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Phase 1 Dose-Escalation Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Tofacitinib in Japanese Healthy Volunteers

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Abstract

The aim of the study was to characterize the pharmacokinetics, safety, and tolerability of tofacitinib, an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis in healthy Japanese volunteers, and to compare these outcomes with those of healthy Western volunteers. Twenty-five volunteers (Japanese, n = 16; Western [white], n = 9) were randomized to receive either 3 escalating single doses of tofacitinib (1, 5, and 30 mg), single-dose tofacitinib (15 mg) followed by multiple doses (15 mg twice daily for 5 days), or placebo. No significant differences in systemic exposure to tofacitinib were detected between the 2 ethnicities. Following single tofacitinib 1, 5, and 30 mg doses, mean area under the plasma concentration–time curve from time zero to infinity ratio (Japanese/Western) values were 96.6%, 93.5%, and 95.6%, respectively. Similarly, mean maximum observed plasma concentration ratio values were 99.5%, 118%, and 119%, respectively. Mean renal clearance was also similar, ranging across doses from 134 mL/min (5 mg) to 162 mL/min (1 mg) in Japanese volunteers, and 124 mL/min (30 mg) to 160 mL/min (1 mg) in Western volunteers. In both ethnicities, most adverse events were mild. No serious adverse events or deaths were reported. The pharmacokinetics of tofacitinib were well characterized in healthy Japanese volunteers and were similar to those in Western volunteers.

Keywords

Japanese, pharmacokinetics, phase 1, tofacitinib, Western

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis,[1–10] psoriatic arthritis,[11–13] and ulcerative colitis.[14–16] JAK signaling is critical for immune cell activation, proinflammatory cytokine production, and cytokine signaling.[17] Tofacitinib is a potent, selective inhibitor of the JAK family of kinases with a high degree of selectivity against other human kinases. In kinase assays, tofacitinib inhibits JAK1, JAK2, and JAK3, and to a lesser extent tyrosine kinase 2. In cellular settings, where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2.[18,19] Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain containing receptors for several cytokines, including interleukin-2, -4, -7, -9, -15, and -21. These cytokines are integral to lymphocyte activation, proliferation, and function; inhibition of their signaling may result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional proinflammatory cytokines, such as interleukin-6 and interferon-γ. At higher exposures, inhibition of erythropoietin signaling could occur via inhibition of JAK2 signaling. Tofacitinib subsequently modulates adaptive and innate immunity with exposure-dependent limited effects on hematopoiesis.[18,20]

Based on prior characterization of pharmacokinetics (PK) in Western healthy volunteers,[21–29] the primary clearance mechanisms for tofacitinib in humans

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were determined to be renal clearance and cytochrome P450 (CYP)-mediated oxidation, at approximately 30% and 70%, respectively.[21,30] Overall renal clearance of tofacitinib was slightly higher than creatinine clearance, suggesting that renal mechanisms involve active tubular secretion in addition to filtration.[21] The predominant pathways of tofacitinib metabolism included oxidation of pyrrolopyrimidine rings, piperidine rings and the piperidine ring side-chain, N-demethylation, and glucuronidation. CYP profiling indicated that 53% of tofacitinib metabolism was via CYP3A4 (53%), with a smaller (17%) contribution from CYP2C19.[21,30] This is important to note, as metabolism by CYP2C19 is thought to be poor in 15% to 20% of the Japanese population.[31] Here, we report the first phase 1 clinical study to characterize the PK, safety, and tolerability of tofacitinib in healthy Japanese volunteers and compare these parameters with those from Western volunteers.

Materials and Methods

This study was conducted at the New Haven Clinical Research Unit in Connecticut, and in compliance with the ethical principles originating in, or derived from, the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Good Clinical Practice Guidelines. In addition, all local regulatory requirements were followed. The study protocol was approved by the Institutional Review Board at the investigational center, and volunteers provided written, informed consent.

Study Design

This was a phase 1, randomized, volunteer- and investigator-blind, sponsor-open, placebo-controlled, dose-escalation study (sponsor protocol number: A3921036). The primary objectives were to characterize the PK and evaluate the safety and tolerability of single and multiple oral doses of tofacitinib in healthy adult Japanese volunteers. Secondary objectives were to compare the PK, safety, and tolerability of escalating single oral doses of tofacitinib between healthy adult Japanese and Western (white) volunteers. The study comprised 2 cohorts: Cohort A and Cohort B. Cohort A assessed tofacitinib dose escalation in Japanese vs Western volunteers; Cohort B evaluated single-dose vs multiple-dose administration of tofacitinib in Japanese volunteers.

Healthy Volunteers

Eligible male or female healthy volunteers were aged 18–55 years, had a body mass index (BMI) of 18–30 kg/m^2, and a total body weight between 50 and 100 kg. *Healthy* was defined as the absence of clinically relevant abnormalities identified by medical history, physical examination, blood pressure and pulse rate measurement, electrocardiogram (ECG), and clinical laboratory tests. Further inclusion criteria included normal renal function (defined as a screening creatinine clearance ≥80 mL/min, normalized to 1.73 m^2) calculated using the Cockcroft-Gault equation.[32] For entry into the study, Japanese volunteers were required to have had 4 biological grandparents of Japanese ethnicity, who were also born in Japan.

Exclusion criteria included evidence or recent history of clinically significant disease; recent history of infection, major trauma, or surgery or a family history of hereditary immunodeficiency; use of prescription or nonprescription drugs, vitamins, and dietary supplements (within 7 days or 5 half-lives [whichever was longer] of the first dose of the trial medication); use of inhibitors of tubular secretion of creatinine, CYP3A4, cyclooxygenase-2, or use of nonsteroidal anti-inflammatory drugs within 14 days; use of herbal supplements, hormonal methods of contraception, and hormone replacement therapy (within 30 days); and use of depot medroxyprogesterone acetate (within 6 months before the first dose of the trial medication).

Volunteer Demographics and Disposition

In total, 25 healthy volunteers were assigned to the study treatment. Cohort A included 8 Japanese volunteers (tofacitinib, n = 6; placebo, n = 2) and 9 Western volunteers (tofacitinib, n = 7; placebo, n = 2). Cohort B included 8 Japanese volunteers (tofacitinib, n = 6; placebo, n = 2). Baseline demographics were generally similar between Japanese and Western volunteers and between treatment groups (Table 1). Most patients were men (100% Cohort A Japanese; 88.9% Cohort A Western; 62.5% Cohort B Japanese), with mean age, height, weight, and BMI in the ranges 34–38 years, 167.6–178.1 cm, 65.4–89.3 kg, and 22.2–28.0 kg/m^2, respectively. BMI and weight were higher for the Western cohort, as expected. Mean (standard deviation [SD]) creatinine clearance at baseline was 117 (14) mL/min for Japanese volunteers in Cohort A, 119 (29) mL/min for Western volunteers in Cohort A, and 104 (18) mL/min for Japanese volunteers in Cohort B. The results of the study were not affected by any protocol deviations that occurred during the study. One volunteer was withdrawn from the study following administration of tofacitinib 1 mg for not meeting the entrance criteria. Another volunteer was withdrawn from the study following administration of placebo due to a treatment-related adverse event (moderate periodontitis).

Plasma samples collected for 2 volunteers 8 hours after a single dose of tofacitinib 5 mg were incorrectly stored and subsequently excluded from the analysis of PK parameters.

Table 1. Volunteer Demographics and Baseline Characteristics

	Cohort A		Cohort B
	Japanese (N = 8)	Western (N = 9)	Japanese (N = 8)
Age (y), mean (SD)	34.1 (5.8)	38.0 (9.6)	35.8 (6.5)
Male, n (%)	8 (100)	8 (89)	5 (63)
Body weight (kg), mean (SD)	66.8 (8.9)	89.3 (11.5)	65.4 (12.0)
Height (cm), mean (SD)	173.1 (6.2)	178.1 (10.3)	167.6 (7.9)
BMI (kg/m^2), mean (SD)	22.2 (1.5)	28.0 (1.8)	23.1 (2.8)
Baseline creatinine clearance (mL/min), mean (SD)	116.6 (14.1)	119.1 (28.7)	103.8 (18.5)

BMI, body mass index; N, total number of patients in each cohort; SD, standard deviation.

Cytochrome P450 2C19

Volunteers were genotyped following treatment (such that investigators were blinded to genotypes during treatment and monitoring) and classified as either "poor" or "extensive" metabolizers according to their CYP2C19 allele profile, to investigate the relationship between tofacitinib exposure and CYP2C19 genotype. The alleles that were genotyped are *1 and *3 on exon 4 and *1 and *2 on exon 5. Poor metabolizers had *2/*2 or *2/*3, and extensive metabolizers had *1/*1, *1/*2, or *1/*3.

Treatments

Japanese and Western volunteers were assigned to Cohort A, stratified by ethnicity (Japanese vs Western), and randomized in a 3:1 ratio to receive either tofacitinib or placebo. Volunteers were admitted to the clinic on day 0 and were discharged from the study following final assessment on day 10. Each volunteer received single oral doses (administered with 240 mL of ambient-temperature water and separated by a 2-day washout period) of tofacitinib 1, 5, and 30 mg or matching placebo on days 1, 4, and 7, respectively. Only Japanese volunteers were assigned to Cohort B and were randomized in a 3:1 ratio to receive either a single dose of tofacitinib 15 mg or matching placebo, on day 1, followed by a multiple-dose regimen of tofacitinib 15 mg twice daily (BID) for 5 days (single dose on the last day) or matching placebo. Cohort B volunteers were discharged from the study after final assessment on day 11. In both cohorts, the final assessments were conducted at 72 hours after the final dose.

Assessments

Pharmacokinetics. For volunteers receiving single tofacitinib doses, blood samples (5 mL, to provide a minimum of 2 mL of plasma for PK analysis) were collected into tubes containing sodium heparin at 0 hour (just before dosing), and at 0.25, 0.5, 1, 2, 4, 8, 12, 16, 24, and 48 hours after dosing. For multiple tofacitinib dose analysis, blood samples (5 mL) were collected just before morning dosing on days 4 to 7, at 0 hour (just before dosing), and at 0.25, 0.5, 1, 2, 4, 8, 12, 16, 24, and 48 hours after dosing on day 8. Blood samples were centrifuged (1000–1200 g at 4°C for 10–15 minutes) within 30 minutes of sample collection, and the resulting plasma was stored at –20°C. Samples were analyzed using liquid chromatography–tandem mass spectrometry (calibration range, 0.100–350 ng/mL). Further details on sample preparation and analysis are provided in the Supplemental Information. Plasma PK parameters assessed included area under the plasma concentration–time curve from time zero to infinity (AUC_{inf}), area under the plasma concentration–time curve over the dosing interval τ (AUC_{τ}); maximum observed plasma concentration (C_{max}); time to reach C_{max}; terminal elimination half-life; and accumulation ratio based on AUC.

Twenty-four-hour urine collections for PK analysis following single tofacitinib doses (Cohort A) were divided into 3 periods on days 1, 4, and 7: 0 to 6 hours, 6 to 12 hours, and 12 to 24 hours, respectively. For volunteers who received multiple tofacitinib doses (Cohort B), 12-hour urine collections were divided into 2 periods on day 8 following multiple dosing: 0 to 6 hours and 6 to 12 hours. In both cohorts, a urine blank sample was collected before dosing. A 20 mL aliquot of each urine sample was frozen at –20°C for tofacitinib analysis. Samples were analyzed using liquid chromatography–tandem mass spectrometry (calibration range, 1.00–100 ng/mL). Urinary PK parameters assessed included cumulative amount of drug recovered unchanged in the urine up to time *t* after dosing (Ae_t) and renal clearance (CL_R).

Pharmacogenomics. For analysis of the CYP2C19 gene, a whole blood sample (2 mL) was collected from each volunteer at the screening visit, in tubes containing ethylenediaminetetraacetic acid. Tubes were immediately and gently inverted 10 to 15 times, and the whole blood sample was then frozen at –70°C or lower. DNA

was extracted from whole blood using a QIAamp kit (QIAGEN, Hilden, Germany). Polymerase chain reaction was used to amplify DNA samples for all assays performed. The TaqMan® (Applied Biosystems, Foster City, California) allelic discrimination procedure was used for detection of CYP2C19 alleles.

Safety. Adverse events, clinical observations, and vital signs were monitored throughout the study. Physical examinations were performed on day 0 and at 72 hours after the final dose. Safety laboratory tests included hematology, chemistry, and urinalysis and were performed at screening, day 0, 48 hours after single doses or 48 hours after the first dose of multiple dosing, and 48 hours after final doses. ECG and fasting lipid measurements were performed at specified time points after dosing.

Statistical Analyses

This was a descriptive, exploratory study, and sample sizes were selected empirically. To analyze individual concentration–time data and estimate PK parameters, standard noncompartmental methods were used. For single- and multiple-dose analysis, the plasma PK parameters C_{max}, AUC_{inf}, AUC_{τ}, time to reach C_{max}, and terminal elimination half-life, and the urinary PK parameters Ae_t, Ae_t% (Ae_t as a percent of the amount of drug administered), and CL_R were summarized descriptively by ethnicity and treatment group. Individual volunteer and arithmetic mean profiles of plasma concentration–time data were plotted by dose using nominal times. C_{max} and AUC_{inf} were plotted against dose and included individual values and geometric means by ethnicity and treatment group. To evaluate the similarity of PK parameters between Japanese and Western volunteers, the ratio of the adjusted geometric means and 90% confidence intervals of the mean differences in AUC_{inf} and C_{max} were estimated using back-transformation from the log-scale analysis of variance with ethnicity as a fixed effect. Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero. Time to tofacitinib steady-state plasma concentration was determined from the time course of individual trough plasma concentrations following administration of multiple oral doses of 15 mg BID for 5 days in Japanese volunteers.

Results

Pharmacokinetics

Single Dose (Cohort A: Japanese and Western Volunteers). No significant differences in systemic exposure to tofacitinib were detected between Japanese and Western volunteers at any of the 3 dose levels by analysis of variance of C_{max} and AUC_{inf}. The plasma PK parameters of tofacitinib following single doses are shown in Table 2. The ratios of mean C_{max} values in Japanese to Western volunteers following single doses in Japanese volunteers were 99.5% (1 mg), 118% (5 mg), and 119% (30 mg). The total systemic exposure (mean AUC_{inf}) was also similar between Japanese and Western volunteers at all 3 dose levels (1 mg, 22.0 vs 22.8 ng • h/mL; 5 mg, 111 versus 119 ng • h/mL; 30 mg, 754 vs 788 ng • h/mL), and the ratios of mean AUC_{inf} values in Japanese to Western volunteers were 96.6% (1 mg), 93.5% (5 mg), and 95.6% (30 mg).

Systemic exposure to tofacitinib in Japanese volunteers increased in an approximately dose-proportional manner, with similar systemic exposure seen in Western volunteers (Table 2 and Figure 1). Mean and individual C_{max} and AUC_{inf} values were compared by ethnicity, and although geometric mean C_{max} following single tofacitinib 5 and 30 mg doses in Japanese volunteers were approximately 19% higher than those observed in Western volunteers, there was some overlap between the distribution of individual values between Japanese and Western volunteers (Table 2 and Figure S1A).

The mean CL_R of tofacitinib was similar between ethnicities, and ranged from 134 mL/min (5 mg) to 162 mL/min (1 mg) in Japanese volunteers and from 124 mL/min (30 mg) to 160 mL/min (1 mg) in Western volunteers across doses following a single dose (Table 2). Mean CL_R was decreased by 8.6% (162 to 148 mL/min) in Japanese volunteers, and by 22.5% (160 to 124 mL/min) in Western volunteers, with increasing dose. Individual CL_R values were variable both between volunteers and between doses (Figure S1B), consistent with the lack of change in the observed median CL_R values across the 3 dose levels (Table 2) and indicative that tofacitinib would not produce a dose-related decrease in CL_R.

Most tofacitinib excreted unchanged in urine (Ae) was recovered by 6 hours after dosing at each dose level, for both Japanese and Western volunteers. The percentages of dose recovered unchanged in urine at 24 hours after dosing (Ae_{24}%) in Japanese volunteers after single doses of 1, 5, and 30 mg were 22.0%, 20.4%, and 22.5%, respectively, and in Western volunteers, 21.2%, 19.9%, and 19.8%, respectively (Table 2).

Multiple Dose (Cohort B: Japanese Volunteers). Plasma concentration following single (15 mg) and multiple doses (15 mg BID for 5 days) of tofacitinib in Japanese volunteers (Cohort B) reached steady state within 24 hours (Figure 2A and B and Figure S2). The multiple-dose PK parameters in Japanese volunteers (Cohort B) of tofacitinib are summarized in Table 3.

The arithmetic mean (SD) percentage of unchanged tofacitinib excreted in urine 24 hours after a single 15 mg dose (Ae_{24}%) was 27.1% (12.4), whereas the

Table 2. Plasma and Urinary PK Parameters of Tofacitinib Following Single Tofacitinib Doses (1, 5, and 30 mg) in Healthy Japanese and Western Volunteers (Cohort A)

		Japanese			Western		
		1 mg (n = 6)	5 mg (n = 6)	30 mg (n = 6)	1 mg (n = 6)	5 mg (n = 6)	30 mg (n = 6)
Plasma PK parameters							
C_{max}, ng/mL	Arithmetic mean (SD)	7.38 (1.05)	43.1 (15.0)	324 (82.7)	7.53 (1.69)	36.0 (9.78)	269 (47.9)
	Geometric mean (%CV)	7.32 (14)	41.3 (35)	315 (25)	7.36 (22)	34.9 (27)	265 (18)
	J/W (%)[a] (90%CI)	99.5 (81.1-122)	118 (87.4-161)	119 (93.0-151)	NA	NA	NA
AUC_{inf}, ng · h/mL	Arithmetic mean (SD)	22.8 (6.37)	114 (25.5)	775 (203)	22.9 (2.52)	120 (16.8)	797 (131)
	Geometric mean (%CV)	22.0 (28)	111 (22)	754 (26)	22.8 (11)	119 (14)	788 (16)
	J/W (%)[a] (90%CI)	96.6 (76.7, 122)	93.5 (76.3, 114)	95.6 (76.1, 120)	NA	NA	NA
t_{max}, h	Median (range)	0.75 (0.50-2.00)	0.50 (0.50-1.00)	0.50 (0.50-1.00)	0.75 (0.50-1.00)	0.50 (0.50-2.00)	0.50 (0.50-1.00)
	J-W[b]	0.00	0.00	0.00	NA	NA	NA
$t_{½}$, h	Arithmetic mean (SD)	1.96 (0.240)	2.49 (0.570)	3.14 (0.497)	2.14 (0.210)	2.85 (0.691)	3.50 (0.349)
	Range	1.69-2.40	2.06-3.60	2.56-3.79	1.80-2.34	2.13-3.93	2.89-3.81
	J-W[b]	−0.19	−0.36	−0.36	NA	NA	NA
Urinary PK parameters							
Ae_6, mg	Arithmetic mean (SD)	0.191 (0.0469)	0.890 (0.327)	5.59 (0.832)	0.169 (0.0128)	0.744 (0.224)	4.15 (1.11)
	%CV	25	37	15	8	30	27
Ae_{12}, mg	Arithmetic mean (SD)	0.215 (0.0527)	0.995[c] (0.367)	6.46 (0.791)	0.199 (0.0127)	0.919[c] (0.265)	5.63 (1.28)
	%CV	25	37	12	6	29	23
Ae_{24}%, %	Arithmetic mean (SD)	22.0 (5.34)	20.4[c] (7.51)	22.5 (3.00)	21.2[c] (0.865)	19.9[c] (5.15)	19.8 (4.11)
	%CV	24	37	13	4	26	21
CL_R, mL/min	Arithmetic mean (SD)	166 (45.2)	137 (33.8)	153 (41.8)	161 (17.7)	141 (40.6)	127 (30.1)
	Geometric mean (%CV)	162 (27)	134[c] (25)	148 (27)	160[c] (11)	136[c] (29)	124 (24)
	Median	144	136	149	158	148	127

Ae_t, cumulative amount of drug recovered unchanged in the urine up to time *t* (hours) after dosing; Ae_t%, Ae_t as a percentage of the amount of drug administered; AUC_{inf}, area under the plasma concentration–time curve from time zero to infinity; CI, confidence interval; CL_R, renal clearance of drug from urine; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; J, Japanese; NA, not applicable; PK, pharmacokinetic; SD, standard deviation; $t_{½}$, terminal elimination half-life; t_{max}, time to reach C_{max}; W, Western.

[a]Ratio of geometric mean (Japanese/Western).

[b]Difference of median or arithmetic mean (Japanese-Western).

[c]n = 5.

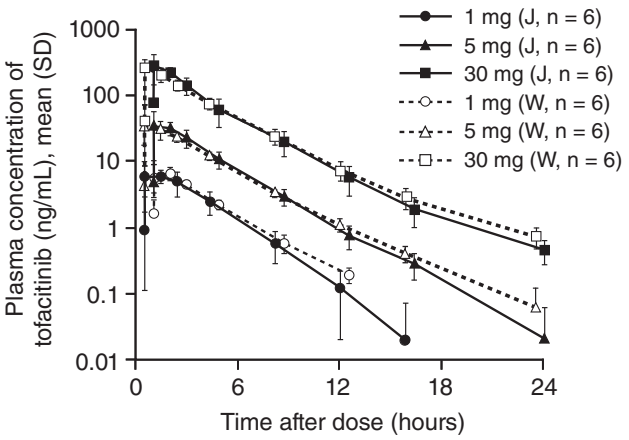

Figure 1. Effect of single tofacitinib dosing (1, 5, and 30 mg) in healthy Japanese and Western volunteers (Cohort A) on mean plasma concentration vs time. Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero. J, Japanese; n, the number of patients in each treatment group; SD, standard deviation; W, Western.

percentage of unchanged tofacitinib 12 hours after the second dose of the 15 mg BID dose (Ae_{12}%) at steady state was 23.3% (11.5). Compared with single-dose administration, the CL_R of tofacitinib was reduced after multiple-dose administration by an average of 24% (from geometric mean [SD] 158 mL/min [53.1] to 120 mL/min [41.2] on average). Examination of individual volunteer creatinine levels (data not shown) measured throughout the study suggested that renal function remained unaffected following repeat administration of tofacitinib.

Cytochrome P450 2C19. Genotyping showed that 2 Japanese volunteers, 1 in Cohort A and 1 in Cohort B, were classified as poor metabolizers by CYP2C19. All other volunteers in Cohorts A and B were extensive metabolizers. The relationship between tofacitinib exposure and CYP2C19 genotype showed no obvious differences in plasma concentration–time profiles observed between poor CYP2C19 metabolizers and extensive metabolizers (Figure 3A and B).

Safety and Tolerability

A summary of the incidence of treatment-emergent all-causality and treatment-related adverse events is shown in Table S1. A total of 42 adverse events were reported by 14 volunteers; 31 adverse events (reported by 10 volunteers) were considered related to the study medication. Of the 42 adverse events reported overall, 39 were mild and 3 were moderate in intensity. All adverse events of moderate intensity occurred in Cohort B and consisted of 1 event of skin irritation following administration of a single dose of tofacitinib 15 mg that was not considered to be related to the study treatment, 1 event of treatment-related constipation following administration of placebo BID, and 1 event of periodontitis following administration of a single dose of placebo that was not considered to be related to the study medication and led to withdrawal.

The most frequently reported adverse event in Cohort A was headache (in 2 Western volunteers receiving tofacitinib single doses [n = 1]; placebo single doses [n = 1]), while in Cohort B (which included only Japanese volunteers) constipation (in 2 volunteers

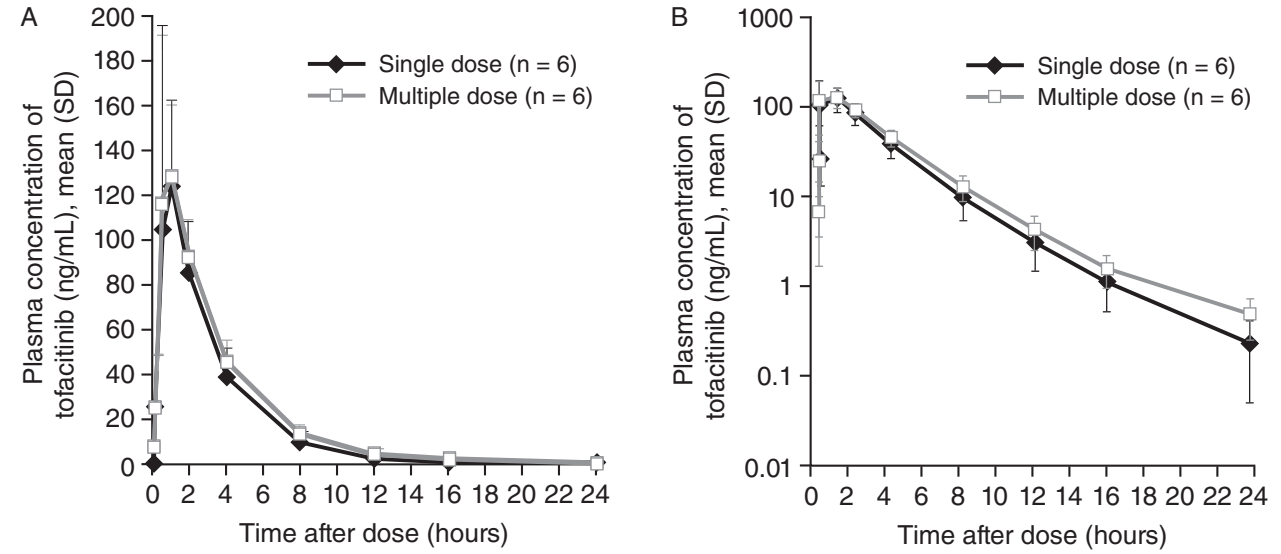

Figure 2. Mean plasma concentrations of tofacitinib vs time in healthy Japanese volunteers following single (15 mg) and multiple (15 mg BID for 5 days) tofacitinib doses (Cohort B) shown as: (A) linear and (B) log scales. Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero. BID, twice daily; n, the number of patients in each treatment group; SD, standard deviation.

Table 3. Plasma PK Parameters of Tofacitinib Following Single (15 mg) and Multiple (15 mg BID for 5 days) Doses in Healthy Japanese Volunteers (Cohort B)

Parameter		Day 1: Single Dose (n = 6)	Day 8: Multiple Dose (n = 6)
C_{max}, ng/mL	Arithmetic mean (SD)	149 (50.6)	143 (45.9)
	Geometric mean (%CV)	141 (34)	136 (32)
AUC_{inf}, ng · h/mL	Arithmetic mean (SD)	417 (133)	NC
	Geometric mean (%CV)	399 (32)	NC
AUC_{τ}, ng · h/mL[a]	Arithmetic mean (SD)	403 (128)	457 (116)
	Geometric mean (%CV)	387 (32)	445 (25)
t_{max}, h	Median (range)	0.75 (0.50-1.00)	0.75 (0.50-1.00)
$t_{½}$, h	Arithmetic mean (SD)	3.14 (0.672)	3.28 (0.544)
	Range	2.36-4.06	2.58-3.97
Rac[b]	Arithmetic mean (SD)	NA	1.15 (0.112)
	Geometric mean (%CV)	NA	1.15 (10)
	Range	NA	0.997–1.31

AUC_{τ}, area under the plasma concentration–time curve over the dosing interval τ; AUC_{inf}, area under the plasma concentration–time curve from time zero to infinity; BID, twice daily; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; NA, not applicable; NC, not calculated; PK, pharmacokinetic; Rac, accumulation ratio based on AUC; SD, standard deviation; $t_{½}$, terminal elimination half-life; t_{max}, time to reach C_{max}.
[a]Dosing interval (τ) was 12 hours.
[b]Rac = AUC_{τ} (day 8)/AUC_{τ} (day 1).

receiving tofacitinib 15 mg BID [n = 1]; placebo BID [n = 1]), hunger (in 2 volunteers receiving tofacitinib 15 mg BID), and skin irritation (in 2 volunteers receiving tofacitinib 15 mg BID [n = 1]; placebo BID [n = 1]) were the most frequently reported adverse events. No new safety risks were identified compared with the known safety profile of tofacitinib in patients with rheumatoid arthritis, psoriatic arthritis, or ulcerative colitis.[1–6,11–16,33,34] All adverse events resolved before the completion of the study. No serious adverse events or deaths were reported, and no volunteers had clinically significant laboratory abnormalities. There were no clinically significant changes in vital signs or ECG measurements, and no findings from physical examinations were reported as adverse events.

Discussion

In this study of healthy Japanese and Western volunteers, the PK of tofacitinib were characterized. Overall, the PK profile of tofacitinib was similar between healthy adult Japanese and Western volunteers. Following single-dose oral administration, systemic exposure to tofacitinib increased with dose in an approximately dose-proportional manner. Consistent with the short terminal elimination half-life of tofacitinib, there was negligible drug accumulation upon repeat dosing, and steady-state concentrations were reached within 24 hours (within the period of 5 half-lives).

The percentage of unchanged tofacitinib excreted in urine (approximately 20%) was similar across doses and ethnicities over 24 hours after single-dose administration. In this study, the CL_R of tofacitinib was slightly reduced (by an average of 24%) after multiple dosing compared with single dosing. It is, however, noted that the mean ratios of CL_R to the total systemic clearance were similar (25% after a 15 mg single dose and 21% at steady state after 15 mg BID), suggesting that the contribution of CL_R to the excretion of tofacitinib was not altered upon repeat dosing. Examination of individual volunteer serum creatinine measured throughout the study suggested that renal function remained unaffected following repeat administration of tofacitinib. This was confirmed by another clinical study,[27] which showed that tofacitinib 15 mg BID did not alter the glomerular filtration rate in healthy volunteers over 14 days.

No obvious differences in the plasma concentration–time profiles were observed between CYP2C19 poor metabolizers and extensive metabolizers after single and multiple doses, although it should be noted that the number of poor metabolizers studied was small; therefore, results should be interpreted with caution. These results suggest that the contribution of the CYP2C19 enzyme to the metabolism of tofacitinib is low. This concurs with findings from a previous study in which healthy Western (white) and Asian volunteers received a supratherapeutic dose of tofacitinib (100 mg): in 6 poor metabolizers (carriers of CYP2C19*2/*2, CYP2C19*2/*3, or CYP2C19*3/*3) the mean C_{max} and AUC_{inf} values were approximately 15% and 17% greater, respectively, than those in 54 extensive metabolizers.[35]

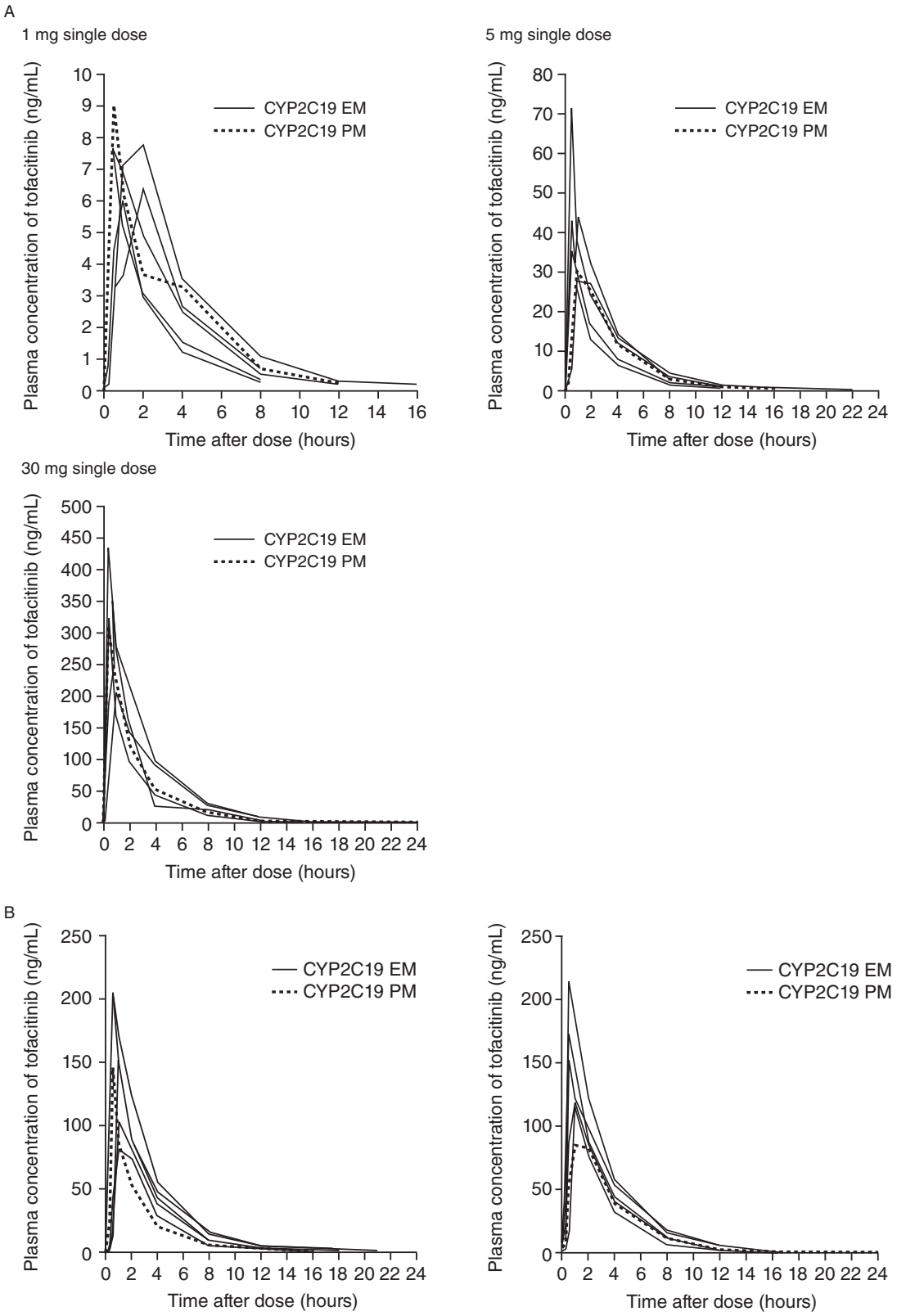

Figure 3. Individual plasma concentrations of tofacitinib vs time in healthy Japanese volunteers by CYP2C19 genotype status (extensive or poor metabolizer) following: (A) single (1, 5, and 30 mg) tofacitinib doses (Cohort A); and (B) single (15 mg) and multiple (15 mg BID for 5 days) tofacitinib doses (Cohort B). Each line represents an individual volunteer. Poor metabolizers had *2/*2 or *2/*3. Extensive metabolizers had *1/*1, *1/*2, or *1/*3. Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero. BID, twice daily; CYP2C19, cytochrome P450 2C19; EM, extensive metabolizer; PM, poor metabolizer.

In conclusion, the results of this Phase 1 study indicate that the PK profile of tofacitinib was similar between healthy adult Japanese and Western volunteers.

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Conflicts of Interest

S.M. is an employee and stockholder of Pfizer Japan Inc; S.T. and H.N. are employees of Pfizer Japan Inc; S.K. and S.H.Z. are employees and stockholders of Pfizer Inc.

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