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ORIGINAL ARTICLE

Evaluation of a Janus kinase 1 inhibitor, PF-04965842, in healthy subjects: A phase 1, randomized, placebo-controlled, dose-escalation study

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AIMS

To determine the safety, tolerability, pharmacokinetics and pharmacodynamics of the Janus kinase 1-selective inhibitor, PF-04965842.

METHODS

This was a phase 1, first-in-human, randomized, double-blind, placebo-controlled, combination single- and multiple-dose escalation, parallel design study in healthy subjects (http://clinicaltrials.gov, NCT01835197). Subjects received a single dose of placebo or 3, 10, 30, 100, 200, 400 or 800 mg PF-04965842 (single ascending dose phase) and placebo or 30 mg once daily (QD), 100 mg QD, 200 mg QD, 400 mg QD, 100 mg twice daily (BID) or 200 mg BID PF-04965842 for 10 consecutive days (multiple ascending dose phase). The primary objective was to determine the safety and tolerability of PF-04965842.

RESULTS

Seventy-nine subjects were randomized and received study treatments. There were no deaths or serious adverse events. The most frequent treatment-emergent adverse events were headache ($n = 13$), diarrhoea ($n = 11$) and nausea ($n = 11$). PF-04965842 was absorbed rapidly (median time at which maximum plasma concentration occurred generally $\leq$1 h following either single- or multiple-dose administration) and eliminated rapidly (mean $t_{½}$ 2.8−5.2 h after 10 days of QD or BID administration in the multiple ascending dose phase). Increases in maximum plasma concentration and area under the concentration–time curve were dose proportional up to 200 mg (single or total daily doses) with an apparent trend towards greater than proportional increases with higher doses. Less than 4.4% of the dose was recovered unchanged in urine. Changes in pharmacodynamic biomarkers were consistent with the known effects of Janus kinase signalling inhibition.

CONCLUSIONS

These results support further evaluation of PF-04965842 for clinical use in patients with inflammatory diseases.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- There remains a need for alternative treatment options for patients with inflammatory diseases such lupus, psoriasis and atopic dermatitis.
- Selective inhibition of Janus kinase (JAK)-1 may provide a more favourable safety profile than pan-JAK inhibitors by avoiding the effects of JAK2 inhibition.

WHAT THIS STUDY ADDS

- This first-in-human study assessed the safety, tolerability, pharmacokinetics and pharmacodynamics of PF-04965842, a potent JAK1-selective inhibitor.
- The favourable safety, tolerability, pharmacokinetics and pharmacodynamics profiles from this study support further evaluation of PF-04965842 for clinical use.

Introduction

Disease-modifying antirheumatic drugs are commonly used for the treatment of inflammatory diseases, including rheumatoid arthritis and psoriasis [1–3]. Despite their proven efficacy and tolerability, there remains a need for alternative treatment options because some patients do not respond, stop responding after an initial positive response or are intolerant to these treatments [4, 5]. Furthermore, an oral treatment may be preferable for some patients.

The Janus kinase (JAK) family of cytoplasmic tyrosine kinases [JAK1, JAK2, JAK3 and tyrosine kinase (TYK) 2] mediates signal transduction critical for leucocyte activation, proliferation, survival and function, via interactions with Type 1 and Type II cytokine receptors [6, 7]. JAK1 pairs with JAK3 to mediate γ-common cytokine signalling and also with JAK2 and TYK2 to transmit the signals of additional cytokines important in inflammation and immune responses. Key cytokines implicated in the pathophysiology of multiple inflammatory diseases, including interferon (IFN)-α and IFN-β (JAK1/TYK2 dependent), IFN-γ (JAK1/JAK2 dependent), interleukin (IL)-6 (JAK1/JAK2/TYK2 dependent) and IL-21 (JAK1/JAK3 dependent), require JAK1 for signal transduction, suggesting that JAK1 inhibition could be efficacious in a broad range of inflammatory diseases [8–10].

Several inhibitors with reportedly greater selectivity for JAK1 than JAK2 or JAK3 are in clinical development, including: filgotinib [11], INCB039110 [12], GSK2586184 [13] and ABT-494 [14]. Several other JAK inhibitors that are less selective for JAK1 are also currently approved or being tested for use in inflammatory diseases (e.g. ruxolitinib, baricitinib and tofacitinib) [8, 15, 16].

The aim of this study was to determine the safety and tolerability, as well as pharmacokinetics (PK) and pharmacodynamics (PD), of PF-04965842, a JAK1-selective inhibitor [17], in healthy adult subjects.

Methods

Study design

This was a phase 1, first-in-human, within-cohort, randomized, double-blind, placebo-controlled, combination single- and multiple-dose escalation, parallel design study in healthy subjects (http://clinicaltrials.gov, NCT01835197). The study was at a single centre in the USA and was subject blind, investigator blind and sponsor open (double-blind with respect to within-group assignments and single-blind for between-group assignments). Subjects were allocated randomization numbers and received treatment according to sponsor-generated randomization codes. Study treatments were provided by the sponsor as bulk powders for preparation of suspensions at the study centre. An unblinded site pharmacist prepared the treatments and provided them to the blinded administrator. Treatments were given to subjects in individual dosing containers that were labelled with the randomization number. The study was approved by the Institutional Review Board IntegReview in Austin (TX, USA; Protocol B7451001, approved 25 April 2013) and was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki (2008) and guidelines for Good Clinical Practice issued by the International Conference on Harmonisation (1996). All subjects gave written informed consent prior to study initiation.

The sample size was based on clinical and pharmacological considerations (no statistical considerations). There were nine cohorts comprising about eight subjects each (Figure 1). Subjects in each cohort were randomized in a 3:1 ratio of PF-04965842:placebo in block sizes of 4. In the single ascending dose (SAD) phase, western subjects in Cohorts 1–7 received a single dose of placebo or 3, 10, 30, 100, 200, 400 or 800 mg PF-04965842 in a dose escalation format. Subjects remained in the treatment facility from day –1 to day 5 in the SAD phase and returned for a follow-up visit on day 8. The multiple ascending dose (MAD) phase was initiated at least 14 days after the start of the SAD phase, and subjects in Cohorts 3–7 received placebo or 30, 100 or 200 mg once daily (QD) or 100 or 200 mg twice daily (BID) PF-04965842 for 10 consecutive days (the evening dose for the BID cohorts was not administered on day 10). In the MAD phase, subjects remained in the treatment facility until day 14 and returned for a follow-up visit on day 28. Cohort 8 consisted of Japanese subjects who received a single dose of placebo or 800 mg PF-04965842 in the SAD phase followed by 200 mg BID PF-04965842 for 10 consecutive days in the MAD phase. Cohort 9 (western subjects) was added to expand the range of QD dosing; subjects received placebo or 400 mg QD PF-04965842 for 10 consecutive days. During both the SAD and the MAD periods, escalation to subsequent dose levels occurred at a minimum of 7 days only if the last dose was well tolerated and after satisfactory review of the available safety and PK data. Dose escalation and stopping rules are described in Supplementary Methods 1.

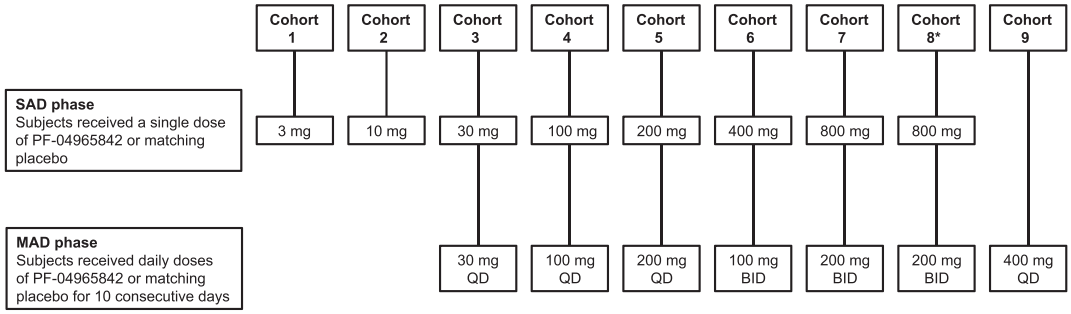

Figure 1

Study design. Subjects in each cohort (n = ~8 per cohort) were randomized 3:1 to PF-04965842:placebo. BID, twice daily; MAD, multiple ascending dose; QD, once daily; SAD, single ascending dose. *Japanese subjects

The primary endpoint was to determine the safety and tolerability of PF-04965842. The secondary endpoint was to characterize the PK and PD of PF-04965842.

Subjects

Eligible subjects included healthy males and postmenopausal/non-childbearing females aged 18–55 years, with a body mass index of 17.5–30.5 kg m^{-2} and a total body weight >50 kg. Exclusion criteria included, but were not limited to: evidence or history of abnormal cardiovascular, pulmonary, renal or hepatic function; white blood cell count below 4.5 × 10^3 mm^{-3}; haematocrit value below 38% (males) or 33% (females); platelet counts <150 × 10^3 mm^{-3}; red blood cell, reticulocyte and lymphocyte counts that fell outside the reference range; any other laboratory parameter with an abnormal value and judged to be clinically significant; treatment with an investigational drug within 30 days or five half-lives (whichever is longer) preceding the first dose of study medication; a history of tuberculosis or active/latent/inadequately treated infection; and history of cancer. Subjects were screened within 28 days before administration of the study drug. Concomitant medication was prohibited unless required for the treatment of adverse events (AEs) and the use of all concomitant medication was recorded.

Safety and tolerability

Subjects abstained from all food and drink (except water) at least 4 h prior to safety laboratory evaluations and 10 h prior to lipid evaluation. All AEs were monitored and recorded daily while the subjects were at the treatment facility, at follow-up visits and as needed in addition to the scheduled timepoints. Vital signs were measured at screening, immediately prior to dosing and at regular intervals postdose. Blood samples for haematology and laboratory tests were taken during screening, on days 0, 2, 3, 5 and 8 during the SAD phase, and days 0, 4, 6, 8, 10 (at 0, 2 and 6 h postdose), 11, 14 and 28 during the MAD phase. Samples for lipid evaluations were taken during screening, on days 0, 2 and 5 during the SAD phase, and days 0, 4, 10, 11 and 28 during the MAD phase. Urine samples for creatinine clearance were collected over 24 h on days 0 and 1 during the SAD phase and on days 0 and 10 of the MAD phase.

PK

Subjects abstained from all food and drink 8 h prior to the collection of predose PK samples (water was permitted until 1 h prior to dosing). Blood samples to assess PF-04965842 concentrations and for the PK endpoints were collected at 0 (predose), 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36 and 48 h postdose during the SAD phase. During the MAD phase, blood samples were collected prior to the morning dose on days 1, 2, 4, 6, 8, and then at 0, 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 48 and 72 h after the last dose on day 10. These were collected in tubes containing dipotassium ethylenediamine tetra-acetic acid, centrifuged at approximately 1700 g for about 10 min at 4°C, and stored at –70°C within 1 h of collection.

During the MAD phase, urine samples for PK analysis were collected on day 0 (predose blank) and day 10 (0–12 h for BID doses and 0–24 h for QD doses). The total volume was measured and recorded at the end of each 12-h or 24-h urine collection period. A 7–8 ml aliquot was withdrawn for measurement of drug concentrations and was frozen at –20°C within 1 h of the end of the collection interval.

Plasma and urine samples were analysed for PF-04965842 concentrations using validated, sensitive and specific liquid chromatography tandem mass spectrometric methods. The lower limit of quantification for PF-04965842 was 1 ng ml^{-1} for plasma concentrations and 10 ng ml^{-1} for urine concentrations. For plasma samples, the between-day assay accuracy, expressed as percent relative error, for quality control (QC) concentrations ranged from –2.8% to 5.0% for the low, medium, high and diluted QC samples. Assay precision, expressed as the between-day percent coefficient of variation (%CV) of the mean estimated concentrations of QC samples ranged from 6.2% to 13.0% for low (3 ng ml^{-1}), medium (60 ng ml^{-1}), high (750 ng ml^{-1}) and diluted (5000 ng ml^{-1}) concentrations. For urine samples, the between-day assay accuracy ranged from –1.2% to 5.0% for the low, medium, high and diluted QC samples. Assay precision ranged from 1.3% to 6.5% for low (30 ng ml^{-1}), medium (600 ng ml^{-1}), high (7500 ng ml^{-1}) and diluted (50 000 ng ml^{-1}) concentrations.

PK parameters were determined with an internally developed and validated software system using standard non-compartmental analysis of concentration–time data. Maximum plasma concentration (C_{max}) was observed directly from data and time at which C_{max} occurred (T_{max}) was defined as the time of the first occurrence of C_{max}. The $t_{1/2}$

was estimated using linear regression of the log-linear concentration–time curve. Areas under the concentration–time curve to time τ (AUC_{τ}), extrapolated to infinity (AUC_{inf}) and to the time of the last quantifiable concentration (AUC_{last}) were estimated using linear/log trapezoidal methods.

PD

PD biomarkers evaluated in this study included interferon gamma-induced protein 10 (IP-10) and high-sensitivity C-reactive protein (hsCRP) measurements from serum and neutrophils, platelets, reticulocytes, lymphocyte subset analysis [CD16+CD56+ natural killer (NK) cells, CD19+ B cells, and T cells including CD3+ (total), CD3+CD4+ helper T cells, CD3+CD8+ cytotoxic T cell subsets] from whole blood. Detailed information on sample collection and analysis of PD parameters are shown in Supplementary Methods 2.

Results

Subjects

Seventy-nine subjects were randomized and received study treatments from 13 May 2013 to 09 June 2014 (Table 1). Eleven subjects discontinued from the study (n = 4 and n = 7 from the SAD and MAD phases, respectively). Reasons for discontinuations, as judged by the investigator, were AEs related to study drug (n = 3), an AE unrelated to study drug (n = 1), lost to follow-up (n = 2) and other (n = 5). All subjects were included in the safety and PD analysis while only subjects treated with PF-04965842 were included in the PK analysis.

Baseline demographic characteristics are shown in Table 2. All but one of the subjects were male, the mean age of the subjects was 37.9 years (range 21–55 years), the mean weight was 80.8 kg (range 51.0–102.7 kg), and the mean body mass index was 26.4 kg m^{-2} (range 17.6–30.5 kg m^{-2}).

Safety and tolerability

There were no deaths or serious AEs during this study. During the SAD phase, 24 subjects had a total of 64 treatment-emergent AEs (TEAEs), 36 of which were considered to be treatment-related. During the MAD phase, 35 subjects had a total of 97 TEAEs, 59 of which were considered to be treatment-related. Most of the TEAEs were mild in severity and occurred at higher frequencies in subjects who received the highest doses in both the SAD (800 mg) and MAD phases (400 mg QD and 200 mg BID). The most frequent TEAEs (Table 3) were headache (n = 13), diarrhoea (n = 11) and nausea (n = 11). Seventeen mild/moderate infections were reported. Eight of these were considered to be treatment-related by the investigator and occurred predominantly in the higher dose cohorts.

There were no temporary discontinuations or dose reductions due to AEs reported in this study. Four subjects discontinued from the study due to AEs. In the SAD phase, one subject in the PF-04965842 100 mg group experienced a second-degree atrioventricular block (attributed to a pre-existing condition and not considered treatment-related by the investigator) and one subject in the PF-04965842 800 mg group experienced an AE of vomiting (considered to be treatment-related by the investigator). In the MAD phase, one subject in the PF-04965842 400 mg QD group experienced an AE of respiratory syncytial virus infection and another experienced vomiting (both AEs were moderate in severity and were reported as treatment-related by the investigator).

Overall, 25 and 40 subjects had laboratory abnormalities during the SAD and MAD phases, respectively, none of which were considered clinically relevant. The most frequently reported laboratory abnormalities were decreased mean platelet volume (<0.9× lower limit of normal, n = 10) and positive urine blood tests (≥1, n = 5) in the SAD phase, and decreased reticulocyte counts (<0.5× lower limit of normal, n = 10), increased lymphocyte counts (>1.2× upper limit of normal, n = 8) and decreased mean platelet volume (n = 7) in the MAD phase. Some subjects had decreases in haematological laboratory values, such as haemoglobin (Grade 1 criteria for haemoglobin, n = 7; Figure S1A), platelet counts (Grade 1 criteria for thrombocytopenia, n = 9; Figure S1B) or white blood cell counts (Grade 2 criteria for leukopenia, n = 4), that met Grade 1 or Grade 2 Common Terminology Criteria for Adverse Events (version 4.0) severity, but these were not associated with any clinical symptoms. All subjects had normal bilirubin and aspartate aminotransferase/alanine aminotransaminase levels.

During the SAD phase, there were increases and decreases in median percent change from baseline in total cholesterol and high-density lipoprotein (HDL) cholesterol levels; the greatest increase at 24 h postdose was in the PF-04965842 800 mg group (10% for both) while the greatest decrease was in the PF-04965842 10 mg group (2% and 9%, respectively). At 24 h postdose, the PF-04965842 100 mg group had the greatest increase (17%) in low-density lipoprotein (LDL) cholesterol level. During the MAD phase, the PF-04965842 200 mg BID group had the highest increase in median percent change from baseline in total cholesterol (22%) and HDL cholesterol (27%), and the 100 mg BID group had the highest increase in LDL cholesterol (42%) at day 10 predose (i.e., day 10, 0 h), as shown in Figure S2.

At 24 h postdose on day 1, median changes from baseline in creatinine clearance ranged between –13 and 10 ml min^{-1} during the SAD phase and between –53 and 8 ml min^{-1} during the MAD phase, with no subjects outside the normal range.

In the SAD phase, four subjects had sporadic measurements of absolute supine systolic blood pressure values <90 mmHg (placebo, n = 1; PF-04965842 800 mg, n = 3) and three subjects had absolute supine diastolic blood pressure values <50 mmHg (placebo, n = 1; PF-04965842 800 mg, n = 2). In the MAD phase, three subjects had occasional absolute supine systolic blood pressure values <90 mmHg (n = 1 each in the PF-04965842 100 mg QD, 400 mg QD and 200 mg BID treatment groups) and seven subjects had absolute supine diastolic blood pressure values <50 mmHg (PF-04965842 100 mg QD, n = 1; PF-04965842 400 mg QD, n = 1; PF-04965842 200 mg BID, n = 1; PF-04965842 200 mg QD, n = 2; placebo, n = 2). One subject in the SAD phase (placebo group) and three subjects in the MAD phase (one each in the placebo, PF-04965842 30 mg QD, and 100 mg QD treatment groups) had a maximum QT

Table 1

Subject disposition

	Number of subjects														
	SAD phase								MAD phase						
	PBO	PF-04965842							PBO	PF-04965842					
	0 mg	3 mg	10 mg	30 mg	100 mg	200 mg	400 mg	800 mg	0 mg	30 mg QD	100 mg QD	200 mg QD	400 mg QD	100 mg BID	200 mg BID
Assigned to study treatment, *n* = 79															
Treated	16	6	6	6	7	6	6	16	14	6	5	6	8	6	14
Completed	16	6	6	6	5	6	6	14	14	5	5	6	5	6	11
Discontinued	0	0	0	0	2	0	0	2	0	1	0	0	3	0	3
Relation to study drug not defined	0	0	0	0	1	0	0	1	0	1	0	0	1	0	3
Lost to follow-up	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0
Other	0	0	0	0	0	0	0	1	0	1	0	0	0	0	3
Relation to study drug	0	0	0	0	0	0	0	1	0	0	0	0	2	0	0
AE	0	0	0	0	0	0	0	1	0	0	0	0	2	0	0
Not related to study drug	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
AE	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Analysed for safety															
AEs	16	6	6	6	7	6	6	16	14	6	5	6	8	6	14
Laboratory data	16	6	6	6	7	6	6	16	14	6	5	6	8	6	14
Analysed for PK															
Parameter	0	6	6	6	7	6	6	15	0	5	5	6	6	6	11
Concentration	0	6	6	6	7	6	6	15	0	6	5	6	7	6	13
Analysed for PD	16	6	6	6	7	6	6	16	14	6	5	6	8	6	14

Discontinuations were attributed to the last study treatment received. AE, adverse event; BID, twice daily; MAD, multiple ascending dose; PBO, placebo; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; SAD, single ascending dose.

Table 2

Baseline demographic characteristics

	PBO			PF-04965842							
	0 mg (SAD) (*n* = 4)	0 mg (SAD) then 0 mg QD or BID (MAD) (*n* = 12)	0 mg QD (MAD) (*n* = 2)	3 mg (SAD) (*n* = 6)	10 mg (SAD) (*n* = 6)	30 mg (SAD) then 30 mg QD (MAD) (*n* = 6)	100 mg (SAD) then 100 mg QD (MAD) (*n* = 7)	200 mg (SAD) then 200 mg QD (MAD) (*n* = 6)	400 mg QD (MAD) (*n* = 8)	400 mg (SAD) then 100 mg BID (MAD) (*n* = 6)	800 mg (SAD) then 200 mg BID (MAD) (*n* = 16)
Sex, *n*											
Male	4	12	2	6	6	6	7	6	8	6	15
Female	0	0	0	0	0	0	0	0	0	0	1
Age, y	34.8 (7.0)	38.0 (6.2)	35.0 (18.4)	39.7 (9.9)	39.0 (10.6)	43.0 (12.3)	32.0 (12.4)	35.8 (5.7)	36.0 (8.6)	36.2 (7.1)	41.2 (8.4)
Race, *n*											
White	1	3	0	3	5	2	4	0	2	1	0
Black	1	5	1	2	0	4	2	4	4	3	4
Asian	0	2	0	0	0	0	0	0	0	0	10
Other	2	2	1	1	1	0	1	2	2	2	2
Weight, kg	87.7 (10.1)	78.1 (11.3)	94.5 (2.5)	81.1 (6.4)	84.1 (5.6)	80.2 (9.3)	78.4 (9.6)	83.3 (14.0)	85.1 (8.1)	86.3 (5.1)	74.2 (13.3)
BMI, kg m^{-2}	26.1 (2.9)	26.3 (3.6)	29.0 (0.7)	26.7 (3.4)	26.6 (2.2)	26.4 (2.3)	25.3 (2.5)	27.2 (2.4)	28.1 (1.6)	27.6 (2.5)	24.9 (3.6)
Height, cm	183.5 (9.1)	172.3 (4.8)	180.5 (4.9)	175.0 (7.6)	177.8 (3.9)	174.2 (5.6)	175.9 (7.6)	174.3 (7.3)	173.8 (4.8)	177.0 (7.3)	172.4 (6.8)

Values are mean (standard deviation) unless otherwise stated. BID, twice daily; BMI, body mass index; MAD, multiple ascending dose; PBO, placebo; QD, once daily; SAD, single ascending dose.

Table 3

Treatment-emergent adverse events occurring in two or more subjects in any dosing group

AEs by SOC and MedRA* preferred term	Number of subjects with treatment-emergent adverse events: all causalities (treatment-related)														
	SAD phase								MAD phase						
	PBO	PF-04965842							PBO	PF-04965842					
	0 mg *n* = 16	3 mg *n* = 6	10 mg *n* = 6	30 mg *n* = 6	100 mg *n* = 7	200 mg *n* = 6	400 mg *n* = 6	800 mg *n* = 16	0 mg *n* = 14	30 mg QD *n* = 6	100 mg QD *n* = 5	200 mg QD *n* = 6	400 mg QD *n* = 8	100 mg BID *n* = 6	200 mg BID *n* = 14
Gastrointestinal disorders	0	0	0	0	0	1 (1)	0	10 (10)	4 (3)	1 (0)	1 (1)	3 (3)	5 (4)	2 (1)	7 (5)
Abdominal discomfort	0	0	0	0	0	1 (1)	0	2 (2)	0	0	0	0	1 (1)	0	2 (2)
Upper abdominal pain	0	0	0	0	0	0	0	0	0	0	0	0	2 (2)	0	1 (1)
Constipation	0	0	0	0	0	0	0	2 (1)	2 (1)	0	0	1 (1)	1 (1)	1 (1)	0
Diarrhoea	0	0	0	0	0	1 (1)	0	1 (1)	1 (1)	0	0	1 (1)	3 (2)	1 (0)	3 (3)
Flatulence	0	0	0	0	0	1 (1)	0	3 (3)	0	0	0	0	0	0	2 (2)
Nausea	0	0	0	0	0	0	0	3 (3)	1 (1)	0	1 (1)	2 (2)	3 (3)	0	1 (1)
Vomiting	0	0	0	0	0	0	0	4 (4)	0	0	0	0	1 (1)	0	0
Infections and infestations	1 (0)	0	0	1 (0)	0	1 (0)	0	2 (2)	1 (0)	1 (0)	0	1 (0)	2 (2)	1 (0)	4 (4)
Upper respiratory tract infection	0	0	0	0	0	0	0	1 (1)	1 (0)	0	0	0	1 (1)	1 (0)	2 (2)
Musculoskeletal and connective tissue disorders	1 (0)	0	0	0	0	0	0	4 (1)	0	0	0	0	1 (0)	1 (0)	1 (0)
Pain in extremity	1 (0)	0	0	0	0	0	0	3 (0)	0	0	0	0	1 (0)	0	1 (0)
Nervous system disorders	0	0	0	0	1 (0)	0	2 (2)	5 (4)	1 (0)	0	1 (1)	4 (3)	2 (2)	1 (1)	3 (3)
Dysgeusia	0	0	0	0	0	0	2 (2)	0	0	0	0	0	0	1 (1)	0
Headache	0	0	0	0	0	0	1 (0)	4 (3)	0	0	1 (1)	3 (1)	2 (2)	0	2 (2)
Somnolence	0	0	0	0	0	0	0	2 (2)	0	0	0	2 (2)	0	0	1 (1)
Respiratory, thoracic and mediastinal disorders	1 (0)	0	0	0	0	0	0	2 (0)	0	0	0	1 (0)	2 (0)	1 (1)	0
Nasal congestion	0	0	0	0	0	0	0	2 (0)	0	0	0	0	0	0	0

(continues)

Table 3
(Continued)

AEs by SOC and MedRA* preferred term	Number of subjects with treatment-emergent adverse events: all causalities (treatment-related)														
	SAD phase								MAD phase						
	PBO	PF-04965842							PBO	PF-04965842					
	0 mg n = 16	3 mg n = 6	10 mg n = 6	30 mg n = 6	100 mg n = 7	200 mg n = 6	400 mg n = 6	800 mg n = 16	0 mg n = 14	30 mg QD n = 6	100 mg QD n = 5	200 mg QD n = 6	400 mg QD n = 8	100 mg BID n = 6	200 mg BID n = 14
Skin and subcutaneous tissue disorders	1 (0)	1 (0)	0	0	1 (0)	1 (0)	0	4 (1)	2 (1)	0	0	2 (0)	1 (0)	1 (1)	6 (3)
Acne	0	0	0	0	0	1 (0)	0	1 (1)	0	0	0	2 (0)	0	1 (1)	3 (3)
Ecchymosis	0	0	0	0	1 (0)	0	0	2 (0)	0	0	0	0	0	0	3 (0)
Skin irritation	0	0	0	0	0	0	0	1 (0)	0	0	0	0	0	0	2 (0)

Includes all data collected since the first dose of study drug. Subjects were counted only once per treatment in each row.
*MedRA version 17.0 coding was applied. AE, adverse event; BID, twice daily; MAD, multiple ascending dose; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; QD, once daily; SAD, single ascending dose; SOC, system organ class.

corrected for heart rate using Fridericia's method (QTcF) interval of 450–<480 ms. These changes were sporadic and not significant clinically.

PK

PF-04965842 PK parameters and plasma concentration *vs*. time profiles are shown in Table 4 and Figure 2, respectively. In the SAD phase (Table 4a, Figure 2A) PF-04965842 was absorbed rapidly following single doses of 3 mg to 200 mg (median T_{max} < 1 h), and more slowly at the higher doses (median T_{max} 1.5–4.0 h for 400 mg and 800 mg). Following attainment of C_{max}, a monophasic decline was observed at the lower doses of 3 mg to 30 mg (mean $t_{½}$ 2.0–2.5 h) while a biphasic decline was observed at doses of 100 mg to 800 mg (mean $t_{½}$ 3.6–5.3 h). Plasma PF-04965842 C_{max} appeared to increase proportionally across the entire dose range, while increases in AUC_{inf} were greater than proportional at single doses of 400 and 800 mg. The difference was most notable in western subjects who received 800 mg. While C_{max} was similar in western and Japanese subjects who received 800 mg, the geometric mean AUC_{inf} was 26% higher in western subjects than that observed in Japanese subjects.

Multiple-dose PK parameters are shown in Table 4b and concentration–time profiles are illustrated in Figure 2B. On day 10, PF-04965842 was absorbed rapidly (median $T_{max} \leq 1$ h) across the entire range of doses, from a total daily dose of 30 mg (30 mg QD) up to 400 mg (200 mg BID or 400 mg QD). Following attainment of C_{max}, a biphasic decline was observed following all but the lowest dose and the mean $t_{½}$ ranged from 2.8 h to 5.2 h. Plasma PF-04965842 C_{max} and AUC_{τ} both showed a trend towards greater than proportional increases with increasing daily dose. Western subjects who received 200 mg BID had the highest dose-normalized AUC_{τ} and C_{max} of any dose level (data not shown), including Japanese subjects who received the same dosing regimen. Geometric mean C_{max} and AUC_{τ} following multiple-dose administration were 17% and 56% higher, respectively, in western subjects than Japanese subjects. Similarly, $t_{½}$ was also longer in western *vs*. Japanese subjects (5.2 h *vs*. 3.6 h, respectively). However, dose normalized AUC_{τ} for western subjects with the same total daily dose (400 mg QD) was similar to that observed for the Japanese subjects who received 200 mg BID, with geometric mean values of 45.51 ng h ml^{-1} $mg^{-1}$and 43.74 ng h ml^{-1} mg^{-1}, respectively. Urinary recovery of PF-04965842 was low (1.0–4.4%) and renal clearance averaged about 0.6 l h^{-1}.

Steady state was reached by day 4 for QD dosing and day 6 for BID dosing, based on comparison of predose trough concentrations across days. Geometric mean values for the observed accumulation ratio (R_{ac}: multiple-dose AUC_{τ}/single-dose AUC_{τ}) were 1.3–1.5 for QD dosing and 1.3–2.3 for BID dosing. Geometric mean values for the steady-state accumulation ratio (R_{ss}: multiple-dose AUC_{τ}/single-dose AUC_{inf}) were consistently >1 (1.3–1.5 for QD dosing and 1.2–2.0 for BID dosing), suggesting that there may be greater than linear increase in PF-04965842 exposure with multiple-dose administration. However, based on R_{ac}, the increase in exposure after 10 days of multiple dosing is less than three-fold for any of the dosing regimens studied.

Table 4

Pharmacokinetic parameters: (a) single-dose phase; (b) multiple-dose phase

(a)									
Parameter[a], units	**3 mg Cohort 1 *N* = 6**	**10 mg Cohort 2 *N* = 6**	**30 mg Cohort 3 *N* = 6**	**100 mg Cohort 4 *N* = 7**	**200 mg Cohort 5 *N* = 6**	**400 mg Cohort 6 *N* = 6**	**800 mg Cohort 7 *N* = 6**	**800 mg Cohort 8 *N* = 10**	**800 mg Cohorts 7 + 8 *N* = 16**
n^1, n^2	6, 5	6, 5	6, 6	7, 5	6, 6	6, 6	5, 5	10, 9	15, 14
AUC_{last}, ng h ml^{-1}	36.8 (84)	135.1 (40)	386.6 (44)	1226 (60)	2878 (29)	10 150 (28)	27 480 (35)	19 810 (53)	22 090 (49)
AUC_{inf}, ng h ml^{-1}	48.8 (64)	142.8 (44)	392.3 (43)	1465 (41)	2886 (29)	10 180 (28)	27 540 (35)	21 860 (43)	23 740 (40)
C_{max}, ng ml^{-1}	17.1 (27)	47.0 (21)	142.5 (50)	459.7 (53)	1072 (35)	2291 (42)	3819 (26)	3660 (48)	3712 (41)
T_{max}, h	0.634 (0.517–1.27)	0.750 (0.500–1.00)	0.792 (0.500–1.08)	0.550 (0.500–1.03)	0.767 (0.500–1.17)	1.50 (0.517–4.03)	4.03 (2.00–4.30)	2.02 (1.00–4.00)	3.92 (1.00–4.30)
$t_{½}$, h	2.09 ± 0.87	1.94 ± 0.55	2.53 ± 1.32	3.59 ± 2.08	3.89 ± 2.20	3.55 ± 1.11	5.27 ± 2.92	4.67 ± 1.57	4.88 ± 2.06
CL/F, l h^{-1}	61.44 (65)	70.02 (44)	76.41 (43)	68.34 (41)	69.31 (29)	39.32 (28)	29.00 (35)	36.61 (43)	33.69 (41)
V_z/F, l	172.5 (26)	190.1 (18)	256.2 (63)	318.5 (66)	343.0 (46)	193.3 (39)	197.1 (77)	235.0 (64)	220.7 (66)

(b)								
Parameter[b], units	**30 mg QD Cohort 3 *N* = 6**	**100 mg QD Cohort 4 *N* = 5**	**200 mg QD Cohort 5 *N* = 6**	**100 mg BID Cohort 6 *N* = 6**	**200 mg BID Cohort 7 *N* = 5**	**200 mg BID Cohort 8 *N* = 9**	**200 mg BID Cohorts 7 + 8 *N* = 14**	**400 mg QD Cohort 9 *N* = 8**
n^1, n^2	5, 5	5, 5	6, 6	6, 6	5, 5	6, 6	11, 11	6, 6
Plasma								
AUC_{τ}, ng h ml^{-1}	500 (38)	1977 (47)	4277 (34)	3107 (31)	13 680 (27)	8754 (30)	10 720 (36)	18 230 (24)
C_{max}, ng ml^{-1}	161 (50)	700 (31)	1199 (23)	773.0 (36)	2691 (8)	2294 (27)	2467 (22)	3334 (17)
T_{max}, h	0.55 (0.50–1.03)	0.55 (0.50–2.02)	1.05 (1.02–1.05)	0.759 (0.50–1.02)	1.02 (0.50–1.07)	0.50 (0.50–1.00)	0.50 (0.50–1.07)	0.767 (0.50–2.05)
$t_{½}$, h	2.76 ± 1.11	2.99 ± 0.76	3.06 ± 0.24	5.03 ± 2.34	5.17 ± 1.60	3.64 ± 0.83	4.34 ± 1.42	4.85 ± 1.86
CL/F, l h^{-1}	59.93 (38)	50.56 (47)	46.76 (34)	32.16 (31)	14.61 (27)	22.86 (29)	18.65 (36)	21.99 (24)
V_z/F, l	223.0 (43)	212.9 (43)	206.0 (29)	212.3 (65)	104.7 (42)	117.8 (31)	111.6 (35)	145.4 (34)
Urine								
Ae_{τ}%	1.03 (74)	1.17 (99)	1.42 (49)	NC[c]	4.38 (51)	2.60 (25)	3.30 (47)	2.64 (37)
CL_r, l h^{-1}	0.618 (33)	0.590 (41)	0.665 (20)	NC[c]	0.639 (40)	0.596 (13)	0.615 (27)	0.579 (23)

Notes (a):
Data for one subject in Cohort 7 (800 mg) were excluded due to vomiting.
[a]Values are geometric mean (geometric percent coefficient of variation) for all except: median (range) for T_{max}; arithmetic mean ± standard deviation for $t_{½}$.
AUC_{last}, area under the concentration–time profile from time zero to the time of the last quantifiable concentration; AUC_{inf}, area under the concentration–time profile from time zero extrapolated to infinite time; CL/F, apparent clearance; C_{max}, maximum plasma concentration; *N*, number of subjects in the treatment group; n^1, number of subjects contributing to the mean; n^2, number of subjects where $t_{½}$, AUC_{inf}, CL/F and V_z/F were determined; $t_{½}$, terminal half-life; T_{max}, time at which C_{max} occurred; V_z/F, apparent volume of distribution.
Notes (b):
Data for one subject in the 400 mg QD (Cohort 9) group were excluded due to vomiting.
[b]Values are geometric mean (percent coefficient of variation) for all except: median (range) for T_{max}; arithmetic mean ± SD for $t_{½}$.
[c]Protocol deviation in urine collection for Cohort 6.
Ae_{τ} %, cumulative percent of dose recovered unchanged in urine over the dosing interval τ; AUC_{τ}, area under the concentration–time curve from time zero to time τ, the dosing interval, where τ = 24 h for QD dosing and 12 h for BID dosing; BID, twice daily; CL/F, apparent clearance; CL_r, renal clearance; C_{max}, maximum plasma concentration; *N*, number of subjects in the treatment group (start of multiple dosing on day 1); n^1, number of subjects contributing to the mean (completed multiple dosing through day 10); n^2, number of subjects where $t_{½}$ and V_z/F were determined; NC, not calculated; QD, once daily; SD, standard deviation; $t_{½}$, terminal half-life; T_{max}, time at which C_{max} occurred; V_z/F, apparent volume of distribution.

PD

In the MAD phase, dose-dependent decreases from baseline in circulating IP-10 (Figure 3A) and hsCRP (Figure 3B) levels were observed as early as day 2 with all PF-04965842 doses. The maximal decreases were at predose on day 10, with 56% decrease in the 100 mg BID group and 54% in the 200 mg

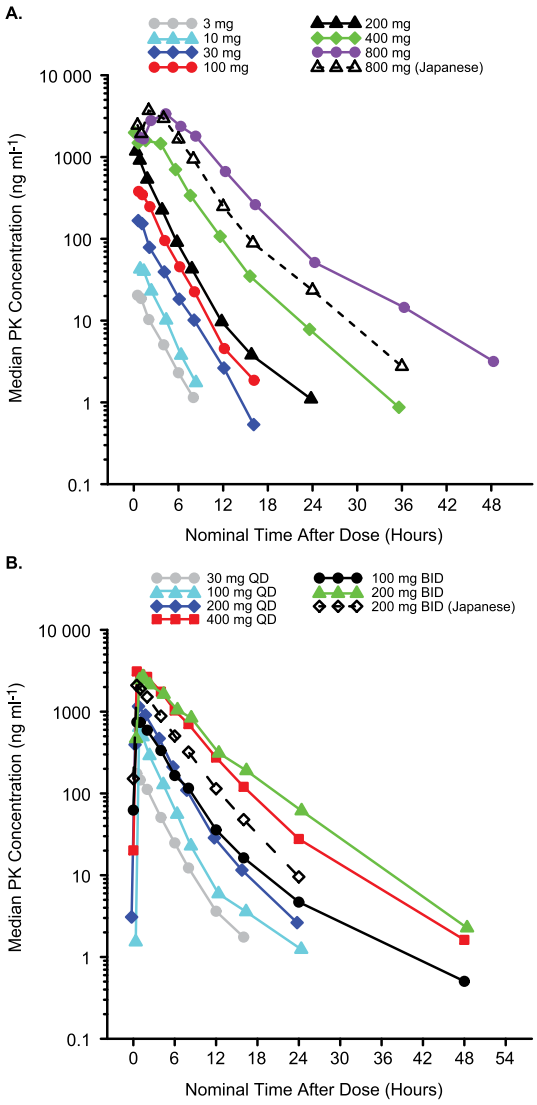

Figure 2

Plasma PF-04965842 concentration *vs*. time profiles. (A) SAD phase. Data for 1 subject in the 800 mg (western) group were excluded due to vomiting. (B) MAD phase. Data shown are for day 10 predose (0 h) up to 72 h postdose. Data for 1 subject in the 400 mg QD group were excluded due to vomiting. BID, twice daily; MAD, multiple ascending dose; PK, pharmacokinetic; QD, once daily; SAD, single ascending dose

BID group in IP-10 and 85% decrease in hsCRP in the 100 mg BID group.

PF-04965842 100 mg BID and 200 mg BID doses led to decreases from baseline in neutrophil counts from day 4 through day 10, but quickly recovered to or above the baseline levels following the termination of dosing on day 10, and this recovery was observed as early as day 11 (24 h post last dose of PF-04965842; Figure 3C). The maximum observed decrease of –47% occurred on Day 10, 6 h postdose in the 100 mg BID treatment group. Decreases from baseline in reticulocytes were observed in the 100 mg BID and 200 mg BID PF-04965842 doses relative to placebo; the maximal reduction was observed at 24 h postdose on day 10 in the 100 mg BID group (54%; Figure 3D).

Fluorescence-activated cell sorting (FACS) assessment of lymphocyte subsets showed varying effects on NK, T and B cells following PF-04965842 doses compared with placebo in the MAD phase. Generally, there were decreases in CD16+CD56+ NK cells, minimal changes in total CD3+ T cells, small increases in CD3+CD4+ T cells, small decreases in CD3+CD8+ T cells, and increases in CD19+ B cells (data not shown).

Discussion

This study in healthy subjects investigated the safety, tolerability, PK and PD properties of PF-04965842, a JAK1-selective inhibitor. There were no deaths, serious AEs, temporary discontinuations or dose reductions due to AEs. The most frequent TEAEs were headache, diarrhoea and nausea, which have previously been reported in healthy volunteers treated with other JAK inhibitors [18–20]. TEAEs were more common with the higher doses (single dose 800 mg and multiple dose 200 mg BID and 400 mg QD), but most were mild in severity. Occurrence of anaemia, thrombocytopenia and infections is of special interest in studies of JAK inhibitors [8, 13, 21]. There were no incidences of anaemia or thrombocytopenia during this study and the incidence of infections was low. Changes in lipid parameters were observed in this study, as has been reported in some studies with other JAK inhibitors [12–14, 22, 23]. The most dramatic effects on HDL and LDL cholesterol were observed in subjects receiving PF-04965842 BID.

Following single doses of PF-04965842, peak plasma concentrations occurred within 1 h for doses up to 200 mg, but were delayed following the 400 mg and 800 mg doses (1.5–4.0 h). Plasma PF-04965842 C_{max} concentrations increased proportionally across the entire dose range, while exposure in terms of the AUC was greater than proportional at doses of 400 mg and 800 mg. A monophasic decline was observed in the disposition of PF-04965842 at the lower doses (3–30 mg) and a biphasic decline was observed at the higher doses, probably due to concentrations for the lower doses declining below the lower limit of quantification before the slower terminal phase was observed. In comparison, a median T_{max} of 0.5–1 h followed by monophasic elimination was observed with single doses of tofacitinib (0.1–100 mg) in healthy volunteers [18]. Dose proportional systemic exposures and a mean $t_{1/2}$ of 2.5 h were observed for tofacitinib ≥3 mg [18]. Ruxolitinib was absorbed rapidly in healthy volunteers, typically attaining peak plasma concentrations within 2 h for single doses of 5–200 mg, and plasma concentration declined in a multiphasic manner with a mean terminal disposition $t_{1/2}$ of 3 h for the five lowest doses and 5 h for 200 mg [20]. C_{max} and AUC increased in a linear, dose-proportional manner for all the ruxolitinib doses [20].

On day 10 following multiple-dose PF-04965842 administration, peak plasma concentrations occurred within 1 h across the entire range of doses and plasma C_{max} and AUC_{τ} both appeared to show a trend towards greater than proportional increases with increasing daily dose. The PK profiles of PF-04965842 were comparable with those of baricitinib in healthy volunteers, with fast absorption (within 1.5 h)

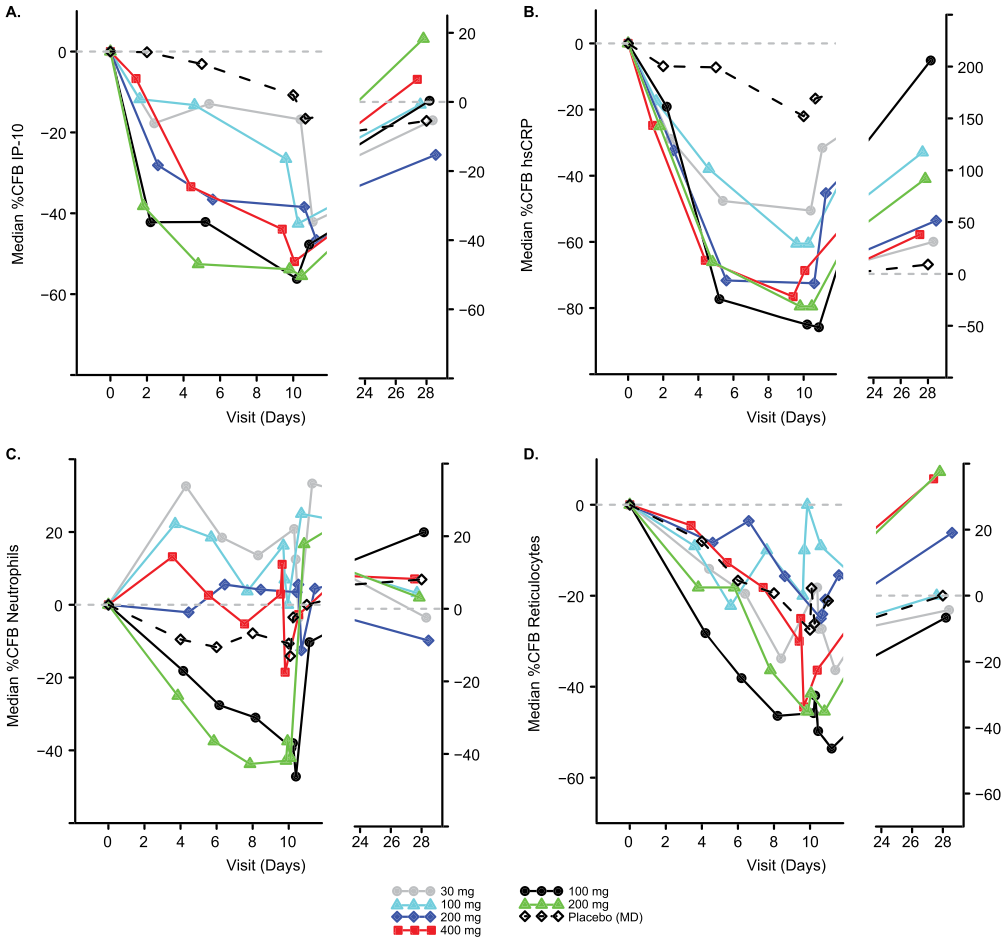

Figure 3

Median percent change from baseline in pharmacodynamic parameters over time (A) IP-10 levels; (B) hsCRP levels; (C) neutrophil counts; (D) reticulocyte counts. BID, twice daily; hsCRP, high-sensitivity C-reactive protein; IP-10, interferon gamma-induced protein 10; MAD, multiple ascending dose; MD, multiple dose; QD, once daily; SAD, single ascending dose

followed by biphasic decline in plasma concentrations [24]. For PF-04965842, steady state plasma concentrations generally appeared to have been reached by day 4 for QD dosing and day 6 for BID dosing, while ruxolitinib and baricitinib reached steady state by day 2 for all regimens [20, 24]. Urinary recovery of PF-04965842 was low, with 1.0–4.4% of the dose recovered unchanged on day 10 of multiple-dose administration, which was higher than the 0.11% urinary recovery reported on day 10 following 100 mg QD dosing of ruxolitinib [20], and lower than the 64.1% reported for baricitinib 2–20 mg QD doses [24]. The PK profiles of the western and Japanese subjects showed that dose adjustment would not be needed for Japanese subjects. However, some variability in geometric mean C_{max}, AUC_{τ} and $t_{½}$ between western and Japanese subjects was observed, suggesting differences in absorption as well as metabolism between the ethnic groups.

Decreases in neutrophil and reticulocyte counts consistent with the known effects of JAK signalling inhibition were greater with BID than with QD doses of PF-04965842. Reduced neutrophil and reticulocyte counts have been reported for healthy volunteers who received ruxolitinib BID [20] and reduced neutrophil counts have also been observed in patients with rheumatoid arthritis and psoriasis who were treated with tofacitinib [25, 26]. The decreases in reticulocyte counts, which were most prominent with BID PF-04965842 administration, may indicate some modulation of JAK2, leading to inhibition of erythropoietin (EPO) signalling [27, 28]. Transient and reversible dose-dependent decline in reticulocyte counts has been reported in patients with psoriasis who received tofacitinib BID [26]. The variability in baseline neutrophil counts observed in this study is not unusual. This variability shows difference by race with the African American subjects having lower neutrophil counts than Caucasians [29].

During the MAD phase, dose-dependent reductions occurred for IP-10 (downstream of IFNγ) [9, 30, 31] and hsCRP (downstream of IL-6) [9, 32, 33], which were included in this study as biomarkers of JAK1 inhibition. Decreases in NK cells and increases in B cells, minimal changes in total T cells, small increases in CD4+ T cells and small decreases in CD8+ T cells were observed. Similar effects have been observed with the JAK inhibitor tofacitinib [31, 34, 35].

In terms of study limitations, the current study only evaluated the effect of PF-04965842 administration over 10 days in healthy subjects. Patients with inflammatory diseases could react differently and additional adverse effects may emerge with prolonged dosing.

The pharmacokinetic and haematological safety data from this Phase 1 study provided upper and lower dose limits for the completed Phase 2 studies in psoriasis (NCT02201524) and atopic dermatitis (NCT02780167), which guided the doses implemented in the ongoing Phase 3 clinical trial for atopic dermatitis (JADE Mono-1; NCT03349060). The PK/PD modelling and simulation supporting dose selection for Phase 3 will be the subject of a separate publication.

In conclusion, the study results indicate that the JAK1 inhibitor PF-04965842 has a favourable safety profile and is well tolerated in healthy subjects, supporting further evaluation of PF-04965842 in patients with inflammatory diseases such as psoriasis and atopic dermatitis.

Competing Interests

E.P., M.R.H., E.K., S.T. and C.B. are employees of Pfizer and M.L.V., K.G. and C.W.A. were Pfizer employees when this study was conducted. All authors own stock in Pfizer.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13612/suppinfo

Figure S1 Median percent change from baseline over time (A) haemoglobin; (B) platelet counts. BID, twice daily; %CFB, percent change from baseline; QD, once daily

Figure S2 Median percent change from baseline over time (A) cholesterol; (B) high-density lipoprotein; (C) low-density lipoprotein. BID, twice daily; %CFB, percent change from baseline; QD, once daily