Effect of food on the pharmacokinetics of erlotinib, an orally active epidermal growth factor receptor tyrosine-kinase inhibitor, in healthy individuals

Jie Ling[a], Scott Fettner[b], Bert L. Lum[a], Myriam Riek[c] and Ashok Rakhit[b]

The effects of food on the pharmacokinetics of erlotinib were investigated in two open-label, randomized studies. In a single-dose crossover study ($n=18$), 150 mg of erlotinib was administered under either fasting or fed conditions. In the first period, an approximate doubling in the area under the plasma concentration–time curve was evidenced by the geometric mean ratio (GMR) of 2.09 observed under fed conditions; whereas, in the second period there was a decrease, with a GMR of 0.93. In a multiple-dose parallel study ($n=22$), 100 mg of erlotinib was administered daily for 8 days, either 7 days of fasting followed by feeding on day 8, or the reverse sequence. In this study, food resulted in an increase in the plasma concentration–time curve on day 1, with a GMR of 1.66 ($P=0.015$). In contrast, there was only a 37% increase on day 7, with a GMR of 1.34 ($P=0.252$). These studies indicate that food can substantially increase plasma exposure to erlotinib. Given the maximum tolerated dose of erlotinib used in clinical practice, we recommend that erlotinib be taken under conditions of fasting.

Anti-Cancer Drugs 19:209–216 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2008, **19:**209–216

Keywords: erlotinib, food effect, pharmacokinetics

[a]Genentech Inc., South San Francisco, California, [b]Department of Clinical Pharmacology, F. Hoffmann-La Roche Inc., New Jersey, USA and [c]Department of Global Drug Development Biostatistics, F. Hoffmann-La Roche Ltd, Basel, Switzerland

Correspondence to Dr Ashok Rakhit, The Medicines Company, 8 Campus Drive, Parsippany, NJ 07054, USA
Tel: +1 973 647 6077; fax: +1 973 656 9898;
e-mail: ashok.rakhit@themedcc.com

Previous presentations of (part of) this work: an abstract relating to this study was presented at ECCO 12 – the European Cancer Conference (Copenhagen, Denmark), 21–25 September 2003. Abstract 552 by Abbas R, *et al.* entitled 'Clinical pharmacokinetics of erlotinib in healthy participants'.

Received 29 May 2007 **Revised form accepted** 29 September 2007

Introduction

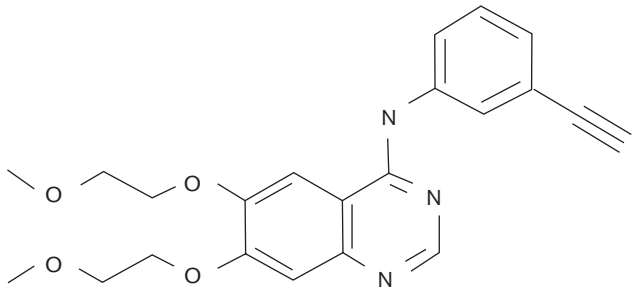
Erlotinib (Fig. 1) is an orally bioavailable, potent, highly selective human epidermal growth factor receptor tyrosine-kinase inhibitor that shows antitumor activity in both preclinical models [1–3] and in clinical studies, whether administered as a single agent or in combination with other anticancer agents [4–9]. Erlotinib is the first drug in its class to demonstrate a significant survival benefit in solid tumors. In advanced non-small cell lung cancer, erlotinib (150 mg) monotherapy produced a significant survival benefit compared with the best supportive care, following failure of at least one chemotherapy regimen [8]. Erlotinib, in combination with gemcitabine, also significantly prolongs survival in patients with locally advanced or metastatic pancreatic cancer [7,10].

In cancer patients, bioavailability of erlotinib following a 150-mg oral dose is about 60%, and mean maximum plasma concentrations occur 4 h after dosing [10]. Following oral absorption, erlotinib is approximately 93% protein bound to albumin and α-1 acid glycoprotein. In-vitro experiments show that erlotinib is extensively metabolized, primarily by cytochrome P450 (CYP) 3A4 (CYP3A4) and, to a lesser extent, by CYP1A2 and the extrahepatic enzyme CYP1A1 [10]. The major metabolites of erlotinib are OSI-420 (Fig. 1), an active moiety, and OSI-413, which differ in the positions of *o*-desmethylation. Following a 100-mg oral dose, 91% of the dose was recovered (83% in feces and 8% in urine) [11]. The elimination half-life of erlotinib in cancer patients is about 36 h, with an apparent volume of distribution of 232 l. No significant relationships were observed between clearance and patient age, body weight, or sex. Smokers, however, had a 24% higher rate of erlotinib clearance, presumably as a result of the induction of the CYP1A1 and/or CYP1A2 enzymes [10]. Healthy participants seem to have a faster rate of erlotinib clearance than cancer patients: it has been speculated that this is, in part, due to the higher concentrations of α-1 acid glycoprotein in cancer patients [12,13].

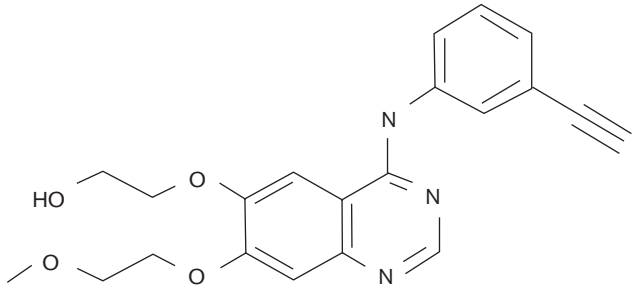
Food can significantly affect the pharmacokinetic profile of orally administered drugs and their metabolites [14,15]. Potential changes in exposure as a result of food–drug interactions might be of particular clinical relevance for erlotinib, as such changes in exposure can affect its antitumor efficacy, in addition to impacting on the incidence of dose-related toxicities [16]. Therefore, we conducted two clinical trials (a single-dose study and

0959-4973 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins

Fig. 1



Erlotinib



OSI-420

Chemical structures of erlotinib and OSI-420.

a multiple-dose study) to determine the effect of food on the pharmacokinetics of erlotinib and its major metabolites in healthy men. This report combines and summarizes the results of these two studies.

Methods

Two randomized, single-center, open-label studies were conducted in healthy men. The first evaluated the effect of food on the single-dose pharmacokinetics of erlotinib (Tarceva; OSI Pharmaceuticals, Melville, New York, USA), and is referred to here as the single-dose study. The second study evaluated the effect of food, the effects of occasional food intake, and the effects of skipping a concomitant meal on the multiple-dose pharmacokinetics of erlotinib; this is referred to here as the multiple-dose study. Both studies were conducted at the Institut de Pharmacologie Clinique Roche (Strasbourg, France), after approval of the protocols and informed consent forms from an independent ethics committee, CCPPRB (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale).

Participants

For both studies, eligible participants were healthy men volunteers aged 18–65 years, with a body mass index of 18–30 kg/m^2. Participants were assessed to be healthy on the basis of physical examination, medical history, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations performed at screening. Participants were excluded if they had any clinically significant abnormal finding or a positive urine drug screen; if they had used any prescription medication within 7 days, or had imbibed a total dose of the medication equivalent to six times its elimination half-life before study drug intake, whichever was longer; or if they smoked more than 10 cigarettes per day. Other exclusion criteria included blood loss (or blood donation) of more than 400 ml during the preceding 3 months, history of past and/or current drug abuse and/or alcoholism, and participation in a clinical study with an investigational drug in the preceding 3 months. During the studies, no medications were permitted, with the exception of those to treat adverse events. In the multiple-dose study, additional exclusion criteria included use of a known oral inhibitor or inducer of CYP3A4 within 4 weeks of dosing.

All participants gave written informed consent before participation in the studies. The studies were conducted according to the principles of the Declaration of Helsinki and its amendments.

Study design

Single-dose study

This was a single-dose, open-label, randomized, two-treatment, two-period, two-sequence crossover study. Twenty-one participants were randomized to two treatment sequences, fasting followed by feeding (AB) or *vice versa* (BA), with a 1-week washout period between treatments. Single, oral 150-mg doses of erlotinib hydrochloride in film-coated tablets were administered with 200 ml of water either after a 10-h overnight fast (A) or within 5 min of consumption of the standard high-fat, high-calorie breakfast (B). During the inhouse phase of the study, standard meals were provided to all participants. All meals and snacks were identical for each period, and were served at the same time relative to drug intake. Tap water was allowed *ad libitum*, beginning 2 h after dosing. Participants were not allowed to consume any food for at least 4 h after study drug administration.

Multiple-dose study

This was a multiple-dose, open-label, randomized, parallel-group study. Thirty-six participants were planned for, and 22 were enrolled and randomized to two groups. Participants in group A (fasting) received oral 100-mg doses of erlotinib hydrochloride in film-coated tablets once daily, under conditions of fasting on days 1–7, followed by a dose after intake of food on day 8. Participants in group B (fed) received the same daily erlotinib dose after food intake on days 1–7, followed by a dose after fasting on day 8. The fasting and food-intake conditions were as described for the single-dose study, and participants remained in the study center from days 1–9. Although 150 mg of medication once daily has been

selected as the therapeutic dose in patients with advanced non-small cell lung cancer, this dose has not yet been tested as a multiple-dose regimen in healthy participants. In the single-dose study, a 100% increase in exposure to a single 150-mg erlotinib dose was observed following administration under food-intake conditions compared with fasting conditions. A daily dose of 100 mg was, therefore, selected for the multiple-dose study. This dose was regarded as being tolerable during a short period of multiple dosing, even under food-intake conditions. On the basis of the observed linearity in erlotinib pharmacokinetics [10], the results obtained from this study can be reasonably extrapolated to a daily dose of 150 mg.

Sample collection and assay methods

Single-dose study

Blood samples (7 ml) for the measurement of erlotinib and its metabolite (the sum of the desmethylated metabolites OSI-420 and OSI-413) concentrations were collected in lithium heparin tubes immediately before drug administration and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, and 96 h after each single erlotinib dose.

Multiple-dose study

Blood samples (7 ml) for the measurement of erlotinib and metabolite concentrations were collected in lithium heparin tubes at the following time points on days 1, 7, and 8: predose (on days 1 and 7), and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 18, and 24 h after the dose. Additional trough (predose) samples were taken on days 3–6, and a further sample was taken on day 9 (36 h after the last dose).

For both single-dose and multiple-dose studies, after centrifugation, plasma samples were separated from whole blood within 1 h of collection, and samples were immediately frozen and stored frozen until analysis.

Assay methods

Plasma concentrations of erlotinib and OSI-420 were analyzed using an isocratic reverse-phase high-performance liquid chromatographic tandem mass spectroscopy method (MDS Pharma Services, Saint-Laurent, Montreal, Quebec, Canada). Briefly, diluted buffered plasma samples were fortified with an internal standard (CP-396,059, a methylated derivative of erlotinib), loaded onto a diatomaceous earth cartridge, and a liquid/liquid extraction performed with t-butyl methyl ether. Following drying and resuspension, the analytes were separated using a Waters Symmetry C-18 column (50×4.6 mm, 3.5 microns) with 30% 10 mmol/l ammonium formate buffer (pH 4.8) and 70% methanol as the mobile phase. Following elution from the column, the analytes were ionized by a Heated Nebulizer, and mass transitions were monitored by the mass spectrometer; 394.3/278.0 m/z for erlotinib and 380.3/278.0 m/z for OSI-420/413. This method does not distinguish between OSI-420 and OSI-413; hence, these molecules are collectively reported as OSI-420. Assay ranges for erlotinib and OSI-420 were 1–3000 and 1–1000 ng/ml, respectively. The lower limit of quantitation (LLOQ) was 1.09 ng/ml for OSI-774 and 1.01 ng/ml for OSI-420. The precision of the assay, as determined from the analyses of quality-control samples, was better than 4.6% for OSI-774 and better than 6.9% for OSI-420. The assay accuracy ranged from 100.7 to 109.1% for OSI-774 and from 99.3 to 111.5% for OSI-420 (unpublished data). The LLOQ was set at the concentration of the lowest nonzero standard (1 ng/ml for each compound). All measures below LLOQ were excluded when calculating pharmacokinetic parameters.

Pharmacokinetic methods

Concentration–time data for plasma erlotinib and its metabolites were analyzed using standard noncompartmental methods (WinNonlinVersion 3.1; Pharsight Inc., Mountain View, California, USA).

Single-dose study

The following pharmacokinetic parameters were determined on the basis of the plasma concentration–time profiles of erlotinib and OSI-420: area under the concentration–time curve from time zero to infinity ($AUC_{0-\infty}$) and from time zero to the time of the last measurable concentration (AUC_{0-t}), using a linear trapezoidal method; peak concentration (C_{max}); time to C_{max} (t_{max}); and lag time for delayed absorption (t_{lag}; only applicable for erlotinib).

Multiple-dose study

The following pharmacokinetic parameters were obtained from the plasma concentration–time profiles of erlotinib and OSI-420 on days 1, 7, and 8: AUC from time zero to 24 h ($AUC_{0-24\,h}$), C_{max}, and t_{max}.

Statistical methods

Statistical analyses were performed using SAS version 6.12 (SAS Institute Inc., Cary, North Carolina, USA). Statistical evaluations of the effect of food on the pharmacokinetics of erlotinib were based on the primary study variables, C_{max} and AUC; measures of the rate and extent of absorption of erlotinib, $AUC_{0-\infty}$ and AUC_{0-24}, were used for the single-dose and multiple-dose studies, respectively.

Single-dose study

Participants who completed both treatments were included in the analysis, with an analysis of variance (ANOVA) model being applied to all available log-transformed pharmacokinetic parameter data for both periods 1 and 2, as follows:

$$y_{ijk} = \mu' + \delta_i + s_{j(i)} + \pi_k + \tau_{[i,k]} + \varepsilon_{ijk} \quad (i = \text{AB, BA}; j = 1, \ldots, N_i; k = 1, 2) \tag{1}$$

where μ' denotes the general mean of the logged variable; δ_i, the effect of sequence i; $s_{j(i)}$, the effect of participant j in sequence i; π_k, the effect of period k; $\tau_{[i,k]}$, the effect of the treatment applied in sequence i and period k; ε_{ijk}, the random deviation; and N_i, the number of participants included in sequence i.

Owing to the significant sequence effect observed on $AUC_{0-\infty}$, ($P = 0.001$), the data for each period were analyzed separately, using the following ANOVA model:

$$y_{ij} = \mu' + \tau_i + \varepsilon_{ij} \quad (i = \text{A, B}; j = 1, \ldots, N_i) \qquad (2)$$

To assess the effect of food, treatment B (food intake) was compared with treatment A (fasting), using treatment A as a reference. The relative exposure of erlotinib (with food versus without food) was estimated, and two-sided 90% confidence intervals (CIs) were calculated.

Multiple-dose study

To assess the effect of food on the multiple-dose pharmacokinetics of erlotinib, an ANOVA model (equation 2) was applied to the log-transformed $AUC_{0-24\,h}$ and C_{max} of erlotinib obtained on days 1 and 7. The ratios of treatment group B (food intake) versus group A (fasting) were estimated, together with the two-sided 90% CIs.

To investigate the effect of occasional intake of food and occasional skipping of the concomitant meal, the following ANOVA model was applied to the log-transformed $AUC_{0-24\,h}$ and C_{max} of erlotinib obtained on days 7 and 8 for each treatment group (A or B) separately.

$$y_{ij} = \mu' + \tau_i + s_j + \varepsilon_{ij} \quad (i = \text{fasted, fed}; j = 1, \ldots, N) \qquad (3)$$

The ANOVA analyses included all randomized participants adherent to the protocol, who had received at least one dose of the study medication, and for whom sufficient concentration measurements were available to calculate at least one pharmacokinetic parameter ($AUC_{0-24\,h}$ or C_{max}).

Safety

Participant safety assessments included adverse events (AEs), clinical laboratory tests (hematology, serum chemistry, and urinalysis), assessment of vital signs, and ECG.

Results

Participant demographics and disposition

Single-dose study

A total of 21 participants (20 Caucasian) participated in the study, with a mean age of 29 years (range 20–59) and a mean weight of 78 kg (range 60–96). Three participants withdrew from the study following a single treatment, (two as a consequence of laboratory abnormalities and one for personal reasons), and were replaced. The final pharmacokinetic population was 18 participants (nine per sequence) who completed the study.

Multiple-dose study

A total of 22 participants (20 Caucasian) participated in the study, with a mean age of 33 years (range 19–59) and a mean weight of 76 kg (range 62–100). All demographic characteristics were well matched between the groups (data not shown). Among these participants, 11 did not complete the scheduled 8 days of treatment. Four were withdrawn as a consequence of AEs or a severe AE (SAE), and another was withdrawn owing to a significant laboratory abnormality. The remaining six were withdrawn for administrative reasons, as the protocol-defined study-stopping criteria had been met by the occurrence of both an SAE and a significant laboratory abnormality. The statistical evaluations of the effect of food on the pharmacokinetics of erlotinib were based on 22 participants for day 1, 14 participants for day 7, and 11 participants for day 8.

All participants who received at least one dose of erlotinib were included in the safety assessment.

Pharmacokinetic and statistical analyses

Single-dose study

Owing to the presence of a formal sequence effect, the table and the plot were organized for each period separately. The most reliable estimate of the effect of food was considered to be from period 1 only.

In period 1, administration of erlotinib with food resulted in an increase in $AUC_{0-\infty}$ and in C_{max} (Table 1), as evidenced by geometric mean ratios (GMRs) for erlotinib C_{max} and $AUC_{0-\infty}$ (under food-intake versus fasting conditions) of 1.64 ($P = 0.0003$; 90% CI, 1.30–2.06) and 2.09 ($P = 0.0024$; 90% CI, 1.65–2.64), respectively. The t_{max} seemed essentially unchanged when erlotinib was administered with food, although t_{lag} was increased by 0.5 h (Table 1 and Fig. 2).

In period 2, no appreciable effect of food on the pharmacokinetics of erlotinib was observed (Table 1).

Multiple-dose study

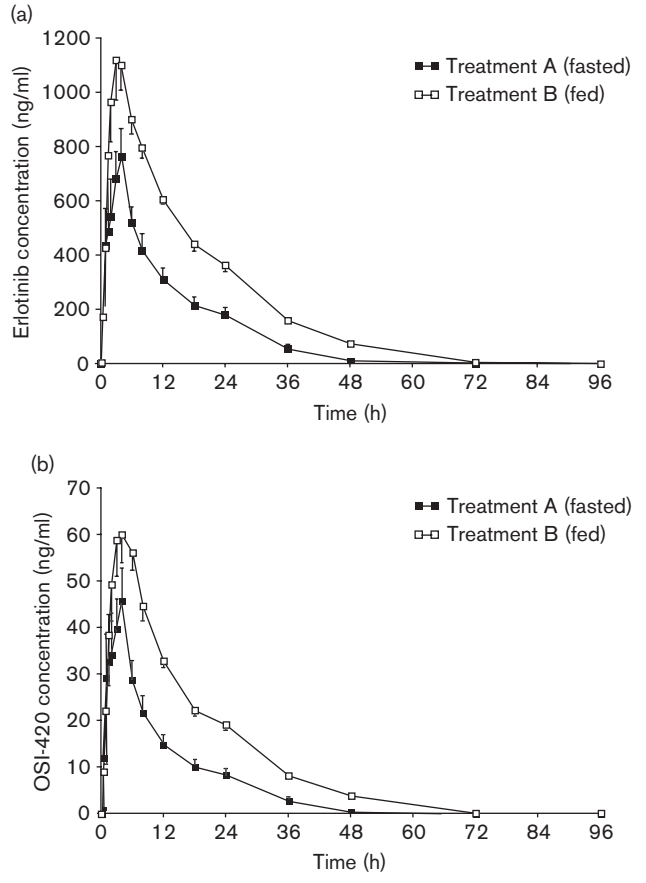
Plasma concentration–time curves of erlotinib are shown in Fig. 3, and the mean pharmacokinetic parameters for erlotinib are presented in Table 2. Food-intake status resulted in an increase in systemic exposure ($AUC_{0-24\,h}$) on day 1, with a GMR of food intake versus fasting of 1.66 (90% CI, 1.20–2.32), indicating a significant food effect ($P = 0.015$). On day 7, the estimated increase in mean $AUC_{0-24\,h}$ of 37% under food-intake versus fasting conditions shows a similar trend to that observed on day 1, but is not statistically significant (90% CI for true mean ratio: 0.87–2.07; $P = 0.252$). Although the

Table 1 Mean erlotinib pharmacokinetic parameters following single oral administration of a 150-mg tablet with and without food ($n=18$)

	C_{max} (ng/ml)	t_{max} (h)	AUC_{0-t} (ng*h/ml)	$AUC_{0-\infty}$ (ng*h/ml)	$t_{1/2}$ (h)	t_{lag} (h)
Period 1						
Fasting condition[a] ($n=9$)	852 (320)	2.78 (1.06)	10171(3937)	10533 (3776)	7.40 (2.24)	0.17 (0.18)
Food-intake condition[a] ($n=9$)	1339 (244)	2.89 (1.52)	20367 (2070)	20775 (1946)	8.85 (1.60)	0.67 (0.60)
Treatment ratio[b]	1.64 (1.30–2.06)	NA	NA	2.09 (1.65–2.64)	NA	NA
Period 2						
Fasting condition[a] ($n=9$)	1078 (326)	2.33 (1.09)	16817 (3331)	16961 (3281)	9.07 (3.20)	0.03 (0.08)
Food-intake condition[a] ($n=9$)	1238 (401)	3.67 (1.58)	15596 (3569)	15982 (3635)	6.53 (2.65)	0.53 (0.20)
Treatment ratio[b]	1.15 (0.91–1.46)	NA	NA	0.93 (0.78–1.12)	NA	NA

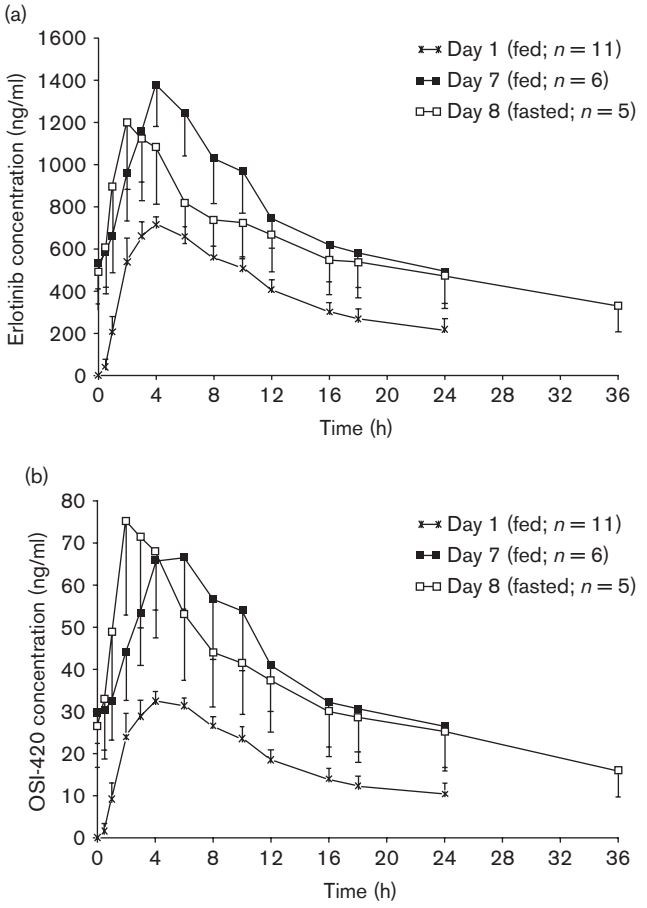
[a]Values shown are arithmetic means (SD).
[b]GMR (food intake/fasting) (90% CIs) presented.
AUC, area under curve; CI, confidence interval; C_{max}, peak concentration; GMR, geometric mean ratio; NA, not applicable; t_{lag}, lag time for delayed absorption; $t_{1/2}$, time to half-life; t_{max}, time to C_{max}.

Fig. 2



Mean (±SE) plasma concentrations of erlotinib and metabolite (OSI-420) over time after single oral administration of a 150-mg tablet of erlotinib in period under food-intake and fasting conditions.

Fig. 3



Mean (±SE) plasma concentrations of erlotinib and metabolite (OSI-420) over time after multiple oral administration of 100-mg tablets of erlotinib. Group B had intake of food on days 1–7, and fasted on day 8.

variability of the pharmacokinetic data was similar on days 1 and 7 (coefficient of variation: 47 versus 45%), the larger width of the 90% CI on day 7 reflects the lower number of participants compared with day 1 (14 versus 22, respectively). Similarly, the GMRs of food-intake versus fasting conditions for C_{max} were estimated to be 1.56 and 1.33 on days 1 and 7, respectively. Owing to the larger variability, the estimated mean increases in C_{max} were not statistically significant on either day ($P > 0.05$).

Table 3 summarizes the estimated geometric least square mean (GLSM) values of food-intake versus fasting

conditions for $AUC_{0-24\,h}$ and C_{max} after occasional intake of food under fasting conditions (group A) and the estimated GMRs of fasting versus food intake after skipping a concomitant meal under food-intake conditions (group B). In group A, an increase in the $AUC_{0-24\,h}$ was observed under food-intake conditions on day 8 compared with fasting conditions on day 7: the ratio of the two GLSM values was 1.33, indicating a clear effect of an occasional intake of food ($P = 0.006$). The GLSM for C_{max} also increased under food-intake condition on day 8, with the ratio of the two GLSM values being 1.35 (90% CI, 1.05–1.75).

In group B, exposure was reduced under fasting conditions on day 8 versus food intake on day 7 for both $AUC_{0-24\,h}$ and C_{max}. This decrease, however, was less than the corresponding estimated increase observed in group A, and does not indicate a clear effect of the occasional skipping of a concomitant meal (AUC_{0-24h}: $P = 0.085$; C_{max}: $P = 0.245$).

Table 2 Mean erlotinib pharmacokinetic parameters following multiple oral administration of 100-mg tablets, with and without food

	C_{max} (ng/ml)	t_{max} (h)	AUC_{0-24} (ng*h/ml)
Day 1			
Fasting condition[a] ($n=11$)	616 (271)	2.64 (1.03)	6336 (2808)
Food-intake condition[a] ($n=11$)	839 (181)	3.91 (2.02)	9734 (2964)
Treatment ratio[b]	1.56 (1.06–2.30)	NA	1.66 (1.20–2.32)
Day 7			
Fasting condition[a] ($n=8$)	1069 (331)	3.00 (1.20)	13739 (5436)
Food-intake condition[a] ($n=5$–6)	1426 (482)	4.17 (0.98)	18823 (9298)
Treatment ratio[b]	1.33 (0.95–1.85)	NA	1.34 (0.87–2.07)

[a]Values shown are arithmetic means (SD).
[b]GMR (food intake/fasting) (90% CIs) presented.
AUC, area under curve; CI, confidence interval; C_{max}, peak concentration; GMR, geometric mean ratio; NA, not applicable; t_{lag}, lag time for delayed absorption; $t_{1/2}$, time to half-life; t_{max}, time to C_{max}.

Table 3 Statistical comparisons of pharmacokinetic parameters of erlotinib following multiple oral administrations of 100-mg tablets, with occasional intake of food under fasting conditions or skipping a concomitant meal under food-intake conditions

Parameter	Treatment	GLSM	Ratio	90% CI
Group A (effect of occasional food intake, $n=6$)				
C_{max} (ng/ml)	Food intake (day 8)	1311	1.35	1.05–1.75
	Fasting (day 7)	969		
AUC_{0-24} (ng*h/ml)	Food intake (day 8)	16453	1.33	1.17–1.50
	Fasting (day 7)	12411		
Group B (effect of skipping a concomitant meal, $n=5$)				
C_{max} (ng/ml)	Fasting (day 8)	1084	0.86	0.67–1.09
	Food intake (day 7)	1264		
AUC_{0-24} (ng*h/ml)	Fasting (day 8)	14542	0.85	0.72–0.99
	Food intake (day 7)	17191		

AUC, area under curve; CI, confidence interval; C_{max}, peak concentration; GLSM, geometric least square mean; GMR, geometric mean ratio; NA, not applicable; t_{lag}, lag time for delayed absorption; $t_{1/2}$, time to half-life; t_{max}, time to C_{max}.

As the trend and percentage changes in the pharmacokinetic parameters of metabolite OSI-420 in the presence of food were similar to those of erlotinib in both single-dose and multiple-dose studies, the detailed metabolite pharmacokinetic results are not presented in this section.

Safety

Single-dose study

Single 150-mg erlotinib doses were well tolerated. No SAEs and no AEs led to premature withdrawal from the study. The most frequent AEs recorded were headache (28.6%) and flatulence (9.5%). Two participants were withdrawn owing to laboratory abnormalities. One of them had elevations in liver enzymes 6 days after dosing, including grade 3 abnormalities in alanine aminotransferase and aspartate aminotransferase levels, as classified by the National Cancer Institute Common Toxicity Criteria (NCI-CTC). The participant also had a grade 2 abnormality in γ-glutamyl transferase about 14–21 days after receiving erlotinib. The other participant was withdrawn owing to worsening hematuria, which had first been detected at baseline.

Multiple-dose study

Consecutive daily doses of 100 mg of erlotinib for up to 8 days led to a high incidence of AEs, with persistent rashes on the faces or upper bodies, in 17 of the 22 volunteers. In most cases, the rash was mild (NCI-CTC grade 1), but was grade 2 in a single participant. The study was prematurely terminated when the protocol-defined stopping criteria were met by one participant having an SAE, and another having a significant laboratory abnormality (NCI-CTC grade 4). The SAE was dyspnea and the event spontaneously resolved. The investigator considered the event to be a panic attack, possibly caused by the participant's simultaneously experiencing facial rash and a painful glossitis. The grade 4 laboratory abnormality was an increase in creatinine phosphokinase. Isoenzyme analysis revealed no cardiac component and the participant denied having undertaken significant physical activity. Gastrointestinal events were also common (mainly loose stools and abdominal pain), although diarrhea was recorded in only one participant, who was successfully treated with loperamide.

No changes in ECG or vital signs, attributable to the study drug, were identified in either study.

Discussion

The aim of these studies was to evaluate the effect of food on the pharmacokinetics of erlotinib and its major active metabolite, OSI-420, in healthy volunteers. Two studies were performed: a single-dose crossover study and a multiple-dose parallel study. The results showed that food substantially increased the systemic exposure of erlotinib, as evidenced by a GMR (food intake versus fasting) value of 2.09 on day 1 after single-dose

administration, and by the corresponding GMR values of 1.66 and 1.34 on days 1 and 7, respectively, after multiple doses. C_{max} values also increased when administered with food, with the relevant GMR values being 1.64 and 1.33–1.56 after single-dose and multiple-dose administrations, respectively. Note that the precision and accuracy of the assays for both studies were deemed satisfactory for the evaluation of food effect on the pharmacokinetics of erlotinib: they were not expected to affect the statistical outcome of either study.

The effect of food on mean erlotinib exposure was inconsistent between periods 1 (97% increase in AUC) and 2 (7% decrease) after the single-dose administration. In the single-dose study, a randomized 2×2 crossover design (two-period, two-treatment, two-sequence) was used, as is most often adopted [17]. Before the study, a 7-day washout period was chosen as being of sufficiently long duration, given the 13–21-h half-life of erlotinib in healthy volunteers [12]. No drug was detectable in plasma at the end of the washout period. The studies were conducted in healthy volunteers to rule out any potential bias caused by the disease. From the ANOVA, a formal sequence effect was observed ($P < 0.001$). In the 2×2 crossover design, a formal sequence effect can arise owing to a treatment-specific carryover, a treatment-by-period interaction, or a difference between the sequence groups. As the first possibility was considered the most likely and because an unbiased estimate for the direct drug effect does not exist for a 2×2 crossover design if there is a treatment-specific carryover [17,18], a between-group comparison of AUC and C_{max} from period 1 was considered to be the least biased and the most appropriate assessment of the effect of food. For future crossover studies, however, longer washout periods or higher-order crossover designs in case of two treatments (i.e. more than two periods, sequences, or both) should be considered.

In the multiple-dose study, food resulted in a 66% increase in systemic exposure on day 1 ($P = 0.015$), but only a 34% increase on day 7 ($P = 0.252$), which was not statistically significant. This is likely due to the lower number of participants on day 7 versus day 1 ($n = 14$ versus 22), although this cannot be confirmed. If this is the case, however, it would mean that the sensitivity of finding evidence for a food effect decreased over time. Given that most participants (86.4%) experienced mild epidermal growth factor receptor inhibitor-associated rash, predominantly located on the face and lasting for as long as several months, further multiple-dose studies in this population might not be warranted.

The degrees of these potential increases in erlotinib exposure when administered with food might be clinically relevant. Phase I trials of erlotinib identified dose-limiting toxicities of rash and diarrhea at 200 mg, which led to a recommended phase II/III single-agent dose of 150 mg [19]. Estimates of the effect of food from the single-dose study differ considerably between periods, and there is also some uncertainty over outcomes from the multiple-dose study. It is therefore not prudent, on the basis of the results of these studies, to recommend administration after food intake as a strategy to increase exposure, while decreasing the dose administered. In contrast, if the same recommended daily dose of 150 mg were given with food, the mean increase in exposure of 66 and 34% on days 1 and 7, respectively, increases the likelihood of unacceptable toxicity, given the fact that the 200-mg/day dose was not well tolerated by a substantial percentage of patients [19]. Therefore, the 'conservative' approach is to administer erlotinib in the absence of food. Taking this into consideration, we therefore recommend that when erlotinib is administered at the maximum tolerated dose of 150 mg used in the clinical setting, it should be given under conditions of fasting. Patients taking this dose of erlotinib in combination with food might have increased drug exposure, and this could potentially lead to unacceptable levels of toxicity.

Our results also suggest that occasional food intake can produce an increase in $AUC_{0-24\,h}$ (estimated 33%) during the administration of erlotinib under conditions of fasting, although the number of participants in this analysis was small ($n = 6$).

The increase in systemic exposure to erlotinib due to food, as observed in the current studies, is primarily because of increased drug absorption [16]. It is not known whether the high-fat, high-calorie meal contains any component that can block CYP enzymes. Possible mechanisms underlying increased drug absorption include decreased first-pass effect (as a result of increased transport of drugs via the lymphatic system) and increased micellar solubilization (as a result of increased bile output, increased binding with lipoproteins, and slowed gastric emptying). Given the high fat content (approximately 50% of the total caloric content of the meal) and the high calorie content (approximately 1000 calories) of the meals used in this study, all of the above common mechanisms could happen, leading to a significant increase in the solubility/dissolution rate of erlotinib and a decrease in its first-pass metabolism by CYP3A4 and CYP1A2.

It was apparent that food increased the t_{max} for erlotinib, indicative of delayed absorption. The major mechanism responsible for delayed drug absorption in the food-intake state is the decrease in the gastric-emptying rate [16]. This, in turn, decreases the rate of drug delivery to the small intestine, where most of the absorption occurs. The magnitude of this increase in t_{max} was, however, not felt to be clinically significant. As with other anticancer drugs

such as fadrozole [20] and letrozole [21], erlotinib is intended for chronic long-term administration, to achieve continuous pharmacodynamic effects. Considering the long plasma half-life of erlotinib (13–21 h), the observed increase in t_{max} (< 2 h) is relatively small, and effective concentrations can be predicted to be maintained for most of the 24-h administration interval. Therefore, the slight increases in the time to maximal concentration of erlotinib are not thought to be of clinical relevance.

In both studies, food also consistently increased t_{max} and AUC for OSI-420, a major active metabolite of erlotinib. The trend and magnitude of the changes in the pharmacokinetic profiles of OSI-420 were very similar to those of erlotinib, suggesting that metabolite production and elimination were rate-limited by the pharmacokinetics of the parent erlotinib. As OSI-420 has activity similar to that of erlotinib, and as it constitutes approximately 10% of the total drug concentration, the contribution of increased OSI-420 to the total increase in systemic exposure would be insignificant.

In summary, the results of these studies indicate that food can substantially increase the systemic exposure of erlotinib. Given that the maximum tolerated dose of erlotinib is used in clinical practice, it is recommended that erlotinib be given on an empty stomach, that is, at least 1 h before or 2 h after the ingestion of food.

Acknowledgements

The authors would like to thank Dr M. Smith, a medical writer with Gardiner-Caldwell Communications, for his assistance in the revision of this manuscript. This study was funded by F. Hoffmann-La Roche Ltd and supported by Hoffmann-La Roche Inc.

References

1 Pollack VA, Savage DM, Baker DA, Tsaparikos KE, Sloan DE, Moyer JD, *et al*. Inhibition of epidermal growth factor receptor-associated tyrosine phosphorylation in human carcinomas with CP-358 744: dynamics of receptor inhibition *in situ* and antitumor effects in athymic mice. *J Pharmacol Exp Ther* 1999; **291**:739–748.

2 Higgins B, Kolinsky K, Smith M, Beck G, Rashed M, Adames V, *et al*. Antitumor activity of erlotinib (OSI-774, Tarceva) alone or in combination in human non-small cell lung cancer tumor xenograft models. *Anticancer Drugs* 2004; **15**:503–512.

3 Ng SS, Tsao MS, Nicklee T, Hedley DW. Effects of the epidermal growth factor receptor inhibitor OSI-774, Tarceva, on downstream signaling pathways and apoptosis in human pancreatic adenocarcinoma. *Mol Cancer Ther* 2002; **1**:777–783.

4 Pérez-Soler R, Chachoua A, Hammond LA, Rowinsky EK, Huberman M, Karp D, *et al*. Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer. *J Clin Oncol* 2004; **22**: 3238–3247.

5 Soulières D, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, Siu LL. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. *J Clin Oncol* 2004; **22**:77–85.

6 Herbst RS, Johnson DH, Mininberg E, Carbone DP, Henderson T, Kim ES, *et al*. Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer. *J Clin Oncol* 2005; **23**:2544–2555.

7 Moore MJ, Goldstein D, Hamm J, Kotecha J, Gallinger S, Au HJ, *et al*. Erlotinib improves survival when added to gemcitabine in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). *Proc ASCO Gastrointest Cancers Symp* 2005; **121**:abstract 77.

8 Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, *et al*., National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; **353**:123–132.

9 Herbst RS, Prager D, Hermann R, Fehrenbacher L, Johnson BE, Sandler A, *et al*., TRIBUTE Investigator Group. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2005; **23**:5892–5899.

10 Prescribing Information. Available from www.Tarceva.com.

11 Ling J, Johnson KA, Miao Z, Rakhit A, Pantze MP, Hamilton M, *et al*. Metabolism and excretion of erlotinib, a small molecule inhibitor of epidermal growth factor receptor tyrosine kinase, in healthy male volunteers. *Drug Metab Dispos* 2006; **34**:420–426.

12 Frohna P, Lu J, Eppler S, Hamilton M, Wolf J, Rakhit A, *et al*. Evaluation of the absolute oral bioavailability and bioequivalence of erlotinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in a randomized, crossover study in healthy subjects. *J Clin Pharmacol* 2006; **46**:282–290.

13 Lu J, Eppler S, Wolf J, Hamilton M, Rakhit A, Bruno R, Lum B. Clinical pharmacokinetics of erlotinib in patients with solid tumors and exposure-safety relationship in patients with non-small cell lung cancer. *Clin Pharmacol Ther* 2006; **80**:136–145.

14 Fleisher D, Li C, Zhou Y, Pao LH, Karim A. Drug, meal and formulation interactions influencing drug absorption after oral administration. Clinical implications. *Clin Pharmacokinet* 1999; **36**:233–254.

15 Welling PG. Effects of food on drug absorption. *Annu Rev Nutr* 1996; **16**:383–415.

16 Singh BN, Malhotra BK. Effects of food on the clinical pharmacokinetics of anticancer agents. *Clin Pharmacokinet* 2004; **43**:1127–1156.

17 Jones B, Kenward MG. *Design and analysis of cross-over trials*. New York: Chapman & Hall/CRC; 2003.

18 Chow SC, Liu JP. *Design and analysis of bioavailability and bioequivalence studies*. New York: Markel Dekker; 2000.

19 Hidalgo M, Siu LL, Nemunaitis J, Rizzo J, Hammond LA, Takimoto C, *et al*. Phase I and pharmacological study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. *J Clin Oncol* 2001; **19**:3267–3279.

20 Choi RL, Sun JX, Kochak GM. The effect of food on the relative bioavailability of fadrozole hydrochloride. *Biopharm Drug Dispos* 1993; **14**:779–784.

21 Sioufi A, Sandrenan N, Godbillon J, Trunet P, Czendlik C, Howald H, *et al*. Comparative bioavailability of letrozole under fed and fasting conditions in 12 healthy subjects after a 2.5 mg single oral administration. *Biopharm Drug Dispos* 1997; **18**:489–497.