Effects of Particle Size, Food, and Capsule Shell Composition on the Oral Bioavailability of Dabrafenib, a BRAF inhibitor, in Patients with BRAF Mutation-Positive Tumors

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ABSTRACT: Dabrafenib is a small-molecule inhibitor of BRAF kinase activity that is currently being developed for the treatment of BRAF V600 mutation-positive melanoma. This clinical, open-label, two-cohort ($n = 14$ per cohort), randomized study was designed to evaluate the effect of drug substance particle size, and food on the plasma pharmacokinetics of a single oral dose of dabrafenib in patients with BRAF V600 mutation-positive solid tumors. In addition, an exploratory cross-cohort comparison of the relative bioavailability of single-dose dabrafenib administered in gelatin and hydroxypropyl methylcellulose (HPMC) capsules was performed. Higher bioavailability was noted with nonmicronized drug substance (larger particle size), under fasting conditions, and with HPMC capsules. Initial dissolution results at pH 1.2 showed higher dissolution of gelatin relative to HPMC capsules inconsistent with clinical data. Subsequent *in vitro* dissolution studies were conducted in fasted-state simulated gastric fluid over a 24-h period and showed that HPMC capsules reached a higher percentage of dabrafenib dissolved than gelatin capsules. The presence of HPMC is believed to inhibit precipitation of dabrafenib as the freebase, thereby maintaining a supersaturated solution over an extended period of time. Dabrafenib has been administered in pivotal clinical studies on an empty stomach using micronized drug substance in HPMC capsules. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:3100–3109, 2013

Keywords: dabrafenib; food effects; particle size; bioavailability; HPMC; gelatin; capsules; supersaturation; dissolution; clinical pharmacokinetics

INTRODUCTION

Dabrafenib (GSK2118436) is a potent and selective small-molecule inhibitor of BRAF kinase activity that is currently being developed for the treatment of BRAF V600 mutation-positive tumors. Dabrafenib has demonstrated antiproliferative activity against multiple BRAF mutation-positive tumor cell lines, and has achieved biomarker suppression and tumor regression in BRAF mutation-positive xenograft models.[1] Clinical activity was first observed in a Phase I, first-time-in-human (FTIH) study, with a

Abbreviations used: FTIH, first-time-in-human; HPMC, hydroxypropyl methylcellulose.

Additional Supporting Information may be found in the online version of this article. Supporting Information

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confirmed response rate of 56% in patients with BRAF V600E mutation-positive melanoma.[2] Efficacy of oral dabrafenib 150 mg twice daily was confirmed in BREAK-3, a Phase III study in patients with BRAF V600E mutation-positive melanoma[3] as well as in BREAK-MB, a Phase II study in patients with melanoma who had brain metastases.[4]

During clinical drug development, dabrafenib has been administered as the mesylate salt, using micronized drug substance. Micronized drug substance was used to mitigate potential risk to content uniformity, especially with the low dosage strength required in the FTIH study, and was continued during drug development. Smaller particle size is typically associated with higher bioavailability for compounds exhibiting solution-/dissolution-rate-limited bioavailability,[5] and the effect of micronization was investigated in the current study.

A preliminary assessment of the effect of food on plasma pharmacokinetics (PKs) was conducted in eight patients enrolled in the FTIH study suggesting a small change in exposure with food as compared with the fasted state. Administration of dabrafenib early formulation in gelatin capsules with a moderate fat/moderate calorie meal at steady state resulted in delayed median time to maximum plasma concentration (t_{max}; 0.50 h), decreased maximum plasma concentration (C_{max}), with a ratio of 0.672 [90% confidence interval (CI) 0.40–1.13], and almost no change in area under the plasma concentration–time curve from time zero to the end of the dosing interval, with a ratio of 1.06 (90% CI 0.67–1.68). A formal assessment of the effect of food using a high-fat, high-calorie meal was investigated in the current study, consistent with regulatory guidances[6] and using the final commercial formulation of dabrafenib.

In early clinical trials,[2,7] dabrafenib mesylate was formulated using a hard gelatin capsule containing a powder blend of drug substance and excipients. Prior to the initiation of pivotal trials,[3,4] the capsule shell was changed from gelatin to hydroxypropyl methylcellulose (hypromellose; HPMC) to improve the shelf life of the product. HPMC capsule shells have been proposed as a good alternative to replace gelatin capsules.[8] On the basis of the original dissolution data, the change in capsule shells was not expected to result in any change in the bioavailability of dabrafenib, consistent with the published data.[9–13]

The current study was designed to evaluate the effect of micronization of the drug substance on the bioavailability of dabrafenib administered using gelatin capsules and to evaluate the effect of a high-fat, high-calorie meal on the bioavailability of dabrafenib administered using HPMC capsules. Because of the safety profile of BRAF inhibitors, which includes the risk of cutaneous squamous cell carcinoma, the study was conducted using single dose administration in patients with BRAF V600E or V600K mutation-positive solid tumors rather than healthy volunteers. Although randomization was not performed across the cohorts, data across cohorts were used to further evaluate the bioavailability of HPMC capsules relative to gelatin capsules. Dissolution studies were conducted *in vitro* to assess the differences between dabrafenib encapsulated in gelatin and HPMC shells and are reported herein.

METHODS

Clinical Study Design

The study protocol (BRF113468, ClinicalTrials.gov registration identifier NCT01231568) was approved by the institutional review boards at each of the four study centers (Pinnacle Oncology, Scottsdale, Arizona; Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah; Karmanos Cancer Institute, Detroit, Michigan; and Sarah Cannon Research Institute/Tennessee Oncology, Nashville, Tennessee), and conducted in accordance with good clinical practice and the guiding principles of the Declaration of Helsinki. All study participants provided written informed consent before study entry.

This was a multicenter, open-label, randomized study in 28 patients with BRAF V600 mutation-positive solid tumors. The study consisted of two cohorts of 14 patients each, and both cohorts were conducted in a randomized two-period, two-sequence, crossover design. Cohort 1 evaluated the effect of particle size using gelatin capsules, whereas Cohort 2 evaluated the effect of food using HPMC capsules. Each patient was enrolled in only one cohort and received the following regimens:

- Cohort 1 (effect of particle size)

  Regimen A: Dabrafenib 150 mg (2 × 75 mg), gelatin capsules with micronized drug substance, and fasted.

  Regimen B: Dabrafenib 150 mg (2 × 75 mg), gelatin capsules with nonmicronized drug substance, and fasted.

- Cohort 2 (food effect)

  Regimen C: Dabrafenib 150 mg (2 × 75 mg), HPMC capsules with micronized drug substance, and fasted.

  Regimen D: Dabrafenib 150 mg (2 × 75 mg), HPMC capsules with micronized drug substance, and fed. The high-fat, high-calorie meal was consistent with regulatory requirements including a total of 1020 calories as 58 g carbohydrates, 33 g protein, and 58–75 g fat.