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Comparative Bioavailability of a Single Dose of Trametinib (TMT212) Containing 9% vs 11% Dimethyl Sulfoxide in Randomized Healthy Volunteers to Assess Long-Term Storage at Room Temperature

Eugene Y. Tan[1], Ovidiu Chiparus[1], Somesh Choudhury[1], Christina Kim[1], Mike Lau[2], Christoph Ziltener[2], and Palanichamy Ilankumaran[1]

Abstract

Storage of trametinib tablets outside of 2-8°C protected from moisture may lead to loss of dimethyl sulfoxide (DMSO) and adversely impact trametinib bioavailability. In this open-label, phase 1, single-dose, randomized, 2-treatment, 2-period crossover study in healthy volunteers, bioavailability of a single 2-mg tablet of trametinib containing 9% DMSO (test formulation), corresponding to the lowest DMSO content in the tablet after storage at 25°C for 36 months, was evaluated vs bioavailability of a 2-mg tablet containing 11% DMSO (reference formulation). Sixty-five percent of subjects (n = 39/65) were men, and mean (standard deviation) age was 45.6 (11.17) years. Time to reach maximum plasma concentration occurred at 1.5 hours after dosing. The geometric mean ratio (90%CI) comparing 2-mg trametinib containing 9% DMSO with 2-mg trametinib containing 11% DMSO for area under the concentration-time curve from time 0 to the last measurable plasma concentration sampling time was 0.890 (0.848-0.935), suggesting the 2 formulations have similar bioavailability. The majority of adverse events were mild, with 1 subject experiencing 1 grade 3 headache. These results indicated that storage of trametinib at room temperatures $\leq$25°C during the overall shelf life of 36 months would not negatively impact trametinib bioavailability.

Keywords

bioavailability, trametinib, healthy volunteers, storage, TMT212

Trametinib (Mekinist) is an allosteric inhibitor of the mitogen-activated kinase 1 and 2 (MEK1 and MEK2) proteins, which play a crucial role in the occurrence and development of several cancers.[1] Trametinib was initially approved as monotherapy for the treatment of adult patients with unresectable or metastatic melanoma and a $BRAF^{V600E}$ *or* $BRAF^{V600K}$ mutation, as these mutations induce hyperactivation of the downstream MEK/extracellular signal-regulated kinase effectors. This approval was based on findings from the phase 3 METRIC (ClinicalTrials.gov: NCT01245062) trial, which demonstrated that trametinib improved progression-free survival and overall survival compared with chemotherapy in patients with unresectable or metastatic cutaneous melanoma with a $BRAF^{V600E/K}$ mutation.[2]

Use of trametinib as monotherapy has been limited by tumor adaptation through activation of parallel pathways, or by acquired resistance through emergence of mutations in *MEK1* and *MEK2*, or through

[1]Novartis Pharmaceuticals, East Hanover, New Jersey, USA
[2]Novartis Pharma AG, Basel, Switzerland

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Corresponding Author:
Eugene Y. Tan, PhD, Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936
(e-mail: eugene.tan@novartis.com)

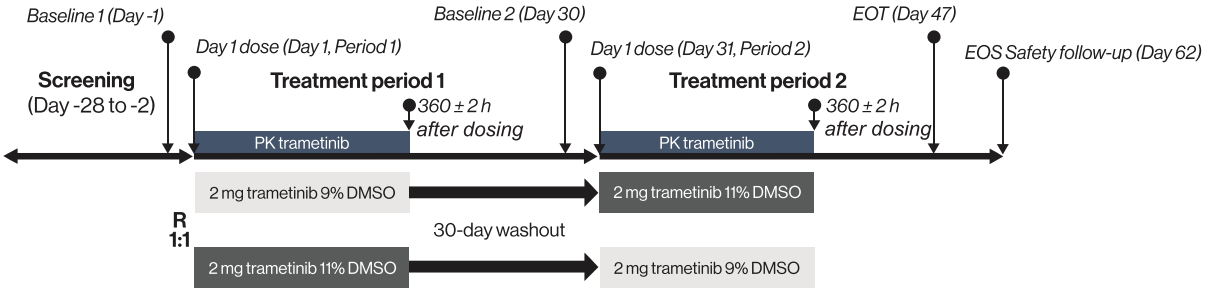

Figure 1. Study diagram. DMSO, dimethyl sulfoxide; EOS, end of study; EOT, end of treatment period; PK, pharmacokinetics; R, randomization.

BRAF^{V600} amplification. The phase 3 COMBI-d (ClinicalTrials.gov: NCT01584648) and COMBI-v (ClinicalTrials.gov: NCT01597908) trials showed that the combination of dabrafenib, a small-molecule inhibitor of BRAF, with trametinib conferred long-term survival benefits in approximately one-third of patients with unresectable or metastatic melanoma,[3] which led to trametinib approval in combination with dabrafenib in this setting. Subsequent trials also led to approval of this combination therapy for the treatment of non–small cell lung cancer,[4] anaplastic thyroid cancer,[5] and for the adjuvant treatment of melanoma with *BRAF*$^{V600E/K}$ mutations.[6]

Trametinib is taken as a 2-mg tablet once daily both in monotherapy and in combination with dabrafenib. The recommended dose of trametinib was based on a phase 1 trial of patients with advanced tumors, which determined that the maximum tolerated dose was 3 mg once daily; however, the 2-mg dose was finally selected based on safety, efficacy, and pharmacology data from the same trial.[7] Pharmacokinetic (PK) studies showed that trametinib is absorbed orally with a median time to achieve peak concentrations (t_{max}) of 1.5 hours after dosing.[7,8] The oral bioavailability of a single 2-mg tablet dose is 72.3%.[8] Elimination of trametinib predominantly occurs via deacetylation alone or in combination with hydroxylation, and most drug-related materials are excreted in the feces.[9]

Trametinib has been developed as a dimethyl sulfoxide (DMSO) solvate form containing ≈11% DMSO because the latter improved trametinib solubility and enhanced its oral absorption over freebase in preclinical studies.[10] Per label requirements, trametinib should be stored refrigerated at 2-8°C (36-46°F) protected from moisture and in the original bottle without removing the desiccant. Storage outside of these conditions may cause loss of DMSO (desolvation), possibly leading to conversion to a less soluble freebase, which subsequently reduces trametinib absorption and bioavailability. However, ambient storage of trametinib tablets may be perceived as more convenient by caregivers and patients. To allow long-term storage of trametinib tablets at up to 25°C, evaluating alterations in DMSO content and associated bioavailability of the active component has been necessary to understand the implications on the intended efficacy. A phase 1 study (ClinicalTrials.gov: NCT01725100) conducted in patients with solid tumors aimed to determine the relative bioavailability of trametinib containing 9.7% DMSO vs trametinib containing 11.3% DMSO showed that the ratio of the geometric least squares mean and 90%CI for corrected area under the concentration-time curve (AUC) over the dosing interval $(AUC)_{0\text{-}t}$, AUC from time 0 extrapolated to infinite time ($AUC_{0\text{-}\infty}$), and maximum (peak) observed plasma concentration (C_{max}) were inside the boundaries (0.8-1.25) for biosimilarity, indicating that the decrease in DMSO content did not alter the bioavailability of the drug (Novartis data on file). In addition, all uncorrected and corrected PK parameters evaluated were similar between the 2 formulations. It is expected that if a 2-mg tablet is stored in climatic zone I (temperate regions with mean annual temperature measured in open air ≤15°C) or zone II (Mediterranean/subtropical regions with mean annual temperature measured in open air of 15-22°C) countries at 25°C for 35 months in a closed bottle and 1 month in-use period, the lowest possible reduction in DMSO content would equal 9%. Therefore, to evaluate the impact of DMSO desolvation on trametinib bioavailability and assess feasibility of long-term storage at room temperature ≤25°C, a single dose of 2-mg trametinib given as a 2-mg tablet containing 9% DMSO was assessed vs a 2-mg tablet containing 11% DMSO.

Methods

Study Design and Implementation

This was an open-label, phase 1, single-dose, randomized, 2-treatment, 2-period crossover study in healthy volunteers conducted between September 13, 2018, and December 2, 2018 (Figure 1). In treatment period 1, subjects fasted for at least 10 hours before being equally randomized to either a single oral dose of trametinib 2 mg given as one 2-mg tablet containing 9% DMSO

(test formulation) or to a single oral dose of trametinib 2 mg given as one 2-mg tablet containing 11% DMSO (reference formulation) and continued to fast for at least 4 hours thereafter. Following a washout period of 30 days after treatment period 1, in treatment period 2, subjects received the treatment that they did not receive previously. This study was performed in accordance with the Declaration of Helsinki and the International Council for Harmonization E6 Guideline for Good Clinical Practice and conducted at the QPS Miami Research Associates Center, South Miami, Florida. The protocol was approved by the Institutional Review Board IntegReview IRB (Austin, Texas). All subjects gave written informed consent before participating and before any study-specific procedures were initiated.

Subjects

Eligible subjects included men and women of non–childbearing potential, aged 18 to 75 years inclusive on the day of the informed consent signature, with body mass index of $\geq$18.0 to $\leq$32.0 kg/m^2 for a total body weight of $\geq$50 kg and $<$150 kg at screening and day –1, and with no clinical or laboratory abnormalities. Subjects were excluded from the study if they had history of clinically significant electrocardiogram (ECG) abnormalities or prolonged QT-interval syndrome, retinal vein occlusion, central serous retinopathy, low left ventricular ejection fraction, cardiac disease, immunodeficiency, or malignant diseases, had a positive hepatitis B surface antigen or hepatitis C test result, had history of drug or alcohol abuse within 12 months before screening, consumed alcohol within 48 hours before dose administration in each period, or donated $\geq$400 mL of blood or plasma within 8 weeks before dosing. Subjects could withdraw from the study at any time or could be withdrawn at any time at the discretion of the investigator or sponsor for safety reasons. Subjects who discontinued study treatment or who decided not to participate in the study further were not to be considered withdrawn from the study unless they withdrew their consent. Where possible, they were required to return for the assessments indicated in the assessment schedule.

Treatment

Both the test (Batch No. 2022508) and the reference (Batch No. 172403926) formulations were provided and supplied by Novartis Drug Supply Management as open-label supplies of 2-mg tablets. Dose adjustments and dose delays were not permitted. Investigator site personnel administered trametinib at 8:00 AM with water to a total volume of 240 mL. Except for medication that may be required to treat adverse events (AEs), no medication (including vitamins and supplements) was allowed from 7 days before day 1 (dose or randomization day) until all treatment evaluations were conducted.

Endpoints

The primary endpoints for this study were PK parameters. Primary PK parameters were AUC from time 0 to the last measurable plasma concentration sampling time ($AUC_{0\text{-last}}$; ng • h/mL), $AUC_{0-\infty}$, and C_{max}. Secondary PK parameters were t_{max}, the elimination half-life associated with the terminal slope of a semilogarithmic concentration-time curve (hours), time of last measurable concentration (hours), and the total apparent body clearance of drug (CL/F [L/h]). Secondary endpoints were safety parameters such as AEs; serious adverse events (SAEs); and changes in hematology and blood chemistry values, vital signs, and ECGs.

Pharmacokinetic Evaluation

Blood samples for PK analysis of trametinib were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 24, 48, 72, 96, 120, 168, 216, 264, 312, and 360 hours after dosing in both treatment period 1 and treatment period 2 for all subjects. Four-milliliter blood samples were collected into tubes containing anticoagulant dipotassium-ethylenediaminetetraacetic acid and gently inverted several times to thoroughly mix the anticoagulant. Tubes were then centrifuged to separate plasma and immediately transferred into labeled 2-mL polypropylene screw-cap tubes. Plasma samples were placed in a freezer in an upright position until shipment to the bioanalytical laboratory.

For the analysis, a 50-μL plasma aliquot was spiked into the appropriate well of the 96-well plate, followed by addition of 25 μL of acetonitrile:water (1:1) to the matrix blank or internal standard to all other samples, and centrifugation. A 600 μL aliquot of the organic layer was evaporated to dryness under a stream of nitrogen, the residue was reconstituted with 200 μL of acetonitrile:water (1:1, v/v) and injected onto the ultra-performance liquid chromatography–tandem mass spectrometric system. Chromatographic separation was achieved with an ACQUITY UPLC BEH C18 (50$\times$2.1 mm, 1.7 μm; Waters Corp., Milford, Massachusetts) column heated to 65°C and a mobile phase gradient at a flow rate of 700 μL/min. Mobile phase A consisted of 0.1% formic acid in water, and mobile phase B consisted of 0.1% formic acid in acetonitrile. The mobile phase composition started at 50% B for 0.1 minutes and increased to 80% B over 1.0 minute. Trametinib and the internal standard detection was done by tandem mass spectrometry (API 5500, Sciex, Framingham, Massachusetts) using positive ion electrospray (IonSpray voltage of 3500 V and temperature at 550°C). The monitored ion transitions were m/z 616 $\rightarrow$ 491 for trametinib and m/z 622 $\rightarrow$ 497 for the

internal standard. Calibration curves were linear over the range of 0.250 to 250 ng/mL using 50 μL of plasma and 1/concentration^2 weighting factor. Analytical runs were considered acceptable if no more than 25% of the calibration standard levels were excluded and a minimum of 6 acceptable levels were included. The utilized back-calculated concentrations were within the range of ±15.0% of nominal concentration (±20.0% at the lower limit of quantification). The lower limit of quantification of trametinib was 0.250 ng/mL. The PK parameters were derived on the basis of the noncompartmental methods using Phoenix WinNonlin version 8.0 software (Certara, Princeton, New Jersey). Missing values for any PK parameters or concentrations were not imputed and were treated as missing. Plasma concentration values below the limit of quantification were treated as 0 and included as such in any calculations of summary statistics, including arithmetic means and standard deviations (SDs), and treated as missing for the calculation of the geometric means and their coefficient of variation (CV%).

Sample Size Calculation

The sample size of 48 evaluable subjects (≈24 per sequence) was selected on the basis of feasibility and to provide reasonable precision of the geometric mean ratio estimate. For an estimated within-subject CV of 53%, the precision or half-width of the 90%CI for trametinib test-reference comparison on the log scale extended 0.170 from the observed difference in means. To account for potential dropouts (≈20%), ≈30 subjects per sequence (60 subjects in total) were enrolled.

Safety Evaluation

All AEs and SAEs, including monitoring of laboratory assessments (hematology, clinical chemistry, urinalysis, and coagulation), physical assessments (physical examination, vital sign, height, and weight), ECG, and dermatological examinations up to 30 days after the last dose, were recorded and summarized by number and percentage of subjects having at least 1 AE, having at least 1 AE in each primary system organ class, and for each preferred term, using the Medical Dictionary for Regulatory Activities coding version 21.1 terminology. A subject with multiple occurrences of an AE were counted only once in the respective AE category. Grading of laboratory values were assigned programmatically as per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Statistical Evaluation

Summary statistics were provided for all subjects, as well as for each treatment sequence. Categorical data were presented as frequencies and percentages. For continuous data, mean, SD, median, minimum, and maximum were presented. Bioavailability between the test and the reference, and PK parameters were analyzed separately using a linear mixed-effect model with log-transformed PK parameters as dependent variables, fitting terms for treatment, period, and sequence as fixed effects, and subject nested within sequence as random effect. For each of the comparisons, a point estimate and the corresponding 2-sided 90%CI for the difference between means of test and reference treatment was calculated. The point estimate and CI were anti–log-transformed to obtain the point estimate and the 90%CI for the geometric mean ratio on the original scale. The model-based intrasubject and intersubject variations and CV% were presented for the primary PK parameters. Individual subject ratios of test vs reference along with geometric mean ratio and 90%CI for primary PK parameters were displayed. Point estimate (median difference) and associated ranges were provided for t_{max}.

Table 1. Subject Baseline Characteristics

Variable	All Subjects, N = 60
Age, y	
Mean (SD)	45.6 (11.7)
Median (min; max)	47.0 (20; 66)
Sex, male, n (%)	39 (65.0)
Race, n (%)	
White	50 (83.3)
Black or African American	10 (16.7)
Weight, kg	
Mean (SD)	80.2 (11.8)
Median (min; max)	79.1 (58.2; 102.0)

SD, standard deviation.

Results

Subject Disposition and Baseline Characteristics

A total of 60 subjects were enrolled in the study and randomized in a 1:1 ratio to either the test or the reference formulation, as previously described. Sixty-five percent of subjects were men, mean (SD) age was 45.6 (11.2) years, mean body mass index (SD) was 28.4 (2.6) kg/m^2, and 83.3% were White (Table 1).

Pharmacokinetic Results

All 60 subjects completed the study and were evaluated for PK parameters. The arithmetic mean plasma trametinib concentration–time is shown in Figure 2. The geometric mean (geometric CV%) $AUC_{0\text{-last}}$ was 328 (26.6%) ng • h/mL for 2-mg trametinib containing 11% DMSO and 289 (36.3%) ng • h/mL for 2-mg trametinib containing 9% DMSO. The geometric mean (geometric

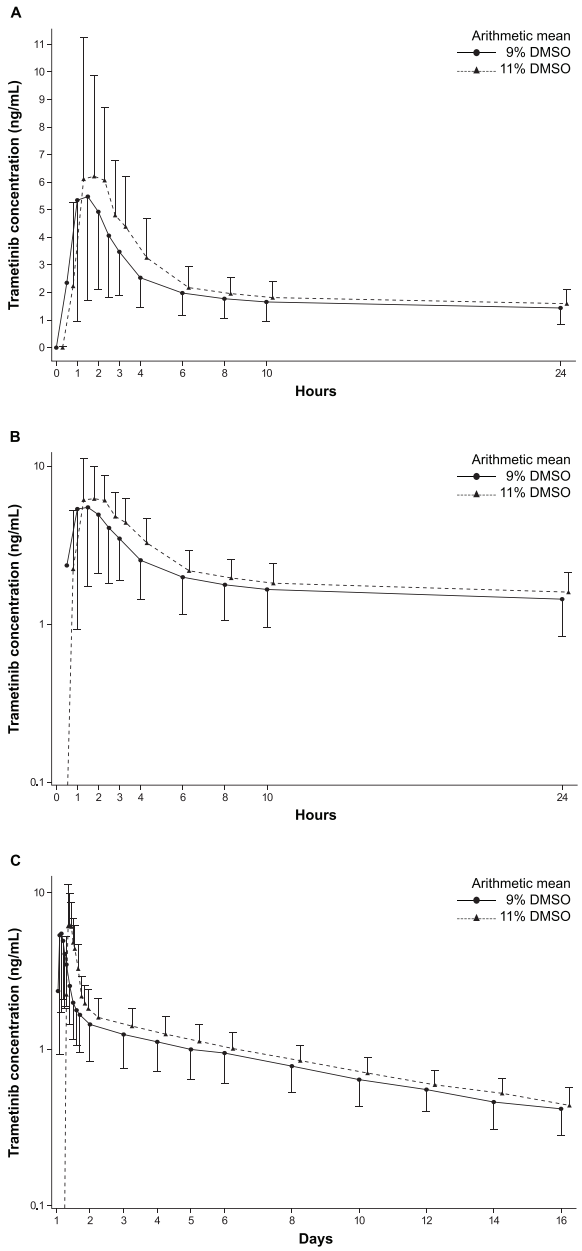

Figure 2. (A) Arithmetic mean plasma trametinib concentration–time linear and (B) logarithmic profiles up to 24 hours following trametinib 2-mg tablet in 11% or 9% DMSO. (C) Logarithmic profiles up to day 16 following trametinib 2-mg tablet in 11% or 9% DMSO. Zero concentrations at individual time points were included in the linear plot A and excluded from the logarithmic plot B. DMSO, dimethyl sulfoxide.

CV%) C_{max} was 7.57 (51.6%) ng/mL for 2-mg trametinib with 11% DMSO and 5.52 (76.4%) ng/mL for 2-mg trametinib with 9% DMSO (Table 2). The extrapolated portion of $AUC_{0-\infty}$ for most of the subjects was >20% of total $AUC_{0-\infty}$. Because of this limitation, $AUC_{0-\infty}$ could only be estimated for 9 profiles (4 for 2-mg trametinib in 9% DMSO and 5 for 2-mg trametinib in 11% DMSO); therefore, this parameter was not used for model-based inference evaluation. The geometric mean ratio (90%CI) comparing trametinib 2-mg tablets containing 9% DMSO with trametinib 2-mg tablets containing 11% DMSO was 0.890 (0.848-0.935) for AUC_{0-last} and 0.734 (0.644-0.836) for C_{max} (Table 3). The estimated intrasubject CV% was 15.8% for AUC_{0-last} and 44.2% for C_{max}. Most of the subjects had individual AUC_{0-last} ratios of 2-mg trametinib with 9% DMSO to 2-mg trametinib with 11% DMSO close to 1, whereas for C_{max} most individual ratios were <1 (Figure 3).

Table 2. Summary Statistics of Pharmacokinetic Parameters

	2-mg Trametinib 11% DMSO N = 60	2-mg Trametinib 9% DMSO N = 60
t_{max}, h		
Median (min; max)	1.50 (1.00; 4.00)	1.50 (0.57; 6.00)
Arithmetic mean (SD)		
$AUC_{0-\infty}$, ng • h/mL[a]	580 (191)[b]	556 (116)[c]
AUC_{0-last}, ng • h/mL	339 (91.1)	306 (107)
C_{max}, ng/mL	8.47 (4.32)	6.72 (4.14)
CL/F, L/h[a]	3.82 (1.47)[b]	3.71 (0.772)[c]
$t_{1/2}$, h[a]	141 (19.7)[b]	133 (15.2)[c]
t_{last}, h	358 (8.69)	357 (17.7)
Geometric mean (geometric CV%)		
$AUC_{0-\infty}$, ng • h/mL[a]	553 (37.0)[b]	547 (21.1)[c]
AUC_{0-last}, ng • h/mL	328 (26.6)	289 (36.3)
C_{max}, ng/mL	7.57 (51.6)	5.52 (76.4)
CL/F, L/h[a]	3.62 (37)[b]	3.65 (21.1)[c]
$t_{1/2}$, h[a]	140 (14.8)[b]	132 (11.4)[c]
t_{last}, h	358 (2.6)	356 (5.7)[c]

$AUC_{0-\infty}$, area under the plasma concentration–time profile from time 0 extrapolated to infinite time; AUC_{0-last}, area under the plasma concentration–time profile from time 0 to the time of the last quantifiable concentration; C_{max}, maximum observed concentration; CL/F, apparent clearance; CV, coefficient of variation; DMSO, dimethyl sulfoxide; t_{max}, time when C_{max} was reached; t_{last}, time of last measurable concentration; $t_{1/2}$, terminal half-life; SD, standard deviation.
[a] Data to be considered with caution due to the limited sample size.
[b] n = 5.
[c] n = 4.

Safety Evaluation

Overall, 55% (33/60) of subjects experienced at least 1 AE of any grade. One subject reported a grade 3 headache (Table 4). The most commonly reported AEs irrespective of treatment relation (≥5%) were headache (13.3%; 8/60), constipation (10.0%; 6/60), abdominal pain, diarrhea, upper respiratory tract infection (7%; 4/60 each), back pain, and dyspepsia (5.0%; 3/60 each; Table 4). A total of 11.7% (7/60) of subjects reported

Table 3. Statistical Analysis of Primary PK Parameters

PK Parameter	Treatment	n	Adjusted Geometric Mean	Geometric Mean Ratio for 2-mg Trametinib 9% DMSO/11% DMSO (Lower; Upper)
$AUC_{0\text{-last}}$, ng • h/mL	2-mg trametinib 11% DMSO	60	328	0.890 (0.848; 0.935)
	2-mg trametinib 9% DMSO	58	292	
C_{max}, ng/mL	2-mg trametinib 11% DMSO	60	7.57	0.734 (0.644; 0.836)
	2-mg trametinib 9% DMSO	58	5.56	

$AUC_{0\text{-last}}$, area under the plasma concentration–time profile from time 0 to the time of the last quantifiable concentration; C_{max}, maximum observed concentration; DMSO, dimethyl sulfoxide; PK, pharmacokinetic; SD, standard deviation.

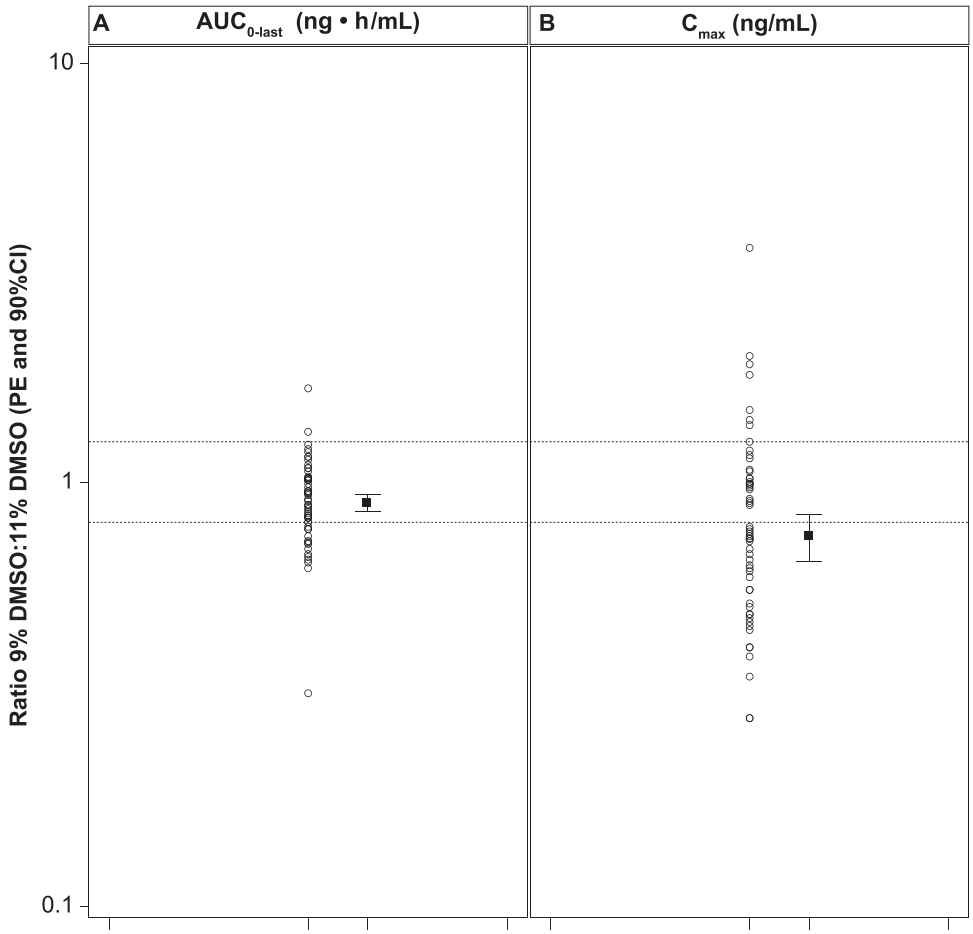

Figure 3. Individual subject and geometric mean ratio (9% DMSO/11% DMSO) for $AUC_{0\text{-last}}$ (A) and C_{max} (B). Point estimate and 90%CI come from a linear mixed-effects model of the log-transformed pharmacokinetic parameters. Included in the model were treatment, period, and sequence as fixed factors and subjects nested within sequences as a random factor. Reference lines are at 0.80 and 1.25. $AUC_{0\text{-last}}$, area under the plasma concentration–time profile from time 0 to the time of the last quantifiable concentration; C_{max}, maximum observed concentration; DMSO, dimethyl sulfoxide; PE, point estimate.

at least 1 treatment-related AE (headache [6.7%, 4/60]; diarrhea [5.0%, 3/60]; abdominal pain [3.3%, 2/60]; nausea [1.7%, 1/60]). None of the treatment-related AEs were grade ≥3. No AEs led to study drug discontinuation. No SAEs and no deaths were reported during the study.

Discussion

Previous studies showed that the nonsolvated form of trametinib has low solubility in water and poor oral exposure in preclinical species.[10] To increase water solubility and oral bioavailability, various solvates were prepared, and the DMSO solvate was selected for

Table 4. Safety Events

Preferred Term, n (%)	All Subjects, All Grades, n (%)	Grade ≥3, n (%)
Subjects with ≥1 AE	33 (55.0)	1 (1.7)
Headache	8 (13.3)	1 (1.7)
Constipation	6 (10.0)	0
Abdominal pain	4 (6.7)	0
Diarrhea	4 (6.7)	0
Upper respiratory tract infection	4 (6.7)	0
Back pain	3 (5.0)	0
Dyspepsia	3 (5.0)	0
Cough	2 (3.3)	0
Hordeolum	2 (3.3)	0
Nasopharyngitis	2 (3.3)	0
Nausea	2 (3.3)	0
Presyncope	2 (3.3)	0
Rash, generalized	2 (3.3)	0
Abdominal discomfort	1 (1.7)	0
Anal fissure	1 (1.7)	0
Anxiety	1 (1.7)	0
Arthralgia	1 (1.7)	0
Dermatitis, contact	1 (1.7)	0
Dry mouth	1 (1.7)	0
Flatulence	1 (1.7)	0
Gingival abscess	1 (1.7)	0
Gingival pain	1 (1.7)	0
Herpes zoster	1 (1.7)	0
Hyperhidrosis	1 (1.7)	0
Ingrown hair	1 (1.7)	0
Muscle spasms	1 (1.7)	0
Musculoskeletal pain	1 (1.7)	0
Pain in extremity	1 (1.7)	0
Palpitations	1 (1.7)	0
Pharyngitis	1 (1.7)	0
Photophobia	1 (1.7)	0
Traumatic hematoma	1 (1.7)	0
Vomiting	1 (1.7)	0

AE, adverse event. Numbers (n) represent counts of subjects. A subject with multiple severity grades for n AE was counted only under the maximum grade.

development, as it showed acceptable oral bioavailability as well as desirable solid-state properties.[10] Stability data indicated that DMSO desolvation was dependent on temperature and moisture; as a consequence, storage in the refrigerator was evaluated as long-term storage condition, equaling to an overall shelf life of 36 months, which is composed of 35 months of storage in a closed bottle and 1 month of in-use period. However, ambient rather than refrigerated storage of the trametinib tablets may be perceived as more convenient by caregivers and patients. To allow long-term storage of trametinib tablets at room temperature up to 25°C, evaluating alterations in DMSO content and associated bioavailability of the active component has been necessary to understand the implications on the intended efficacy.

The tested 9% DMSO content was based on the maximum estimated DMSO loss over the 36-month shelf life of a tablet with 10.7% to 12.4% DMSO content limit, based on tablet release specifications. A statistical safety margin was also added to consider differences in DMSO loss over time in different batches. In the present study, the ratio of $AUC_{0\text{-last}}$ and C_{max} between the 2 formulations were close to 1 and within the boundaries for biosimilarity, indicating that storage of trametinib at controlled room temperature up to 25°C would not affect the bioavailability of trametinib. In addition, all other PK parameters were also similar, albeit interpretability of some of these findings warrant caution due to a low sample size. Of note, the geometric mean C_{max} for the test formulation was slightly lower than the geometric mean C_{max} for the reference formulation, equaling 26.6% lower drug concentration with the 9% DMSO formulation compared with the 11% formulation, which was within the CV% (52%-76%). However, since the trametinib exposure profile was previously shown to allow constant target inhibition with a low C_{max}, no efficacy difference is anticipated.[7]

The majority of AEs were mild. One subject experienced grade 3 headache, and no grade 4 or grade 5 AEs were reported. No new safety findings were observed.

Conclusions

Oral bioavailability of 2-mg trametinib with 9% DMSO was similar to the oral bioavailability of 2-mg trametinib with 11% DMSO, indicating that modest desolvation would not affect trametinib bioavailability. This suggests that trametinib could be stored at room temperature in climatic zone I (temperate regions with mean annual temperature measured in open air ≤15°C) or zone II (Mediterranean/subtropical regions with mean annual temperature measured in open air of 15-22°C) countries during its entire shelf life of 36 months.

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Conflicts of Interest

All authors are employees of Novartis Pharmaceuticals Corporation. E.Y.T., C.K., C.Z., and P.I. are Novartis shareholders. No authors have disclosed that they are Fellows of the American College of Clinical Pharmacology.

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