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ORIGINAL ARTICLE

The effect of dacomitinib (PF-00299804) on CYP2D6 activity in healthy volunteers who are extensive or intermediate metabolizers

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Abstract
Purpose This study evaluated the effect of a single 45-mg dose of dacomitinib (PF-00299804), an irreversible small-molecule inhibitor of human epidermal growth factor receptors-1, -2, and -4, on CYP2D6 activity in healthy volunteers (HV) using dextromethorphan (DM), a selective CYP2D6 probe.
Methods Fourteen male HVs were enrolled in this open-label, randomized, cross-over, single-dose study of DM alone or with dacomitinib. Each HV received both treatments separated by a 14-day washout period. The pharmacokinetics of DM, dextrorphan (DX; the major DM metabolite), dacomitinib and PF-05199265 (an active metabolite of dacomitinib) were calculated.
Results When combined with dacomitinib, the ratio of adjusted geometric means (90% CI) of DM area under the concentration–time curve $(AUC)_{last}$ was 955% (90% CI: 560%, 1,630%) and maximum plasma concentration (C_{max}) was 973% (90% CI: 590%, 1,606%), compared with DM alone. For dacomitinib plus DM, exposures were consistent with those in patients receiving single-dose dacomitinib. Terminal elimination half-life ($t_{1/2}$) was 51.4 h. Mild and moderate treatment-related adverse events were reported. No HV withdrew from the study.
Conclusions Single-dose administration of dacomitinib plus DM was safe and well tolerated in HVs and resulted in a significant increase in systemic exposures of DM in extensive metabolizers. No effect was observed on the pharmacokinetics of dacomitinib. Drug–drug interaction may occur when dacomitinib is concomitantly administered with therapeutic agents metabolized by cytochrome P450 (CYP) 2D6. Administration of drugs which are highly dependent on CYP2D6 metabolism may require dose adjustment, or substitution with an alternative medication.

Keywords Dacomitinib · PF-00299804 · Healthy volunteers · CYP2D6 extensive metabolizers · Dextromethorphan · Drug–drug interaction (DDI)

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Introduction

Dacomitinib (PF-00299804) is an orally administered, highly selective and irreversible small-molecule inhibitor of epidermal growth factor receptors (EGFR; human epidermal growth factor receptor [HER]1), HER2, and HER4 tyrosine kinases [1, 2]. In the clinic, dacomitinib has shown promising activity in patients with advanced non-small-cell lung cancer [3–9], as well as preliminary activity in patients with squamous cell carcinoma of the head and neck [10].

Dacomitinib appeared to be a potent cytochrome P450 (CYP) 2D6 inhibitor; in human liver microsomes in vitro,

dacomitinib inhibited CYP2D6 with an IC_{50} of approximately 60 nM (Pfizer Inc. Data on file), indicating that a drug–drug interaction could occur when it is concomitantly administered with medications metabolized by CYP2D6. Approximately 25% of commonly prescribed and clinically important drugs, including tricyclic antidepressants, selective serotonin reuptake inhibitors, opioids, anti-arrhythmics, antipsychotics, and some beta-blockers, are known to be CYP2D6 substrates [11–14]. However, CYP2D6 is characterized by a wide range of inter-individual and inter-ethnic differences in activity (resulting in poor, intermediate, extensive and ultrarapid metabolizers), which is partly accounted for by extensive genetic polymorphism [12, 15]. The observed phenotypic variation in CYP2D6 activity can lead to substantial (30- to 40-fold) differences in substrate drug clearance, with the potential for severe adverse effects and/or lack of response to medication [11, 16, 17].

We present the results of a study in healthy volunteers (predominantly extensive metabolizers) with the primary objective of examining the effect of a single dose of dacomitinib on CYP2D6 activity. Dextromethorphan-hydrobromide (DM) was used as the CYP2D6 probe. DM is a widely used antitussive drug found in many over-the-counter cough and cold medicines, and is a recognized, selective probe for evaluating CYP2D6 activity [12, 18, 19]. While regulatory guidance generally recommends the use of multiple doses of study medication in drug–drug interaction trials in order to fully inhibit or induce a particular enzyme, this trial utilized a single dose of the potentially inhibiting drug, dacomitinib. The decision to use a single 45-mg dose of dacomitinib was based upon previous reports indicating relatively low induction of CYP2D6 activity by its substrates in vitro [20, 21].

Patients and methods

Study objectives

The primary objective of this study was to estimate the effect of a single 45-mg dose of dacomitinib on the pharmacokinetics of a single 30-mg dose of DM in healthy volunteers. Secondary objectives were to assess the pharmacokinetics of a single dose of dacomitinib in healthy volunteers and to assess the safety and tolerability of dacomitinib and DM in healthy volunteers. The study was fully supported by Pfizer Inc. The study was conducted at one site (Pfizer Clinical Research Unit, Brussels, Belgium), and study drug was supplied by Pfizer Inc.

Subjects

The trial enrolled healthy male or female (non-childbearing potential) subjects, aged 18–55 years, who were CYP2D6 extensive metabolizers, ultrarapid metabolizers, or intermediate metabolizers, as predicted by CYP2D6 genotyping. Other key eligibility criteria included body mass index of 17.5–30.5 kg/m^2 and a total body weight >50 kg; absence of any condition affecting drug absorption; negative urine drug screen; alcohol consumption ≤14 drinks/week for females or 21 drinks/week for males; corrected QT interval ≤450 ms; no investigational drug within at least 30 days or 5 half-lives, and no prescription or non-prescription drugs or dietary supplements within 7 days or 5 half-lives before the first dose of study drug; and no blood donation of approximately 500 ml within 56 days before first dose of study drug. All subjects provided written informed consent prior to study entry. The study was approved by the Institutional Review Board/Independent Ethics Committee at the participating study site and was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines, in addition to meeting all local regulatory requirements.

A complete medical history and physical examination, including standard 12-lead electrocardiogram (ECG), were undertaken for each subject as part of a screening procedure within 28 days prior to the administration of study drug. Blood and urine specimens for safety laboratory tests were also collected following a 4-h fast, in addition to a urine drug test and a blood sample for CYP2D6 genotyping analysis.

Trial design and treatment

This was an open-label, randomized, two-period, two-treatment, two-sequence, cross-over, single-dose study of DM given alone and in combination with dacomitinib to 14 healthy adult volunteers. Each subject received two treatments (A and B) separated by a washout period of at least 14 days. Treatment A comprised a single 30-mg oral dose of DM; Treatment B consisted of a single 45-mg oral dose of dacomitinib administered as three 15-mg tablets followed 4 h later by a single 30-mg oral dose of DM.

Pharmacokinetic analyses

Healthy volunteers were to abstain from alcohol and caffeine-containing products for 24 h prior to admission until after collection of the final sample for pharmacokinetic assessment of each study period. Subjects were also required to abstain from all food and drink (except water) at least 8 h before the start of pharmacokinetic sample

collection. Consumption of grapefruit or grapefruit-related citrus fruits was not permitted from 7 days before the first dose of study drug until collection of the final pharmacokinetic blood sample. Strenuous exercise was prohibited for at least 48 h before each blood collection.

Whole blood samples were collected for pharmacokinetic analysis at the following times:

Treatment A: for analysis of DM and dextrorphan (DX; the major DM metabolite), collections pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 h after DM dosing; Treatment B: for analysis of DM and DX, collections pre-dose and at 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 28, and 52 h after DM dosing; Treatment B: for analysis of dacomitinib and PF-05199265 (a newly identified, active metabolite of dacomitinib), collections pre-dose and at 1, 2, 4, 6, 8, 12, 16, 24, 48, and 144 h after dacomitinib dosing on Day 1.

Plasma concentrations of dacomitinib and PF-05199265 were measured at Alta Analytical Laboratory (El Dorado Hills, CA, USA), while those of DM and DX were measured at WuXi AppTech (Shanghai, China) using validated liquid chromatography coupled with tandem mass spectrometry methods. Pharmacokinetic parameters were calculated for each subject for each treatment using a non-compartmental analysis of concentration–time data.

Evaluation of safety

Safety was assessed by monitoring adverse events throughout the trial, by clinical laboratory tests, vital signs (pulse rate and blood pressure), and by 12-lead ECG. Subjects were required to abstain from all food and drink (except water) at least 4 h before any safety laboratory evaluations.

The investigator was required to assess causality for all adverse events (i.e. whether there was a reasonable possibility that the study drug caused or contributed to an adverse event). For each adverse event, the maximum intensity/severity was to be described by the investigator as mild (did not interfere with the subject's usual function), moderate (interfered to some extent with the subject's usual function), or severe (interfered significantly with the subject's usual function). In addition to the severity grading, an adverse event was to be considered serious if it resulted in death, was life-threatening, required inpatient hospitalization/prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or in congenital anomaly/birth defect.

Pharmacogenomic evaluations

Blood samples collected from each subject at screening were genotyped for CYP2D6 using the Roche CYP2D6 AmpliChip® methodology (samples were analyzed by the DNA VISION SA, Gosselies, Belgium), in compliance with Pfizer standard operating procedures.

Statistical analyses

All subjects who had at least one of the pharmacokinetic parameters of primary interest in at least one treatment period were included in the pharmacokinetic analysis population.

A mixed-effects model based on natural log-transformed data was used to analyze the interactive effect on pharmacokinetic parameters; 90% confidence intervals (CIs) were constructed around the estimated difference between 'test' and 'reference' treatments (DM plus dacomitinib, and DM alone, respectively). Natural log-transformed AUC_{inf}, AUC_{last}, and C_{max} for DM and DX were analyzed separately using a mixed-effects model, with sequence, period, and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (test–reference) and corresponding 90% CIs were obtained from the model. The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference) and 90% CIs for the ratios.

Results

Patient characteristics and disposition

All 14 healthy volunteers enrolled completed the study and were included in safety and pharmacokinetic analyses of both treatments. The study population was comprised exclusively of Caucasian males with a mean (standard deviation) age of 39.3 (10.1) years, weight of 79.9 (8.8) kg, and body mass index of 25.1 (2.5) kg/m^2.

Thirteen of 14 subjects were confirmed to be CYP2D6 extensive metabolizers as determined by CYP2D6 genotyping at baseline; one subject was an intermediate metabolizer.

Pharmacokinetics

When administered with dacomitinib 45 mg, exposure (AUC_{last} and C_{max}) to DM was substantially increased when compared with DM alone (Table 1); the ratios of the adjusted geometric means of AUC_{last} and C_{max} were 955% and 973%, respectively (Table 2). The rate of absorption of DM also increased in the presence of dacomitinib (Table 1).

Once C_{max} was reached, median concentration–time profiles appeared to decline in parallel (Fig. 1a), with mean DM half-life estimated to be 8.44 and 9.88 h with and

Table 1 Summary of dextromethorphan (DM) and dextrorphan (DX) pharmacokinetic (PK) parameters when given alone or in combination with dacomitinib

Parameters[b]	Dextromethorphan PK		Dextrorphan PK	
	Treatment A[a]	Treatment B[a]	Treatment A[a]	Treatment B[a]
N, *n*	14, 3	14, 9	14, 10	14, 14
AUC_{inf}, ng h/ml	31.47 (118)[e]	85.49 (72)	2,239 (20)	1,935 (29)
AUC_{last}, ng h/ml	5.509 (420)	52.63 (148)	2,049 (24)	1,908 (29)
C_{max}, ng/ml	0.6801 (190)	6.621 (109)	273.4 (20)	223.6 (39)
T_{max}, h[c]	5.99 (2.00–6.03)	3.00 (2.00–4.00)	3.00 (2.00–4.00)	3.01 (2.00–6.00)
$t_{1/2}$, h[d]	9.880 (30)[e]	8.443 (20)	5.514 (23)	6.902 (23)
CL/F, ml/min	15,900 (118)[e]	5,849 (72)	NR	NR
Vz/F, l	13,110 (90)[e]	4,206 (54)	NR	NR

N = number of subjects; *n* = number of subjects contributing to $t_{1/2}$, AUC_{inf}, CL/F, and Vz/F (DM PK) or to $t_{1/2}$, AUC_{inf} (DX PK); NR = not reported

[a] Treatment A = DM 30 mg; Treatment B = DM 30 mg + dacomitinib 45 mg

[b] Geometric mean values (coefficient of variation; CV%) presented except for [c] T_{max} where median (range) presented and [d] $t_{1/2}$ where arithmetic mean (CV%) presented

[e] Summary statistics where <50% of subjects have reportable parameter values

Table 2 Summary of statistical analysis of plasma dextromethorphan and dextrorphan exposure

Parameters, unit	Test[a]	Reference[a]	Ratio, %[b]	90% confidence interval, %	
				Lower	Upper
Dextromethorphan					
AUC_{inf}, ng h/ml	87.27	24.13	361.71	276.94	472.43
AUC_{last}, ng h/ml	52.63	5.509	955.44	560.02	1,630.08
C_{max}, ng/ml	6.621	0.6801	973.54	590.03	1,606.32
Dextrorphan					
AUC_{inf}, ng h/ml	1,935	2,014	96.10	92.03	100.34
AUC_{last}, ng h/ml	1,908	2,049	93.15	88.38	98.17
C_{max}, ng/ml	223.6	273.4	81.78	71.15	94.00

Test = dacomitinib 45 mg + dextromethorphan 30 mg

Reference = dextromethorphan 30 mg

[a] Adjusted geometric mean values

[b] Ratio of adjusted geometric means (test/reference)

without dacomitinib, respectively. It is noted that the mean half-life for DM given alone is based on data from only three subjects and may not, therefore, reflect the majority of subjects within the group. Concentration–time profiles exhibited high inter-subject variability, reflected in the coefficient of variation (CV%) for exposure estimates, AUC and C_{max} (Table 1).

Median peak plasma concentrations (C_{max}) of DX were approximately 18% lower in the presence of dacomitinib. However, total exposure (AUC) to DX, T_{max} and decline in median DX plasma concentration–time profiles following C_{max} were similar when DM was given alone and combined with dacomitinib (Tables 1, 2; Fig. 1b).

The 90% CIs for the AUC ratio of test/reference for DX were completely contained within the 80–125% range, indicating that there was no clinically relevant effect of dacomitinib on total exposure to DX (Table 2).

When administered with DM, single doses of dacomitinib led to total exposures (AUC_{last} and C_{max}) consistent with those seen after single oral 45-mg doses of dacomitinib in patients with advanced malignant tumors (Pfizer Inc, Data on file). The rate of absorption was moderate, with a median T_{max} of 6 h. The decline in median dacomitinib plasma concentration–time profiles after C_{max} was multiphasic, with an estimated $t_{1/2}$ of 51.42 h (Table 3; Fig. 2).

The pharmacokinetic profile of the dacomitinib metabolite, PF-05199265, resembled that of the parent drug, with a similar T_{max} and $t_{½}$ (Table 3; Fig. 2). Exposure to PF-05199265 was approximately 31% of parent drug exposure.

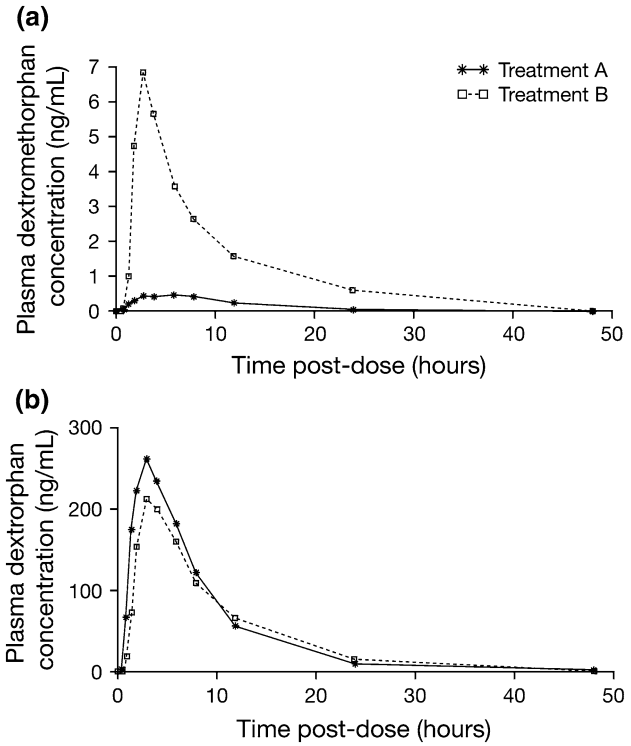

Fig. 1 Median concentration–time profiles of **a** dextromethorphan and **b** dextrorphan for Treatments A and B

Table 3 Summary of dacomitinib and PF-05199265 pharmacokinetic parameters for Treatment B (dacomitinib 45 mg + dextromethorphan 30 mg)

Parameters, unit[a]	Dacomitinib	PF-05199265
N, *n*	14, 13	14, 8
AUC_{inf}, ng h/ml	1,271 (26)	541.6 (39)
AUC_{last}, ng h/ml	1,098 (23)	340.2 (53)
C_{max}, ng/ml	24.68 (31)	6.149 (65)
T_{max}, h[b]	6.00 (6.00–8.03)	6.00 (3.92–6.08)
$t_{1/2}$, h[c]	51.42 (18)	51.60 (14)
CL/F, ml/min	590.0 (27)	NR
Vz/F, l	2,588 (24)	NR

N = number of subjects; *n* = number of subjects contributing to $t_{1/2}$, AUC_{inf}, CL/F, and Vz/F (dacomitinib) or to $t_{1/2}$, AUC_{inf} (PF-05199265); NR = not reported

[a] Geometric mean values (coefficient of variation; CV%) presented except for [b] T_{max} where median (range) presented and [c] $t_{1/2}$ where arithmetic mean (CV%) presented

Safety and tolerability

Six and nine subjects experienced treatment-emergent adverse events on Treatments A and B, respectively. These adverse events were all mild or moderate, with gastrointestinal disorders most commonly reported (Table 4).

No subjects discontinued treatment either temporarily or permanently due to an adverse event of any cause, nor were there any serious adverse events or deaths during the study period. There were no clinically significant laboratory test abnormalities during the study. One subject had a supine pulse rate <40 beats per minute 4 h post-dose (Treatment B). Changes in ECG were similar during the two treatment periods.

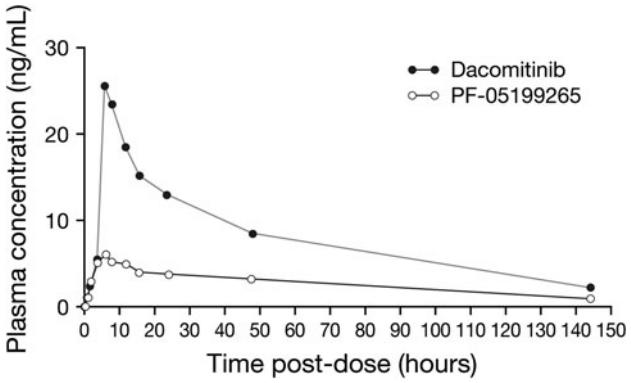

Fig. 2 Median concentration–time profiles of dacomitinib and PF-05199265 (Treatment B)

Table 4 Incidence and intensity of treatment-emergent adverse events

Adverse events	Treatment A[a]			Treatment B[a]		
	Mild	Moderate	Total[b]	Mild	Moderate	Total[b]
Diarrhea	5	0	5	6	0	6
GI sounds abnormal	2	0	2	2	0	2
Abdominal discomfort	1	0	1	0	0	0
Abdominal distension	1	0	1	0	0	0
Abdominal pain	1	0	1	1	1	2
Arthralgia	1	0	1	0	0	0
Flatulence	1	0	1	1	0	1
Hemorrhoids	1	0	1	0	0	0
Wound	1	0	1	1	0	1
Back pain	0	0	0	0	1	1
Headache	0	0	0	2	0	2

GI = gastrointestinal; mild = did not interfere with the subject's usual function; moderate = interfered to some extent with the subject's usual function

[a] Treatment A = dextromethorphan 30 mg; Treatment B = dacomitinib 45 mg + dextromethorphan 30 mg

[b] There were no severe adverse events

Discussion

In this open-label, two-treatment, cross-over study in healthy volunteers, single-dose dacomitinib in combination

with DM was safe and well tolerated. When co-administered with single-dose dacomitinib, systemic exposure of DM increased by almost 900% when compared with DM administration alone, although exposure of DX, the major metabolite of DM, was unaffected.

The pharmacokinetic profile, and exposure to dacomitinib in the presence of DM in healthy volunteers, was similar to that observed following single-dose dacomitinib alone in patients with solid malignancies (Pfizer Inc, Data on file) and resulted in exposures of the metabolite PF-05199265 that were approximately 31% of the parent drug.

Studies investigating metabolic inhibitors, such as dacomitinib, have commonly used repeated doses of the inhibitor in order to achieve steady-state concentrations and saturate the metabolizing enzyme (in this case CYP2D6) before administering a test substrate. However, administration of multiple doses of dacomitinib to healthy volunteers is not recommended. The use of a single dose of dacomitinib in this study was based upon published reports indicating relatively low induction of CYP2D6 activity by its substrates in vitro in cultured human hepatocytes and human liver slices [20–22]. The results of this study provide a clinically meaningful insight into the magnitude of the effect of dacomitinib on CYP2D6 activity.

This study enrolled healthy subjects who were predominantly (13/14 subjects) extensive CYP2D6 metabolizers, as determined by genotyping. Extensive metabolizers comprise the majority (70–80%) in European Caucasian populations [23, 24], but the distribution of CYP2D6 ultrarapid, extensive, intermediate, and poor metabolizers is unequal between major ethnic groups [11, 14]. For example, the incidence of poor metabolizers has been estimated at 6–10% in Caucasians [24–27] and at 0–1.2% in Asian populations [25, 28, 29].

The pharmacokinetic impact of the wide inter-individual variation in the enzymatic activity of CYP2D6 has been well documented for many substrates [14, 30]; however, the clinical impact, with respect to therapeutic response, adverse effects and dosing of drugs metabolized by CYP2D6, is less clear. There are data to show that for agents where CYP2D6 represents a substantial metabolic pathway either in the formation of active metabolites or clearance of the drug, and polymorphisms can affect activity or lead to increased adverse effects. For example, there is evidence of therapeutic failure following tamoxifen treatment in poor metabolizers (who are unable to convert parent drug to the more potent metabolite endoxifen) and a greater incidence of adverse effects with tamoxifen in ultrarapid metabolizers [31, 32]. Similarly, a trend toward an increased incidence of adverse effects from drugs primarily cleared by CYP2D6 metabolism has been identified in intermediate and poor metabolizer psychiatric patients compared with ultrarapid and extensive metabolizers [17]. However, no significant association between CYP2D6 phenotype and adverse effects was reported in patients (extensive and ultrarapid metabolizers vs. poor and intermediate metabolizers) treated with the CYP2D6 metabolized beta-blocker metoprolol, despite the marked differences in metoprolol plasma concentrations between metabolizer groups [23].

As there is currently some uncertainty with regard to relationships between CYP2D6 genotype–phenotype and pharmacokinetics, dosing, clinical activity and adverse effects of specific drugs, dose adjustment based strictly on CYP2D6 phenotype is not currently recommended. However, genotype testing merits further research as dose adjustments and avoidance of some drug combinations may be required in certain individuals to ensure an optimal response and to minimize adverse effects of treatment.

This study has clearly demonstrated that co-administration of the CYP2D6 inhibitor dacomitinib with a drug that is metabolized by CYP2D6 can have a dramatic effect on the pharmacokinetics of that drug in subjects who are CYP2D6 extensive metabolizers. While the study did not explore the effects of dacomitinib in subjects within the other CYP2D6 metabolizer categories (ultrarapid, intermediate or poor), the present results would indicate a worst case scenario, as the inhibitory effect of dacomitinib on poor or intermediate metabolizers would be expected to be less than on extensive metabolizers [33].

Based on the findings of this study, administration of drugs which are highly dependent on CYP2D6 metabolism may require dose adjustment or substitution with an alternative medication.

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