie, reference) in healthy Korean male subjects for the purpose of registration approval of the test formulation.

SUBJECTS AND METHODS

Subjects

Healthy Korean male volunteers aged 20 to 45 years with a body mass index of 18 to 29.9 kg/m^2 were enrolled in the present study. They were judged by physicians to be healthy based on the results of a detailed physical examination, 12-lead ECG, vital signs, and laboratory tests, including chemistry, hematology, and urinalysis. Participants were not eligible if they had any of the following: a history or evidence of a hepatic, renal, gastrointestinal, or hematologic abnormality; hepatitis B, hepatitis C, or HIV infection based on laboratory findings; any other acute or chronic disease; a history of hypersensitivity to imatinib; a history of clinically significant allergic disease; a history of alcohol or drug abuse; repeated medication use within 1 month from the day medicated at another clinical trial; smoked >10 cigarettes daily; consumed >5 glasses daily of beverages containing xanthine derivatives; or used any medication having the potential to affect the study results within 14 days before the start of the study.

The purpose and procedures of the study were explained in detail to the participants before study initiation, and all subjects provided written, informed consent before participating in the study. Participants were supplied with written information that included the study purpose, methods, possible risks, and details of the honorarium that was paid to all participants.

Study Design

This study was performed as a single-dose, randomized, open-label, 2-sequence, 2-period, comparative crossover study with a washout period of 14 days. Thirty subjects were randomly assigned to receive the test or the reference formulation at the beginning of the study in accordance with randomization code generated by SAS version 9.2 (SAS Institute, Inc, Cary, North Carolina).

This study was conducted at the Clinical Trial Center of Anam Hospital, Korea University College

*Trademark: Leukivec® (Chong Kun Dang Pharmaceutical Corp, Seoul, Korea); batch number, MQ001; expiration date, October 12, 2012.

†Trademark: Gleevec® (Novartis Korea, Co, Ltd, Seoul, Korea); batch number, S106; expiration date, January 31, 2013.