NIHS No. 2685

May 9, 2002

To the Director-General, Pharmaceutical Bureau,
Ministry of Health, Labour and Welfare
The Director of the National Institute of Health Sciences

Evaluation Report

This is to report the outcome of the evaluation of the approval application of the drug by the Pharmaceuticals and Medical Devices Evaluation Centre.

Evaluation Result

9th May 2002

Omitted

Evaluation Report (1)

18th April 2002

1. Approval Application

[Product Name]	Iressa Tablet 250
[Non-Propriety Name]	Gefitinib
[Applicant]	AstraZeneca KK
[Date of Application]	25th January 2002 (Import Approval Application)
	[Dosage Form and Contents] A film coat tablet formulation containing 250 mg of gefitinib per tablet
	[Filed Indication] Non-small cell lung cancer
	[Filed Dosage and Administration] Usually in adult, orally administer 250 mg of gefitinib once daily
	[Remarks] Priority Evaluation

2. Overview of the submitted data and summary of review by the Evaluation Centre

A. Data on origin, discovery and overseas usage

The expression levels and expressivities of Epidermal Growth Factor Receptor (EGFR), which belong to the receptor tyrosine kinase family, are known to be higher in tumour cells than in normal cells, and EGFR is overexpressed in many solid cancers, including head & neck cancer, breast cancer, lung cancer, colon cancer, prostate cancer, uterine cancer, ovarian cancer and urinary bladder cancer. It is also known that these are often closely related to prognosis (Invest New Drugs 17: 259-269, 1999, etc.). Transmission of growth signals activated by binding of ligand to EGFR is also known to be deeply involved in immortalisation of tumours, angiogenesis, infiltrations and metastasis. Molecules involved in transmission of signals including EGFR are considered to be one of the new target molecules for treating cancers. Since 1990, AstraZeneca screened

around 1500 in-house compounds with EGFR preparations derived from A431 human cancer cells. As a result, several nuclei including 4-anilinoquinazoline were found to have effects on EGRFs. After syntheses and screenings, gefitinib was chosen for development as a compound with EGFR inhibitory actions and tumour growth suppressive actions.

At the moment, gefitinib has not been approved in any country. The FDA of the USA approved use of gefitinib for treatment of advanced non-small cell lung cancer as a fast-track drug development program on dd/yy, and a study of gefitinib monotherapy as a third-line therapy in advanced small cell lung cancer patients who were previously treated with a platinum compound and docetaxel was implemented. The approval application in the USA will be made shortly. In Europe, clinical studies in previously untreated non-small cell lung cancer patients are currently conducted investigating survival of patients receiving gefitinib in combination with ether cisplatin + gemcitabine or carboplatin + paclitaxel. Based on the outcome of survival in the studies, AZ is planning to make application in Europe and the USA in yy. For indications other than lung cancer, currently (an) international phase II clinical study/ies in xxx patient is/are underway in Japan and (a) clinical study(ies) in xxx xxxx xxxx patients is/are conducted abroad.

B. Data on physical and chemical properties, specifications and test methods

Omitted

C. Data on stability

Omitted

D. Data on toxicity

Omitted

E. Data on pharmacological actions

Omitted

F. Data on absorption, distribution, metabolism and excretion

1. Summary of submitted data

(1) Absorption

Omitted

(2) Distribution

Omitted

(3) Metabolism

Omitted

(4) Excretion

Omitted

(5) Pharmacokinetics in humans

A study in which 14 healthy Western male volunteers received a single dose of 50, 100, 250 and 500 mg of gefitinib (Study 1839IL/0033; xxxx) investigated plasma gefitinib concentration profiles determined by the LC/MS/MS method. It showed that Tmax was between 3 and 8 hours and the plasma concentration fell biphasically after achieving Cmax. The half-life of the terminal phase was around 24 to 32 hours. Pharmacokinetic parameters of gefitinib showed large inter-subject variability and Cmax and AUC had 8-fold variations (60 to 130% of CV). Inter-subject variability of the half-life was relatively small and CV was about 60% in all dose levels. Looking at relationships of Cmax and AUC to the dosed amount, these parameters were increased with an increase in the dosed amount, but statistical dose proportionality was not confirmed. A comparison of dose adjusted AUC and Cmax for each dose suggested that the reason for failing to see dose proportionality was due to the significantly high value at 500 mg compared to the values at 50 mg and 250 mg. The degree of divergence from dose proportionality was that AUC and Cmax were on average about 18% higher than AUC and Cmax expected from when the dose level was twice as high. As the main metabolising enzyme of gefitinib is

CYP3A4, in order to investigate a possibility that inter-subject variations in the expression level of CYP3A4 were involved in the inter-subject variations of the pharmacokinetics of gefitinib, the applicant determined pharmacokinetics with an oral dose of 7.5 mg midazoram, which is a probe base of CYP3A4, assessed a relationship between AUC of gefitinib and AUC of midazoram, and investigated a relationship of CYP3A4 expression levels and pharmacokinetics of gefitinib in this study. AUC of the plasma mizodarum concentration profiles in 14 subjects showed inter-subject variations suggesting presence of inter-subject variations in the CYP3A4 expression levels, but no relationship between gefitinib's AUC and midazoram's AUC was observed.

A study in which 11 healthy Western male volunteers orally received 14-day repeated dose of gefitinib (Study 1839IL/0034; xxx) compared the plasma gefitinib concentration profiles measured by the LC/MS/MS method with the profiles after a single dose. After a single dose, Cmax (23.6 to 57.8 ng/mL) was reached 3 to 7 hours after dosing, and then the plasma concentration fell biphasically with the half-life of the terminal phase of 13.7 to 42.2 hours. After repeated dose, the plasma gefitinib concentration profile on day 14 showed that Cmax (16.8 to 108 ng/mL) was at 3 to 7 hours after dosing, the plasma concentration fell biphasically, and the half-life of the terminal phase was 14.1 to 57.5 hours. Ten out of 11 subjects showed an increase in the plasma gefitinib concentration with repeated dosing. The accumulation ratio, which was obtained comparing AUC_{0-24} after the first dose (308 to 927 ng·hr/mL) and AUC_{0-24} after the 14^{th} dose (272 to 1997 ng·hr/mL), was between 1.26 and 2.80. In the repeated dose in this study, the subjects received two doses at a 12-hour interval only on the first day. It showed that, with the loading dose, the plasma concentration reached steady state within 3 to 5 days.

A phase I study in which 64 Western patients with advanced solid cancer orally received 50 to 700 mg of gefitinib once daily for 14 consecutive days (Study 1839IL/0005; xxx) investigated plasma gefitinib concentration profiles determined with the LC/MS/MS method. To begin with, 8 subjects received a single oral dose of 50 mg of gefitinib and plasma pharmacokinetics with the single dose were assessed. Tmax was at 1 to 5 hours and Cmax reached 27 to 62 ng/mL and then eliminated biphasically. The terminal phase started at 12 to 24 hours after dosing.

The elimination half-life of the terminal phase was 27 to 49 hours. $AUC_{0-\infty}$ was 769 to 2090 ng/mL and Cmax, AUC_{0-24} and $AUC_{0-\infty}$ showed 2 to 3-fold inter-subject variations. Following this, groups of 7 to 10 subjects received either 100, 150, 225, 300, 400, 525 or 700 mg of gefitinib once daily for 14 days and plasma gefitinib concentrations immediately before dosing (Cmin) on day 2, day 3, day 7, day 10 and day 14 were determined. In most patients receiving a repeated dose of between 50 and 700 mg, Tmax was between 1 and 7 hours, in a similar way to the single dose. The plasma concentration after achieving Cmax was eliminated biphasiclly and the terminal phase started at 12 to 24 hours after dosing. The elimination half-life of the terminal phase was 23.9 to 85.0 hours. With repeated doses for 14 days, the Cmax and AUC_{0-24} increased by 2 to 7 times compared with those after a single dose. Good correlations between Cmin and Cmax, and Cmin and $AUC_{0-\infty}$ were observed. Based on the elimination half-life after a single dose of 50 mg, plasma gefitinib concentration after once daily repeated dose was calculated. According to the calculation, it was estimated that steady state will be reached in 6 to 10 days and exposure will be increased by 2 to 3 times. In all dose groups, Cmin suggested that steady state was reached by day 14 of the dosing and at the dose level of 50 mg, Cmax was increased by 1.5 to 4 times and AUC_{0-24} by 1.9 to 4.3 times with repeated dose, which were roughly within expectations. However, some patients showed higher values than what was expected from the single dose data. It was considered to be because clearance and/or bioavailability with repeated dose had inter-subject variations. The dose proportionality of 14-day repeated dose at 50 to 700 mg was investigated. At 700 mg, Cmax and $AUC_{0-\infty}$ showed higher values than values expected from the proportionality seen in the dose range between 50 and 525 mg. This was considered to be because of a presence of large inter-subject variations in clearance and bioavailability of gefitinib and a chance result due to the limited number of the study subjects.

A phase I/IIa study in which 69 solid cancer patients in the West received oral repeated dose of 150 mg to 1000 mg of gefitinib once daily for 28 days (Study 1839IL/0011; xxxx) assessed plasma gefitinib concentration profiles with the LC/MS/MS method. The plasma gefitinib concentration in the majority of the patients reached steady state by day 7 of dosing. Trough plasma unchanged gefitinib

concentration at steady-state (Css min) showed 3 to 10-fold inter-subject variations in all dose levels, but no specific change in the inter-subject variations was observed with increases in dose levels. In patients from whom Css min was taken at at least 3 points, intra-subject variations of Css min were investigated. Their CV was between 4 and 42%. Css min at all dose levels obtained in this study were compared with the results of Study 1839IL/0005. Spread of data in these two studies generally overlapped.

A similar phase I/IIa study in which 88 solid cancer patients in the West received oral repeated dose of 150 to 1000 mg of gefitinib once daily for 28 days (Study 1839IL/0012; xxxx) assessed plasma gefitinib concentration profiles with the LC/MS/MS method. In the first month, trough plasma gefitinib concentration was measured before dosing at weekly intervals. It showed that most of the patients achieved Css min by day 7 of the treatment. At all dose level, 3 to 10-fold inter-subject variations in Css min were seen, but no specific change in the inter-subject variations was observed with the increase in the dose level. In patients from whom Css min was taken at at least 3 points, intra-subject variations of Css min were investigated. Their CV was between 2 and 49%. Css min at all dose levels obtained in this study were compared with the results of Study 1839IL/0005. The spread of data in these two studies generally overlapped.

A phase I study in which 31 Japanese solid cancer patients received a single and repeated oral dose of gefitinib (Study V-15-11; xxxxx) assessed plasma gefitinib concentration profiles with the LC/MS/MS method. After a single dose of 50, 100 and 225 mg of gefitinib, plasma concentrations were measured for 6 days. Tmax was seen at 3 to 7 hours. Although Cmax (the mean Cmax of 50, 100 and 225 mg were 33.1, 48.9 and 188 ng/mL, respectively) and AUC_{0-24} (the mean AUC_{0-24} of 50, 100 and 225 mg were 410, 579 and 2224 ng·hr/mL, respectively) showed 2 to 8-fold inter-subject variations, they increased roughly proportionally to the dose levels. After achieving Cmax, plasma concentrations showed biphasic elimination and the half-life of the terminal phase was 19.3 to 48.7 hours. The 400, 525 and 700 mg groups received repeated oral dose from the start and plasma gefitinib concentrations up to 24 hours from the initial dosing were investigated. In 9 out of 16 subjects, Tmax was 3 to 7 hours and in the remaining 7 subjects, it was 1 hour (n=1), 12 hours

(n=4) and 24 hours (n=2). Cmax (the mean Cmax of 400, 525 and 700 mg were 315, 316 and 401 ng/mL, respectively) and AUC_{0-24} (the mean AUC_{0-24} of 400, 525 and 700 mg were 3274, 5547 and 5554 ng·hr/mL, respectively) showed 3 to 8-fold inter-subject variations. After repeated oral dose of 50, 100, 225, 400, 525 and 700 mg once daily for 14 days, the mean Cmax was 73.8, 110, 384, 861, 999 and 1251 ng/mL, respectively, and the mean AUC_{0-24} was 1236, 1971, 5877, 12981, 18962 and 23356 ng·hr/mL. Although they were increased 2 to 8 times compared with those after the single dose, they were roughly proportional to the dose level. The elimination half-life in the terminal phase obtained from plasma gefitinib concentrations after the final dose was 27.8 to 79.7 hr. AUC_{0-24} after the first dose and AUC_{0-24} on day 14 were compared in the 50, 100 and 225 mg groups. AUC_{0-24} on day 14 showed 84 to 234% of expected values from the single dose data. It was explained with a presence of large inter-subject variations in clearance and/or bioavailability. In contrast, the presence of a good correlation was confirmed between Cmin and Cmax, and Cmin and $AUC_{0-\infty}$. In all subjects in groups receiving 225 to 700 mg and one subject in the 100 mg group, plasma α_1-AGP concentrations were measured and relationships with dose-adjusted Cmax and AUC_{0-24} after a single and repeated gefitinib were investigated. It showed that, in patients with high plasma α_1-AGP concentrations, Cmax and AUC_{0-24} tended to be higher. It was suggested that clearance may be reduced with an increase in protein binding of gefitinib. Contribution of plasma α_1-AGP concentrations on the inter-subject variations in Cmax and AUC_{0-24} was 15 to 30%.

In a study in which 209 Japanese and Western advanced non-small cell lung cancer patients who had previous chemotherapy received continuous repeated oral dose of 250 or 500 mg of gefitinib once daily (one course of treatment: 28 days) (Study 1839IL/0016; xxxxx), Css min before dosing at the end of each course of the treatment was determined with the LC/MS/MS method and PPK analysis was carried out, in which data (520 in total) obtained from randomised patients who had at least one Css min datum (176 subjects) were used. Css min of gefitinib were plotted against sampling times after dosing in a graph and visually assessed. The sampling time points were spread between 18 and 34 hours after dosing. The mean sampling point was 25.8 hours and 95% CI was 20.5 to 31.2 hours. Plotting of the measured

Css min values showed that distribution of Css min of patients receiving 500 mg was higher than those receiving 250 mg. The analyses showed that Css min with 250 mg dose was 264 ng/mL and 95% CI (based on inter-subject variations) was 92.2 to 755 ng/mL. When the dosed amount was increased from 250 mg to 500 mg, Css min was increased 1.95 times (95% CI: 1.59 to 2.29 times), showing a proportional relationship of the dosed amounts. Css min with 250 mg and 500 mg were estimated using a basic pharmacokinetic model with associated inter-subject variations, and the measured values were fitted to the basic pharmacokinetic model. Each estimated Css min and measured Css min showed good correlations. An assessment of statistically significant correlations between various demographic and ecophysiological co-variances and estimated Css min in a structural model showed no correlations in the age, ethnic group, sex, height, liver function, HSA concentration, serum α_1-AGP concentration and total protein concentration. However, the bodyweight and creatinine clearance (CL_{CR}) showed a clinically negligible level of effects. When a change in estimated Css min was looked at regarding bodyweight of patients as a variance, it showed a 2.4 ng/mL reduction per 1 kg. With CL_{CR}, a 1.6 ng/mL reduction per 1 mL/min was observed. When those two co-variants were included into the pharmacokinetic model, reductions in the inter-subject variations were less than 5%. Effects of concurrent medications on Css min of gefitinib were investigated. There was no clear relationship between a concurrent use of CYP inhibitors (antifungal agents, imidazole derivatives, macrolide antibiotics, triazole antifungal agents, calcium channel inhibitors) and anti-acids (proton pump inhibitors and H_2 receptor inhibitors) with Css min. As only a limited number of patients used concurrent CYP derivatives (fenitoin, phenobarbitals and quinidines), relationships of CYP derivatives and Css min were not analysed. A significant overlap of estimated Css min for Japanese and the Western population were observed and no statistically significant ethnic difference in Css min of the ethnic groups was shown. Pharmacokinetics of Japanese solid cancer patients in Study V-15-11 was compared with pharmacokinetics of Western solid cancer patients in Study 1839IL/0005, which had a similar study design. Cmax and AUC_{0-24} showed up to 8-fold inter-subject variations in all dose groups, but there were no differences between Japanese and Western patients when they received oral dose of 50 to 525 mg. Css min data from

Study V-15-11 were compared with Css min data from the two overseas studies (Study 1839IL/0011 and Study 1839IL/0012). There was no clear ethnic difference. PPK analysis of data on plasma gefitinib concentrations from Study 1839IL/0005 and Study V-15-11 (1567 data from 95 patients) were carried out with NONMEM. Based on estimated pharmacokinetic parameters from the basic pharmacokinetic model, apparent clearance (CL/f) was about 39.7 L/hr (662 mL/min), area of distribution in the central compartment was 1300L and that in the terminal compartment was 1200L. The estimated lag time was 40 minutes. Inter-subject variations of pharmacokinetic parameters were large and the coefficient of variation for all pharmacokinetic parameters was over 50%. CL/f was estimated using bodyweight and CL_{CR}, which were shown to have statistically significant effects on pharmacokinetics of gefitinib in PKK analysis in Study 1839IL/0016, as variants. In this analysis, no relevancy was observed. Distribution volumes of CL/f and steady state were assessed. There was no difference in distribution of CL/f in the Western patients (Study 1839IL/0005) and that in Japanese subjects (Study V-15-11). Distribution volume at apparent steady state was over 2600L, but there was no change with bodyweight. Cmin at estimated steady-state (dose adjusted to 250 mg) in the Western patients (Study 1839IL/0005) and the Japanese patients (Study V-15-11) was assessed. The distributions were similar and they also showed a good agreement with the analysis result of Study 1839IL/0016. Estimated half-life also confirmed similarities in the Western patients (Study 1839IL/0005) and the Japanese patients (Study V-15-11).

A study in which 17 Western solid cancer patients received a single intravenous continuous administration of 50 mg of gefitinib and a single oral dose of 250 mg (Study 1839IL/0035; xxxx) assessed plasma gefitinib concentration profiles with the LC/MS/MS method. When 50 mg of gefitinib was intravenously administered for 5 minutes, plasma gefitinib concentration showed a triphasic elimination after reaching Cmax. The plasma concentration in the α phase was reduced to 5 to 15% of Cmax by 5 minutes after dosing. This phase lasted until 1 hour after dosing, then the β phase followed until 8 hours from dosing, then the γ phase was seen until 24 hours post-dose. Plasma clearance of gefitinib was high (geometric mean: 513.6 mL/min) and an approximately 7-fold inter-subject variation was observed (194 to 1460

mL/min). Vss was also high (mean: 1400L) and a 3-fold inter-subject variation was observed (830 to 2710L). The average elimination half-life at the terminal phase was 48.3 hr. An inter-subject variation of elimination half-life amongst subjects with detectable elimination half-life at the terminal phase was 8-fold. When 250 mg of gefitinib was orally dosed, the average Tmax was 3 hours (1 to 8 hours) and the geometric average of Cmax was 159.4 ng/mL, with a 6-fold inter-subject variation (48.7 to 324 mg/mL). After reaching Cmax, plasma concentrations eliminated biphasically. The average elimination half-life in the terminal phase was 50.5 hours and an inter-subject variation of elimination half-life amongst subjects with detectable elimination half-life at the terminal phase was 4-fold (27.0 to 111 hours). Absolute bioavailability obtained from the geometric least square mean of dose-adjusted AUC after a single intravenous administration of 50 mg gefitinib and a single oral dose of 250 mg gefitinib was 59% (90% confidence interval: 51 to 69%).

A study in which 52 Western healthy male volunteers received a single oral dose of 250 mg gefitinib (Study 1839IL/0036; xxxxx) investigated effects of meals and gastric pH on pharmacokinetics of gefitinib. Comparisons of pharmacokinetics with and without food revealed that, with food, Cmax geometric least square mean was increased by 32% and AUC geometric least square mean was increased by 37%. Considering the degree of the effects, they were considered to have no clinical significance. When ranitidine (450 mg x 2) was concomitantly used to increase gastric pH, Cmax geometric least square mean was reduced to 29% and AUC geometric least square mean was reduced to 53% compared with when gefitinib was dosed on its own. The applicant considered that it was clinically significant and use of gefitinib in patients who were using an agent that increases gastric pH continuously (proton pump inhibitors, etc.) required cautions.

In a study in which 6 Western healthy male volunteers received a single oral dose of 50 mg of ^{14}C-labelled gefitinib (Study 1839IL/0003; xxxxx), radioactivity in the plasma and plasma gefitinib concentrations determined with the LC/MS/MS method were compared. After administration of 50 mg of ^{14}C-labelled gefitinib, plasma gefitinib concentration was 14 to 20% of the total radioactivity, suggesting a presence of metabolites in the circulation. At all sampling points, radioactivity in the plasma was lower than in the whole blood and the ratio of radioactivity in the plasma

against that in the whole blood was 0.7. In the sampling period over 10 days, about 90% of dosed radioactivity was excreted to the urine and the faeces, the majority being in the faeces. Less than 4% of the dosed radioactivity was excreted in the urine. About 60% of all radioactivity excreted in the faeces was excreted within 48 hours of administration and the elimination rate fell after that. About 10% of the dosed radioactivity was not excreted even after sampling on day 10.

As *in vitro* studies demonstrated that CYP3A4 was extensively involved in metabolism of gefitinib, suggesting a possibility of a CYP3A4 inhibition leading to an increase in gefitinib exposure, effects of a CYP3A4 inhibitor, itraconazole (200 mg/day for 4 consecutive days) in combination with a single oral dose of 250 mg and 500 mg gefitinib on the pharmacokinetics were investigated in 47 Western healthy male volunteers (Study 1839IL/0051; xxx). When itraconazole was used concomitantly, the geometric least square mean of Cmax was increased by 51% in subjects received 250 mg gefitinib and by 33% in those that received 500 mg, the mean $t_{1/2}$ was increased by 25% in those that received 250 mg and by 22% in those that received 500 mg, the geometric least square mean of AUC was increased by 78% in those that received 250 mg and by 61% in those that received 500 mg. It was concluded that this may have clinical effects and we need to pay attention to concomitant use of CYP3A4 inhibitors, such as itraconazole and ketoconazole.

Also, as induction of CYP3A4 may reduce gefitinib exposure, effects of a CYP3A4 inducer, rifampicin (600 mg/day for 10 consecutive days), in combination with a single oral dose of 500 mg gefitinib on the pharmacokinetics were investigated in 18 Western healthy male volunteers (Study 1839IL/0030; xxx). When rifampicin was used concomitantly, no effect on Tmax was observed, but the geometric least square mean of Cmax was reduced to up to 35%, the mean $t_{1/2}$ was reduced by up to 61% and the geometric least square mean of AUC was reduced by up to 17%. According to comparisons of AUC in individual subject, AUC was reduced to about 14 to 20% with concomitant rifampicin, but degrees of reductions in AUC and changes in the elimination half-life were not consistent. It was concluded that rifampicin reduced gefitinib exposure to a clinically significant degree and, although concomitant use of CYP3A4 inducers (e.g., refampicin) would not present specific safety issues, they should call for attention to the possible reduction of the effect of gefitinib.

As *in vitro* studies showed an inhibitory effect of gefitinib on CYP2D6, suggesting a possibility of increases in the plasma concentration of CYP2D6 substrates with concomitant gefitinib, effects of concomitant gefitinib (500 mg/day for 15 consecutive days, twice daily on the first day) on pharmacokinetics of a single oral dose (50 mg) of a CYP2D6 substrate, metoprolol, was investigated in 15 Western solid cancer patients (Study 1839IL/0038; xxx). When gefitinib was used concomitantly, the geometric least square means of Cmax, $AUC_{0-\infty}$ and AUC until the last sampling point (AUC_{0-t}) of metoprolol were increased by 12%, 50% and 35%, respectively, and the mean $t_{1/2}$ was increased by 8%. Only 2 subjects out of 15 subjects in the assessment showed more than 2-fold increases in AUC_{0-t}. It was considered that there would be no interaction between metoprolol and gefitinib that presents clinical issues and, as metoprolol was a probe substrate of CYP2D6, concomitant use of gefitinib with a drug metabolised by CYP2D6 would not have a clinically significant effect on pharmacokinetics of the drug.

In clinical studies at an early stage of the development, 25 mg brown coloured tablets and 100 mg brown coloured tablets were used, and in clinical studies at a late stage of the development, 50 mg brown coloured tablets and 100 mg brown coloured tablets as well as tablets of the filed formulation (250 mg brown coloured tablets) were used. The formulation used in the early development was different from the formulation used in the late development. Dissolution tests at pH 1 to 7 showed no difference in dissolution rate of the 25 mg brown coloured tablets and the 100 mg brown coloured tablets used in the early development. Also, dissolution tests at pH 1 to 7 showed no difference in dissolution rate of the 100 mg brown coloured tablets used in the early development and the 100 mg brown coloured tablets used in the late development. Moreover, dissolution tests at pH 3 showed no difference in dissolution of two 25 mg brown coloured tablets + two 100 mg brown coloured tablets used in the early development and the 250 mg brown coloured tablets used in the late development. Furthermore, dissolution tests at pH 1 to 7 showed no difference in the dissolution rates of the 50 mg brown coloured tablets and the 100 mg brown coloured tablets used in the late development and dissolution tests at pH 1.2 to 6.8 showed no differences in the dissolution rates of the 100 mg brown

coloured tablets and the 250 mg brown coloured tablets used in the late development.

2. Details of Evaluation by the Evaluation Centre

Omitted

G Data on Clinical Study Results

1. Overview of the submitted data

1-1. Clinical Studies in Japan

(1) Phase I study (Study V-15-11 (xxx), published in Proc Am Soc Clin Oncol 37: abstr 1292, 2001)

Targeting solid cancers that had been reported to show EGFR overexpression (including non-small cell lung cancer (NSCLC), colorectal cancer), a phase I study investigating safety, efficacy and pharmacokinetics of oral single and repeated dose of gefitinib (after a single dose, subjects were observed for 10 to 14 days, and then received the same dose for 14 consecutive days) was conducted. In a period from August 1998 and March 2001, 31 subjects (5 in the 50 mg group, 4 in the 100 mg group, 6 in the 225 mg group, 4 in the 400 mg group, 6 in the 525 mg group and 6 in the 700 mg group) were enrolled (including 23 with NSCLC). The applicant stated that, as dose-limiting toxicities (adverse drug reactions of CTC Grade 3 or 4, see below) were observed in 2 out of 6 subjects in the 700 mg, higher dose levels were not investigated. It stated that all enrolled subjects were included in safety and efficacy analyses (for pharmacokinetics, refer to Section F).

With regard to the safety (in this and the following studies, the severity was assessed in accordance with the Common Toxicity Criteria, version beta 2.0 by the US National Cancer Institute (NCI-CTC)), adverse events were observed in all 31 subjects who received up to 700 mg. Common adverse events included diarrhoea in 45.2% (14/31), leukocytosis, leukopenia, increased lactose dehydrogenise (LDH) and rash in 41.9% (13/31) each, anorexia in 35.5%

(11/31), nausea, vomiting, increased alkaline phosphatase (ALP) and increased serum AST (GOT) in 32.3% (10/31) each, abdominal pain, headache and increased serum ALT (GPT) in 25.8% (8/31) each, and fever, bodyweight loss, increased coughing, pharyngitis and seborrhoea in 22.6% (7/31) each. In total, 19 Grade 3 adverse events in 8 subjects were observed, consisting of 1 event each of increased AST, increased ALT, increased ALP, dyspnoea, malaise and arterial fibrillation (all other than arterial fibrillation was in one subject) in the 50 mg group, 1 event each of hypoxemia, increased AST and increased ALT (all in one subject) in the 225 mg group, 1 event each of constipation and bodyweight gain (all in one subject) in the 400 mg group, 1 event each of increased AST and increased ALT (all in one subject) in the 525 mg group, increased ALT and bone pain in one subject, diarrhoea in one subject and anaemia and lymphopenia in one subject in the 700 mg group. Of these, relevancy to gefitinib was suspected with increased AST in 2 subjects, increased ALT in 3 subjects and diarrhoea in 1 subject. No Grade 4 adverse events or deaths during the study and within 30 days from the end of the study treatment were reported. With regard to effects on the eyes expected from non-clinical studies, conjunctivitis and corneal lesions of Grade 1 to 2 were observed in 16.1% (5/31) and 12.9% (4/31), respectively, but they were reported to be recovered without medical interventions or with administration of steroid eye drops, etc.

With regard to efficacy (the anti-tumour effect assessment criteria were based on the “assessment criteria for direct effects of chemotherapy for solid cancers” (the Journal of Japan Society for Cancer Therapy 21: 931-942, 1986)), it reported that partial response (PR) was observed in 5 subjects (1 in the 225 mg group, 1 in the 400 mg group, 2 in the 525 mg group and 1 in 700 mg group), who were all patients with NSCLC.

1-2. Overseas Clinical Studies

(1) Phase I study (Study 0005 (xxxx), published in Pro Am Soc Clin Oncol 19, abstr 5E, 2000)

Targeting solid cancers known to have EGFR overexpression (NSCLC, colorectal cancers, etc.,) a phase I study investigating safety, efficacy and

pharmacokinetics of administration of 50 to 925 mg/day of gefitinib for 14 days was conducted. From April 1998 until January 2001, 64 subjects (8 in the 50 mg group 7 in the 100 mg group, 8 in the 150 mg group, 7 in the 225 mg group, 8 in the 300 mg group, 7 in the 400 mg group, 10 in the 525 mg group and 9 in the 700 mg group) were enrolled (including 16 with NSCLC). The applicant stated that, as dose-limiting toxicities (adverse drug reactions of CTC Grade 3 or 4) were observed in 3 out of 9 subjects in the 700 mg group, higher dose levels were not investigated. It stated that all enrolled subjects were included in safety and efficacy analyses (for pharmacokinetics, refer to Section F).

With regard to the safety, adverse events were observed in all 64 subjects who received a maximum of 700 mg. Common adverse events included diarrhoea in 51.6% (33/64), nausea in 35.9% (23/64), asthenia and rash in 34.4% (22/64) each, acne in 29.7% (19/64), dyspnoea in 28.1% (18/64), vomiting in 26.6% (17/64), abdominal pain in 25.0% (16/64), constipation and anorexia in 23.4% (15/64) each, pain in 21.9% (14/64), and increased coughing and somnolence in 20.3% (13/64) each. Adverse events in Grade 3 and 4 were; Grade 3 increased ALP in 2 subjects and Grade 3 headache, hyperkalaemia, increased AST, increased ALT and hypercalcaemia in 1 subject each in the 50 mg group; Grade 3 asthenia, back pain, pain, venous thrombosis, pleural fluid and urinary tract infection in 1 subject each in the 100 mg group; Grade 4 venous thrombosis and pulmonary embolism in 1 subject each, Grade 3 asthenia in 2 subject and Grade 3 venous thrombosis, dyspnoea, somnolence and conjunctivitis in 1 subject each in the 150 mg group; Grade 4 pleural fluid in 1 subject, Grade 3 dyspnoea in 2 subjects, Grade 3 abdominal pain, increased AST, hyperbilirubinaemia, dehydration, hypokalaemia, pleural fluid, agitation, confusion, constipation, oesophagitis, gastrointestinal bleeding, nausea, anaemia, thrombocytopenia and bone pain in 1 subject each in the 225 mg group; Grade 4 respiratory distress syndrome in 1 subject, Grade 3 asthenia in 2 subjects and 1 event each of Grade 3 infection, hypophosphataemia, dyspnoea, somnolence, dizziness, dysphagia, jaundice, stomatitis and diabetes in the 300 mg group; Grade 4 increased AST, dyspnoea, rectal bleeding, anaemia and pneumonia in 1 subject each, Grade 3 anaemia in 2 subjects and Grade 3 infection, chest pain, increased ALT, atrial

fibrillation, dyspnoea, apnoea, pneumonia, dizziness, convulsion, abnormal sensation, dysphagia and gastrointestinal tract obstruction in 1 subject each in the 400 mg group; Grade 3 pain, hypoxemia, atrial fibrillation, dyspnoea, increased coughing and acne in 1 subject each in the 525 mg group; Grade 4 diarrhoea in 1 subject, Grade 3 diarrhoea in 2 subjects and Grade 3 abdominal pain, generalised oedema, dyspnoea, aphasia and vomiting in 1 subject each in the 700 mg group. Of these Grade 3 and 4 adverse events, relevancy to gefitinib was suspected with increased AST and increased ALT in 1 subject each in the 400 mg group (the same subject), acne in 1 subject in the 525 mg group, diarrhoea in 3 subjects and abdominal pain and vomiting in one subject each (the same subject as the one with diarrhoea) in the 700 mg group. During the study period, 12 deaths were reported and of those, the cause of death in 10 subjects was deterioration of the original disease. Remaining 2 deaths were considered to be unrelated to gefitinib. One subject who was in the 300 mg group (4x years old, male, head and neck cancer, case no.xxxx) was withdrawn from the study treatment on day 42 because of respiratory distress syndrome and he died 26 days after the withdrawal. Another subject who was in 400 mg group (5x years old, female, breast cancer, case no.xxxx) was withdrawn from the study treatment on day 70 because of deterioration of the original disease and she died 21 days after the withdrawal due to pneumonia.

With regard to efficacy (the anti-tumour effect assessment criteria were based on the UICC (Union Internationale Contre Le Cancer; Eur J Cancer 13: 89-94, 1977)/WHO criteria (WHO offset Publication No. 48, 1979)), it reported that PR was observed in 4 subjects (1 each in the 300 mg group, the 400 mg group, the 525 mg group and the 700 mg group), who were all NSCLC patients.

(2) Phase I/II studies (Study 0011 (xxxx) and Study 0012 (xxxx), published in Revnu des Respiratories 18 (suppl 1): 1S42, 2001 and J Clin Oncol 20:110-124, 2002, respectively)

Targeting NSCLC, head and neck cancer, ovarian cancer, hormone-refractory prostate cancer and colorectal cancer untreatable with a standard therapy, a phase I/II study (Study 0011) mainly investigating safety, efficacy and pharmacokinetics

of oral dose of gefitinib for 28 consecutive days was conducted in the US. From April 1999 till October 2000, 71 subjects were enrolled and 69 subjects received gefitinib (the number of subjects in each group and the median and the range of treatment periods (days) were; 13 subjects (35 days, 26-443) in the 150 mg group, 13 subjects (58 days, 1-506) in the 225 mg group, 13 subjects (56 days, 28-361) in the 300 mg group, 13 subjects (61 days, 7-404) in the 400 mg group, 6 subjects (120 days, 9-395) in the 600 mg group, 6 subjects (67 days, 38-221) in the 800 mg group and 5 subjects (21 days, 7-226) in the 1000 mg group). Of those, 39 subjects had NSCLC.

Parallel to this, a phase I/II study (Study 0012) using the same protocol as Study 0011 was conducted in Europe. From February 1999 till August 2000, 92 subjects were enrolled and 88 subject received gefitinib (the number of subjects in each group and the median and the range of treatment periods (days) were; 6 subjects (36 days, 12-458) in the 150 mg group, 14 subjects (72 days, 10-371) in the 225 mg group, 14 subjects (56 days, 29-252) in the 300 mg group, 14 subjects (57 days, 11-173) in the 400 mg group, 14 subjects (34 days, 7-266) in the 600 mg group, 14 subjects (29 days, 5-154) in the 800 mg group and 12 subjects (31 days, 6-195) in the 1000 mg group). Of those, 22 subjects had NSCLC (Refer to Section F for pharmacokinetics in these studies).

With regard to safety in Study 0011, adverse events were seen in 68 out of 69 subjects received gefitinib (98.6%). Common adverse events included diarrhoea in 65.2% (45/69), asthenia in 49.3% (34/69), rash in 46.4% (32/69), nausea in 39.1% (27/69), anorexia in 33.3% (23/69), dry skin in 27.5% (19/69), vomiting in 24.6% (17/69) and increased coughing in 23.2% (16/69). In 26 subjects who received 225 mg or less, 26 subjects who received 300 to 400 mg and 17 subjects who received 600 mg or more, 46.2% (12/26), 34.6% (9/26) and 52.9% (9/17), respectively, had Grade 3 and 4 adverse events. Of these, Grade 3 diarrhoea in the 300 mg group (case no.xxxx, NSCLC), Grade 3 diarrhoea in the 600 mg group (case no.xxxx, prostate cancer), Grade 3 corneal ulcer and rash in the 800 mg group (case no.xxxx, prostate cancer) and Grade 3 dehydration in the 1000 mg group (case no.xxxx, prostate cancer) were cited as serious adverse events that may be associated with gefitinib. In 7 subjects out of 69 (2 in the 600 mg

group, 4 in the 800 mg group and 1 in the 1000 mg group), the dose was reduced by one level because of adverse events associated with gefitinib. Eleven subjects in this study died and all of them died within 30 days from the end of the gefitinib treatment. The cause of deaths was deterioration of the original disease in all subjects and causal relationship to gefitinib was reported to be absent.

With regard to efficacy (anti-tumour effect was assessed following the RECIST criteria (J Natl Cancer Inst 92: 205-216, 2000)), one subject with NSCLC (case no.xxx, the 150 mg group) showed PR.

During the gefitinib treatment (at around day 28), biopsy of normal skin was taken and EGFR expression was analysed as a pharmacological marker of the gefitinib effect. The result showed suppressions of EGFR in all dose levels, from 150 mg to 1000 mg, but no apparent dose correlation was seen.

With regard to safety in Study 0012, adverse events were seen in 87 out of 88 subjects receiving gefitinib (98.9%). Common adverse events included diarrhoea in 58.0% (51/88), rash in 47.7% (42/88), nausea in 35.2% (31/88), vomiting in 34.1% (30/88), asthenia in 30.7% (27/88), acne in 23.9% (21/88), dry skin in 22.7% (20/88), anorexia and somnolence in 21.6% (19/88) each, and abdominal pain in 20.5% (18/88). In 20 subjects who received 225 mg or less, 28 subjects who received 300 to 400 mg and 40 subjects who received 600 mg or more, 45.0% (9/20), 46.4% (13/28) and 50.0% (20/40), respectively, had Grade 3 and 4 adverse events. Of these, Grade 3 nausea in the 225 mg group (case no.xxxx, prostate cancer), Grade 3 diarrhoea in the 600 mg group (case no.xxxx, ovarian cancer), Grade 4 asthenia (case no.xxxx, colorectal cancer) and Grade 3 nausea (case no.xxxx, colorectal cancer) in the 800mg group, Grade 3 diarrhoea (case no.xxxx, colorectal cancer), Grade 3 dehydration (case no.xxxx, ovarian cancer), Grade 3 asthenia (case no.xxxx, prostate cancer) and Grade 3 hypokalaemia (case no.xxxx) in the 1000 mg group were cited as serious adverse events that may be associated with gefitinib. In 9 subjects out of 88 (1 in the 300 mg group, 1 in the 400 mg group, 1 in the 600 mg group, 2 in the 800 mg group and 4 in the 1000 mg group), the dose level was reduced because of adverse events associated with gefitinib. Sixteen subjects in this study died and 2 of them died during the gefitinib treatment and 14 of them died within 30 days from the end of

the gefitinib treatment. The cause of deaths was deterioration of the original disease in all subjects and a causal relationship to gefitinib was reported to be absent.

With regard to the efficacy (anti-tumour effect was assessed following the RECIST criteria), no subject showed anti-tumour effects classified as PR or above.

During the gefitinib treatment (at around day 28), biopsy of the normal skin was taken and EGFR expression was analysed as a pharmacological marker of the gefitinib effect. The result showed suppressions of EGFR in all dose levels, from 150 mg to 1000 mg, but no apparent dose correlation was seen.

(3) A phase II study in NSCLC patients who were previously treated with platinum compounds and taxanes (Study 0039 (xxxx), unpublished)

Targeting NSCLC patients who were previously treated with platinum compounds and taxanes, a double-blinded randomised phase II comparative study investigating efficacy (shrinkage, overall survival time, etc.,) and safety of 250 mg and 500 mg gefitinib was conducted (for randomisation, the minimization technique was employed with the country and the performance status (PS) as allocation factors). From November 2000 till April 2001, 221 subjects were enrolled and 216 received gefitinib (102 subjects in the 250 mg group and 114 in the 500 mg group). It was defined by the protocol that the gefitinib treatment was to continue until disease progress was observed. At data-cut off point (yy,mm,dd), which was 4 months after enrolment of the last subject, 18 subjects in the 250 mg group and 21 subjects in the 500 mg group were continuing with the gefitinib treatment and the median (range) of the treatment duration of the groups was 56 days (2-213) and 53 days (2-232), respectively.

With regard to the safety, adverse events were seen in 99.0% (101/102) in the 250 mg group and 98.2% (112/114) in the 500 mg group. Common adverse events included diarrhoea (56.9% (58/102) in the 250 mg group and 74.6% (85/114) in the 500 mg group), rash (48.0% (49/102) in the 250 mg group and 55.3% (63/114) in the 500 mg group), asthenia (28.4% (29/102) in the 250 mg group and 36.0% (41/114) in the 500 mg group), acne (25.5% (26/102) in the

250 mg group and 33.3% (38/114) in the 500 mg group), nausea (26.5% (27/102) in the 250 mg group and 27.2% (31/114) in the 500 mg group), dyspnoea (28.4% (29/102) in the 250 mg group and 22.8% (26/114) in the 500 mg group), anorexia (23.5% (24/102) in the 250 mg group and 27.2% (31/114) in the 500 mg group), dry skin (16.7% (17/102) in the 250 mg group and 26.3% (30/114) in the 500 mg group) and increased coughing (21.6% (22/102) in the 250 mg group and 20.2% (23/114) in the 500 mg group). Grade 3 and 4 adverse events were seen in 40.2% (41/102) in the 250 mg group and 46.5% (53/114) in the 500 mg group. The most frequently seen events included dyspnoea (12.7% (13/102) in the 250 mg group and 13.2% (15/114) in the 500 mg group), asthenia (7.8% (8/102) in the 250 mg group and 8.8% (10/114) in the 500 mg group), pneumonia (5.9% (6/102) in the 250 mg group and 5.3% (6/114) in the 500 mg group), pleural fluid (2.9% (3/102) in the 250 mg group and 4.4% (5/114) in the 50 mg group), dehydration (2.0% (2/102) in the 250 mg group and 5.3% (6/114) in the 500 mg group), vomiting 2.9% (3/102) in the 250 mg group and 3.5% (4/114) in the 500 mg group) and diarrhoea (1.0% (1/102) in the 250 mg group and 5.3% (6/114) in the 500 mg group). Of these, Grade 4 thrombocytopenia and Grade 3 rectal disorder and nasal haemorrhage (case no.xxxx), Grade 4 asthenia (case no.xxxx), Grade 3 asthenia (case no.xxxx) and Grade 3 scrotal oedema and peripheral oedema (case no.xxxx) in the 250 mg group; and Grade 4 dehydration (case no.xxxx), Grade 4 pulmonary haemorrhage (case no.xxxx), Grade 4 increased ALT and Grade 3 increased AST (case no.xxxx), Grade 3 dehydration (case no.xxxx), and Grade 3 dehydration, nausea and vomiting (case no.xxxx) in the 500 mg group were cited as serious adverse events that may be associated with gefitinib. The percentages of subjects who required withdrawal due to adverse events were 14.7% (15/102) in the 250 mg group and 22.8% (26/114) in the 500 mg group. The percentages of subjects who required dose reductions (to 100 mg once daily for those in the 250 mg group and to 250 mg per dose for those in the 500 mg group) were 1.0% (1/102) and 8.8% (10/114), respectively. Twenty-two subjects in the 250 mg group (21.6%) and 27 subjects in the 500 mg group (23.7%) died in the study (during gefitinib treatment or within 30 days from the end of the treatment). Of these,

21 deaths in the 250 mg group and 26 deaths in the 500 mg group were due to deterioration of the original disease. The cause of deaths of the 1 remaining subject in the 250 mg group (5x years old, male, case no.xxxx) and 1 subject in the 500 mg group (5x years old, male, case no.xxxx) was myocardial infraction and causal relationship to gefitinib was reported to be absent. One subject in the 500 mg group (7x years old, male, case no.xxxx) had pulmonary haemorrhage on day 3 of gefitinib treatment and died on day 11. It was reported that the death of this subject was 'relevant to gefitinib', as well as deterioration of the original disease.

With regard to the efficacy (anti-tumour effect was assessed following the UICC/WHO criteria), 12 subjects in the 250 mg group and 10 subjects in the 500 mg group were reported to show PR and the response rate (the rate of complete response (CR) + PR) was 11.8% (12/102) (95% confidence interval (CI): 6.2-19.7) and 8.8% (10/114) (95% CI: 4.3-15.5), respectively.

1-3. International Study

(1) A phase II study in NSCLC patients who were previously treated with platinum compounds (Study 0016 (xxxxxx), published in AACR-NCI-EORTC International Conference 12: abstr 630A, 2001)

Targeting NSCLC patients who were previously treated with platinum compounds, a double-blind, randomised phase II comparative study investigating efficacy (tumour shrinkage rate, time to progress (TTP), etc.) and safety of 250 mg and 500 mg gefitinib was conducted. This study was also aiming to compare efficacy and safety in Japanese and non-Japanese populations and planned to enrol and randomise 100 subjects each in Japan and abroad. Between October 2000 and January 2001, 19 Japanese centres enrolled 102 subjects and 24 overseas centres enrolled 108 subjects. All subjects in Japan (51 in the 250 mg group and 51 in the 500 mg group) and 107 subjects abroad (52 in the 250 mg group and 55 in the 500 mg group) received gefitinib. At data cut-off point (yy,mm,dd), which was 4 months after enrolment of the last subject, 37 subjects in Japan (21 in the 250 mg group and 16 in the 500 mg group) and 16 subjects abroad (5 in the 250 mg group and 11 in the 500 mg group) were continuing with

gefitinib treatment and the median (range) of the treatment period for each group was 102 days (19-227) and 85 days (13-219) in Japan, respectively, and 56 days (1-212) and 55 days (1-162) abroad, respectively.

With regard to safety, adverse events were seen in all subjects in Japan (51 subjects in the 250 mg group and 51 in the 500 mg group), and 50 subjects out of 52 subjects in the 250 mg group and all 55 subjects in the 500 mg group abroad. The common adverse events included, in Japan, rash (64.7% (33/51) in the 250 mg group and 80.4% (41/51) in the 500 mg group), diarrhoea (60.8% (31/51) in the 250 mg group and 74.5% (38/51) in the 500 mg group), pruritus (51.0% (26/51) in the 250 mg group and 56.9% (29/51) in the 500 mg group), dry skin (35.3% (18/51) in the 250 mg group and 41.2% (21/51) in the 500 mg group), increased ALT (29.4% (15/51) in the 250 mg group and 37.3% (19/51) in the 500 mg group), increased AST (29.4% (15/51) in the 250 mg group and 35.3% (18/51) in the 500 mg group), pharyngitis (27.5% (14/51) in the 250 mg group and 41.2% (21/51) in the 500 mg group), nausea (23.5% (12/51) in the 250 mg group and 35.3% (18/51) in the 500 mg group) and anorexia (21.6% (11/51) in the 250 mg group and 37.3% (19/51) in the 500 mg group); and abroad, diarrhoea (36.5% (19/52) in the 250 mg group and 60.0% (33/55) in the 500 mg group), asthenia (34.6% (18/52) in the 250 mg group and 25.5% (14/55) in the 500 mg group), rash (30.8% (16/52) in the 250 mg group and 60.0% (33/55) in the 500 mg group), dyspnoea (26.9% (14/52) in the 250 mg group and 21.8% (12/55) in the 500 mg group), nausea (25.0% (13/52) in the 250 mg group and 34.5% (19/55) in the 500 mg group), dry skin (23.1% (12/55) in the 250 mg group and 18.2% (10/55) in the 500 mg group) and vomiting (21.2% (11/52) in the 250 mg group and 32.7% (18/55) in the 500 mg group). Grade 3 and 4 adverse events were seen in 17.6% (9/51) in the 250 mg group and 37.3% (19/51) in the 500 mg group in Japan, and 46.2% (24/52) in the 250 mg group and 63.6% (35/55) in the 500 mg group abroad. The most frequently seen events included, in Japan, increased ALT (3.9% (2/51) in the 250 mg group and 9.8% (5/51) in the 500 mg group), diarrhoea (2.0% (1/15) in the 250 mg group and 11.8% (6/51) in the 500 mg group), pneumonia (5.9% (3/51) in the 250 mg group and 2.0% (1/51) in the 500 mg group), constipation (2.0% (1/51) in the

250 mg group and 5.9% (3/51) in the 500 mg group), and asthenia (2.0% (1/51) in the 250 mg group and 3.9% (2/51) in the 500 mg group); and abroad, dyspnoea (15.4% (8/52) in the 250 mg group and 14.5% (8/55) in the 500 mg group), anaemia (7.7% (4/52) in the 250 mg group and 9.1% (5/55) in the 500 mg group), asthenia (5.8% (3/52) in the 250 mg group and 7.3% (4/55) in the 500 mg group), pain (1.9% (1/52) in the 250 mg group and 9.1% (5/55) in the 500 mg group), chest pain (3.8% (2/52) in the 250 mg group and 5.5% (3/55) in the 500 mg group), rash (9.6% (5/52) in the 250 mg group and 9.1% (5/55) in the 500 mg group) and bone pain (1.9% (1/52) in the 250 mg group and 5.5% (3/55) in the 500 mg group). Of these, Grade 3 bundle branch block (case no. xxxx, an overseas subject), and Grade 3 dehydration (case no. xxxx, overseas) in the 250 mg group, and Grade 4 deep vain thrombosis (case no. xxxx, a Japanese subject) Grade 4 anaemia and shock and Grade 3 gastrointestinal haemorrhage and melaena (case no. xxxx, overseas), Grade 4 pneumonia (case no. xxxx, overseas), Grade 3 dyspnoea and interstitial pneumonia (case no. xxx, Japanese), Grade 3 anaemia and hypoproteinaemia (case no. xxxx, Japanese), Grade 3 pneumonia and hypoxemia (case no. xxx, Japanese), Grade 3 asthenia (case no. xxxx, overseas), Grade 3 acne (case no. xxx, overseas), Grade 3 diarrhoea (case no. xxxx, overseas) and Grade 3 diarrhoea (case no. xxxx, overseas) were cited as serious adverse events that may be associated with gefitinib. The percentages of subjects who required withdrawal due to adverse events in the 250 mg group and the 500 mg group were, 19.6% (10/51) and 33.3% (17/51) in Japan, respectively, and 11.5% (6/52) and 23.6% (13/55) abroad, respectively. Subjects who required dose reductions (to 100 mg per dose for those in the 250 mg group and to 250 mg per dose for those in the 500 mg group) were, for the 250 mg group, none in Japan and abroad and for the 500 mg group, 7.8% (4/51) in Japan and 12.7% (7/55) abroad. Deaths in the study (during gefitinib treatment or within 30 days from the end of the treatment) were 3 in Japan and 32 abroad. Of these, 2 deaths in Japan and 28 abroad were due to deterioration of the original disease. The one remaining subject in Japan (7x years old, male, the 250 mg group, case no.xxxx) was withdrawn from the treatment on day 19 due to pneumonia and died on 11 days after the withdrawal, and it was assessed as ‘not

relevant' to gefitinib. The causes of death of 3 out of the 4 remaining subjects abroad (all in the 250 mg group) were said to be deterioration of general status, haemoptysis fatal and pneumonia, and they were assessed as 'not relevant' to gefitinib. The one remaining patient (6x years old, female, the 500 mg group, case no.xxxx) was withdrawn from gefitinib treatment on day 59 due to pneumonia and died on two days after that from respiratory failure. This case was assessed as 'relevant' to gefitinib.

With regard to the efficacy (anti-tumour effect was assessed following the UICC/WHO criteria), in Japan, 14 subjects with PR in the 250 mg group and 1 subject with CR and 13 subjects with PR in the 500 mg group were reported, making the response rate in both groups 27.5% (14/51) (95% CI: 15.9-41.7). Abroad, 5 subjects with PR in the 250 mg group and 6 subjects with PR in the 500 mg group were reported, making the response rates 9.6% (5/52) (95% CI: 3.2-21.0) and 10.9% (6/55) (95% CI: 4.1-22.2), respectively.

2. Evaluation by the Evaluation Centre

The evaluation centre discussed mainly the following points.

[Clinical positioning of gefitinib and history of development]

Lung cancer is currently one of malignant tumours with the highest mortality rate in the world and it is the malignant tumour causing most death in Japan (Cancer Statistics in Japan 2001, Federation for Promotion of Cancer Research, Tokyo, 2001). NSCLC, which makes up about 80% of lung cancer, is often already advanced and inoperable by the time the patient is diagnosed and the prognosis is very poor with the 5-year survival rate of around 1%. On treatment of advanced NSCLC, it has been internationally recognised that prognosis of patients is improved when patients with good PS (generally PS 0 or 1) receive chemotherapy with platinum compounds mainly based on cisplatin (CDDP). Especially in recent years, combinations of a new anticancer agent, such as irinotecan (approved on 19th January 1994), docetaxel (approved on 9th October 1996), paclitaxel (TXL) (approved on 10th February 1999), vinorelbine (approved on 12th March 1999) and gemcitabine (GEM) (approved on 12th March 1999), with a platinum

compound are found to be useful (Clinical Oncology 2nd Edition: p941-972, Cancer and Chemotherapy Publishers INC., Tokyo, 1999, NCI PDQ: http://www.cancer.gov/cancer_information/cancer_type/lung/, Jpn J Clin Oncol 31: 299-304, 2001). However, those treatments only provide as little as 2 months extra survival compared with the previous generation of chemotherapies (CDDP + vindesine, etc.), and development of more useful drugs and therapies are awaited.

Considering this situation, the Evaluation Centre inquired on the applicant's clinical positioning of gefitinib in treatment of NSCLC and the history of development. The applicant responded as follows.

Gefitinib is what is called "molecular targeting therapy" that has a different mode of action from existing anti-cancer drugs, and it suppresses growth of tumour cells by inhibiting tyrosine kinase of EGFR. EGFR is known to overexpress in solid tumours, including lung cancer, head and neck cancer and breast cancer, and its involvement in prognosis has also been reported. The phase I studies in Japan and abroad (Study 0005 (xxxx), Study V-15-11 (xxxx)) and the phase I/II studies abroad (Study 0011 (xxxx), Study 0012 (xxxx)) were conducted in patients with these solid cancers known to have EGFR overexpression. In these studies, 4 cases, 5 cases and 1 case of PR were observed, respectively (PR was not observed in Study 0012), and all those cases were NSCLC patients. As the mode of action of gefitinib differs from existing anti-cancer agents, additive effects with other agents have been expected from an early stage of development. Large-scale comparative studies (a study comparing CDDP + GEM with or without gefitinib (Study 0014) and a study comparing carboplatin + TXL with or without gefitinib (Study 0017)) are still ongoing. However, results of the above phase I studies and phase I/II studies raided hopes for usefulness of gefitinib monotherapy for NSCLC and a new development program of gefitinib monotherapy was considered. As a result, a phase II study (Study 0039 (xxxx)) investigating usefulness of gefitinib third-line therapy after docetaxel therapy, which is the current standard second-line therapy for NSCLC, was conducted in the US. At the same time, in Japan and Europe, investigation of usefulness of gefitinib as a second-line therapy after treatment with anti-cancer platinum compounds was proposed and an international phase II study (Study 0016 (xxx)) was conducted as a bridging study for extrapolation of results of other overseas clinical studies to Japan. The study demonstrated that gefitinib (250 mg) was a useful

drug for NSCLC, with a response rate of NSCLC patients after prior standard chemotherapy with platinum compounds being 27.5% (14/51) and 9.6% (5/52) in Japan and abroad, respectively, and without serious adverse drug reactions being observed. Based on this result, this approval application was made.
The Evaluation Centre accepted the applicant's response with an understanding that this application was made because clinical usefulness of gefitinib as a second-line therapy for advanced NSCLC was demonstrated at this stage of development.

[Scope of NSCLC to be indicated]

The Evaluation Centre asked the applicant if the indication should be limited to a more appropriate target, such as "inoperative non-small cell lung cancer previously treated with chemotherapy" rather than the filed indication "non-small cell lung cancer", as the data submitted in this application only verify, as stated above, usefulness of gefitinib as second-line therapy for advanced NSCLC. The applicant replied as follows.
Study 0014 and Study 0017 (mentioned above) investigating usefulness of gefitinib in previously untreated patients completed the enrolment on mm, yy, (1093 and 1037 patients were enrolled, respectively) and survival data will become available in yy. In Japan, as clinical studies of combination chemotherapy with gefitinib in previously untreated patients, xxxxxxxxxx bridging study xxxxxxxxx, and xxxxx study xxxxxxxxx are planned. On xxxxxxx, xxxxxxxxxxxxxx targeting xxxxxxx in Japan xxx also planned.
NSCLC with previous chemotherapy is the only target in which usefulness of gefitinib has been verified by clinical study results currently available, but considering that indications of already approved anti-malignant tumour drugs usually do not distinguish previously untreated and treated cases and restrictions on use in post-operative adjuvant therapy are provided in Precautions for Use rather than in Indications, the Indication should state the targeted disease 'non-small cell lung cancer' rather than the targeted patient population (of the studies). Restrictions on use in patient populations that are still under investigation or planned to be investigated could be dealt by providing a restriction in Precautions for Use, for example, 'efficacy and safety in xxx have not been demonstrated.' As the safety of gefitinib is high, it is supposable that gefitinib is useful for patients who are not suitable for chemotherapy with existing anti-cancer agents, such

as elderly patients and patients with poor general status. If the indication is limited to 'patients who received previous chemotherapy', such patients will lose the chance to receive gefitinib treatment. Taking all these into account, no specific issues are thought to be associated with setting the indication of gefitinib as 'non-small cell lung cancer'.
Recently in Japan, medical treatment based on scientific rationales (what is called evidence based medicine) has been spreading widely, and the Evaluation Centre thinks that it is becoming more important to make a decision on the scope of application of a drug, which is presented in Indication, on a basis of clinical positioning of the drug and scientific clinical data. At this moment, the only available verification on usefulness of gefitinib is that gefitinib was used as second-line therapy (or third-line therapy) in advanced NSCLC patients who were previously treated with a platinum compound in Japan and abroad and the clinical usefulness in the targeted patients were demonstrated from efficacy and safety points of view.
Pathology after surgical removal of cancer is clearly different from cancer-bearing state, which was investigated in the gefitinib clinical studies so far, and in long-term treatment lasting several years, which is expected as postoperative adjuvant therapy, we cannot ignore concerns such as incidences of corneal disorders. In fact, the applicant is planning to conduct a carcinogenicity study for the analogy of the long-term safety. Therefore, the Evaluation Centre thinks that clinical usefulness of gefitinib in postoperative adjuvant therapy should be judged carefully considering results of the planned xxxxx clinical study for the filed indication. With regard to the first-line treatment of advanced NSCLC, outcome of the overseas large-scale comparative studies (Study 0014 and Study 0017) will become available on yy, and also the applicant presented plans of a bridging study xxxx in xx patients and xxxx study xxxxxxx in Japan, but the clinical usefulness has yet to be shown at the moment. Furthermore, the applicant provided a reply supposing that gefitinib is going to be used as the first-line therapy in elderly patients and patients with poor state, but simply safety being high does not provide good enough rationale for using gefitinib in those patients and usefulness including efficacy needs to be verified in an appropriately designed clinical study. The applicant actually indicated in a part of response that xxxxxxxxxx xxxxxxx xxxx in the planning stage abroad.
Considering the above, the Evaluation Centre thinks that in order to ensure correct use of gefitinib, which has less severe adverse drug reactions than existing anti-cancer agents

and is an oral formulation that maybe used with relative ease, the indication of gefitinib should read 'non-small cell lung cancer (inoperative or recurrent)', Precautions for Use concerning Indication should state 'efficacy and safety of postoperative adjuvant chemotherapy has not been established' and the package insert should alert that 'clinical usefulness of gefitinib' as a first-line therapy for advanced NSCLC 'has not been established' at the moment. The Evaluation Centre would like to make a careful decision on the indication of gefitinib considering the discussion at the expert review.

[Appropriateness of dosage and administration]

The Evaluation Centre asked the applicant about the rationale for the dosage of gefitinib, 250 mg once daily. The applicant replied as follows.

In the phase I and phase I/II studies in Japan and abroad, responses were observed at dose between 150 mg and 800 mg, but no dose response was shown. On safety, serious adverse drug reactions such as NCI-CTC Grade 3 diarrhoea and rash were more frequently seen with dose levels above 600 mg than lower dose levels and more patients had dose reductions. Based on these, 250 mg and 500 mg were compared in the phase II studies and the results showed that the efficacy was about the same at both dose levels and 250 mg was safer. Based on this result the applicant decided that the dose of gefitinib should be 250 mg.

The Evaluation Centre accepted the applicant's reply.

The Evaluation Centre asked the applicant to explain the appropriateness of choosing to administer consecutive days in the phase I/II studies (Study 0011 and Study 0012) onwards, although regimen used in the phase I studies in Japan and abroad (Study C-15-11, Study 0005) was repeats of dosing gefitinib for 14 consecutive days then withdrawing for 14 days.

The applicant replied; (1) the study results with a nude mouse graft system showed that suppression of tumour growth by gefitinib was reversible and re-growth of tumours was observed after withdrawal, (2) in a clinical study (Study 0005), re-growth of tumours during withdrawal was observed in some subjects, and (3) with regard to safety, there was no big difference in the adverse drug reaction profile of 64 and 31 subjects who received intermittent treatment (50 to 700 mg) in Study 0005 and Study V-15-11,

respectively, and that of 69 and 88 subjects who received treatment continuously (150 to 1000 mg) in Study 0011 and Study 0012. Therefore, the applicant judged that continuous treatment was more appropriate.

The Evaluation Centre investigated details of clinical progresses of subjects who had re-growth of tumours in a withdrawal period of gefitinib in phase I studies in Japan and abroad (subject nos.xxx, xxx, xxx, xxx, xxx, xxx, xxx in Study 0005). Although when chest CT images of the above subject xxx at the end of the second treatment period (15 days from the start of the treatment) and 14 days after completion (28 days from the start of the treatment) were compared, enlargement of tumour was observed on the latter image, the Evaluation Centre believes that the hypothesis, tumours would deteriorate more with intermittent treatment than continuous treatment, could not be verified without comparing two regimes in a randomised comparative study. However, according to the expected mode of action of gefitinib and results of nonclinical studies, a possibility of tumour growth during withdrawal periods is present and clinical results from phase I/II studies onwards with treatment on consecutive days support usefulness of gefitinib for NSCLC from safety and efficacy point of view, as mentioned below. Therefore, the Evaluation Centre judged that administration of gefitinib on consecutive days was appropriate.

[Difference in response rates in Japan and abroad]

The Evaluation Centre asked the applicant what could be the reason for the large difference in the response rate of the 250 mg group in Japan and abroad (27.5% (14/51) and 9.6% (5/52), respectively) in the international phase II study (Study 0016). The applicant replied as follows.

In the international phase II study, response rates of Japanese and non-Japanese subjects showed a statistically significant difference (p=0.0023, Fisher's direct probability test). However, the result of analysis of contributions of subject's background factors on efficacy (anti-tumour effects as PR or CR) with logistic regression model showed that factors such as PS (0, 1 or 2) and tissue types (adenocarcinoma or non-adenocarcinoma) had bigger effects (odds ratios: 6.26 and 3.45, respectively) than ethnic factors (Japanese or non-Japanese, odds ratio: 1.64). That is to say, more subjects in Japan having

adenocarcinoma (76.5% in Japan: 50.0% abroad) and fewer subjects in Japan being PS2 (8.8% in Japan: 16.7% abroad) maybe resulted in the differences in the response rates in Japan and abroad.

The Evaluation Centre thinks that it is reasonable for a population with a higher number of subjects with poor PS to have a lower rate of completing the study treatment and as a result, their efficacy rate to be lowered (in fact, the duration of gefitinib treatment was shorter abroad than in Japan, the median being 56 days abroad and 90 days in Japan). Furthermore, the Evaluation Centre asked the applicant if a difference in treatments received before the enrolment to the study in Japan and abroad was one of the causes for poorer PS in subjects abroad. The applicant showed that the median of durations of previous treatments in Japan and abroad was 8.5 weeks and 18.0 weeks, respectively, indicating that subjects abroad had more than twice as long on previous treatment as subjects in Japan. The applicant stated that the duration of previous treatment was not a factor that affected efficacy according to the above-mentioned analysis results with the logistic regression model. However, the Evaluation Centre believed that it could not rule out a possibility that more subjects in poor conditions due to longer previous treatment were enrolled abroad, which as a result, lead to the lower response rate. Considering such differences in patient background, the Evaluation Centre judged that the response rate 9.6% in the 250 mg group abroad did not necessarily disclaim the efficacy of gefitinib. Furthermore, the Evaluation Centre believes that the response rate 11.8 (12/102) in the 250 mg group in the overseas phase II study (Study 0039) in “subjects who had previous platinum compound and taxian treatments”, which targeted more advanced patients than those enrolled in the international phase II study, also supports clinical usefulness of gefitinib.

However, as differences in background of the patients in Japan and abroad in the international phase II study were so big and they affected the efficacy and the safety (mentioned later), this study cannot be seen as a perfect bridging study. Therefore, the Evaluation Centre believes that results of the planned new bridging study (xxxx a bridging study xxx) and other studies need to be fully examined when extrapolating overseas clinical studies in future.

[Possibility of mechanisms of action other than EGFR inhibition]

Considering that most responders with PR or CR seen in clinical studies including the Japanese phase I study and the international phase II study had adenocarcinomas and a few responders had squamous carcinoma, which are said to have high expressivities of EGFR (in Study 0016, the response rate was 7.0% in those with squamous carcinoma and 26.0% in those with adenocarcinoma), the Evaluation Centre asked the applicant if it is possible that the gefitinib's anti-tumour action is based on mechanisms other than the EGFR inhibition. The applicant replied as follows.

Gefitinib clinical studies showed numerically higher response rates in adenocarcinoma than in squamous carcinoma, however, the applicant believed that improvements in parameters such as the clinical improvement rating were confirmed in all tissue types of NSCLC. Although it is generally believed that EGFR expressivities in squamous carcinoma is higher than in adenocarcinoma, there is no standard technique to assay EGFR expression in reality. The applicant has established an immunohistochemical assay technique for EGFR expression, but a scoring system of stained sample slides has yet to be developed, as there are unresolved technical problems in the staining and other processes. When investigating collected tumour tissues in the clinical trials of gefitinib, unevenness in sampling timing and sampling sites caused confusions in interpreting clinical effects and EGFR expressions. Therefore, at the present time, evaluation of relationships between EGFR expression and clinical effects is still at an exploratory stage. Although the applicant thinks that gefitinib exerts its anti-tumour activities through the EGFR inhibition, it may not be the only factor and a possibility of an involvement of unknown mechanisms other than the EGFR inhibition cannot be ruled out.

The Evaluation Centre judged that it is not possible to verify that gefitinib exerts its anti-tumour effects through a mode of action only consists of the EGFR inhibition, since we cannot ensure reliability of EGFR measurements at this time in moment, as the applicant stated. More detailed information on the mechanisms of the action of gefitinib will be obtained from future researches, including a clinical study xxxx investigating genetic expression profiles specific to responders to gefitinib using xxxxx, which is currently underway in Japan.

[Effect of gefitinib on the normal organs]

As it has been known that EGFR is expressed in the normal cells as well as the cancer cells, the Evaluation Centre asked the applicant to discuss possible adverse events when gefitinib inhibits EGFR. The applicant replied as follows.

It has been reported that, in humans, EGFR is located in the skin, gastrointestinal system, eyes, reproductive system, respiratory system and urinary system and they were thought to be involved in maintenance of homeostasis, reproduction, etc., in those organs. Together with adverse event data obtained from the gefitinib clinical studies so far, the applicant presented discussions on each organ as follows.

In the human skin tissues including the hair root, EGFR is known to have effects such as promotions of keratinocyte growth, stimulations of cell migration and promotions of wound healing (J Invest Dermatol 78:482-487, 1982, J Invest Dermatol 82: 165-169, 1984, J Invest Dermatol 94: 164S-170S, 1990) (EGFR expression in skeletal muscles has not been reported). Expected events caused by their inhibition include dermatitis and embrittlement of body hairs. In fact, in clinical studies, rash, dry skin, pruritus, acne, etc., were observed and they were thought to have some relevancies to the EGFR inhibition by gefitinib. However, most of them were mild and recovered after withdrawal without medical interventions.

In the human gastrointestinal system, EGFR expression has been reported in the oral cavity, stomach, small intestine, large intestine, liver and pancreas, and its involvement in maintenance of functions of the gastrointestinal mucosal epithelium, tissue regenerations at liver damage through their stimulatory effects on cell growth, etc., have been suggested (Arch Oral Biol 38: 823-826, 1993, Gastroenterol 98: 961-967, 1990, Gut 39: 262-266, 1996, Early Human Devel 65: 1-9, 2001, Hepatol 9: 126-138, 1989, Teratog Carcinog Mutagen 15: 231-250, 1995). Expected events caused by their inhibition are abnormalities due to general reductions in gastrointestinal functions, such as anorexia, nausea, vomiting, diarrhoea and liver dysfunction. In fact, in clinical studies, adverse events such as diarrhoea, nausea, vomiting, anorexia, stomatitis, increased ALT and increased AST were observed. Of these, the incidence of diarrhoea was the highest (57.9% (121/209) in Study 0016). Although most were mild and recovered after

withdrawal without medical interventions, some NCI-CTC Grade 3 diarrhoea required drugs to control intestinal function and antidiarrhoeal drugs (4.8% (10/209) in Study 0016). In "Precautions for Use (draft) Important Basic Precautions", the applicant is going to call for cautions on diarrhoea, stating "appropriate actions should be taken, for example withdraw gefitinib, if diarrhoea as an adverse drug reaction develops and makes continuation of the treatment difficult."

With regard to the eyes, a presence of EGFR in the human cornea, limbus and conjunctiva are confirmed by immunostaining and it is thought to contribute to promotions of wound healing on cornea and maintenances of their functions (Cornea 20: 81-85, 2001, Exp Eye Res 72: 511-517, 2001, Exp Biol Med 226:653-664, 2001). Expected events caused by inhibitions of these include atrophy of cornea. In fact, atrophy of limbus in the 1-month toxicity studies in rats and dogs, opaque cornea in the dog 6-month toxicity study, etc., were observed (refer to the next section for the effect of gefitinib on the cornea).

In the human reproductive system, a presence of EGFR in the testis and prostate are confirmed in males and thought to be involved in spermatogenesis, proliferations of prostate and maintenances of homeostasis. In females, EGFR expression in the ovary, uterus and vulva are confirmed and it has been reported to be involved in functions including stimulations of ovarian epithelial cell growth, promotions of follicle formation and growths of endometrium (J Clin Endocrinol Metab 58: 589-594, 1984, J Biol Chem 275: 18297-18301, 2000, Prostate 14, 123-132, 1989, World J Urol 13: 290-296, 1995, Am J Obstet Gynecol 164: 745-750, 1991, J Cancer Res Clin Oncol 115: 259-263, 1989, Int J Gynecol Pathol 9: 263-271, 1990, Obstet Gynecol 76: 381-387, 1990). If it is inhibited, decreased spermatogenesis and prostate functions in males, and decreased ovary functions, such as suppressions of ovulation, and decreased uterine functions in females may be caused. However, no adverse drug reactions related to the reproductive system have been observed so far in the clinical studies. Epidermal growth factors are also deeply involved in development and differentiation of the foetus and if the clinical dose (250 mg) is administered to a pregnant woman, it may affect the foetus. In the clinical studies, pregnant woman or women with childbearing potential were excluded. The applicant is planning to call for cautions on post-market use in females by stating "gefitinib should only be used in pregnant or possibly pregnant women if clinical benefit

outweighs the risks" and "women who are receiving the gefitinib treatment should be advised to avoid becoming pregnant" in the package insert.

In the human respiratory system, it has been confirmed that EGFR is located in the basal cell layer of the bronchial epithelium and in the alveolar epithelium. It is thought to be involved in repairing wounds on the respiratory tract, etc., through its promoting effect on epithelium growth, etc. (Mod Pathol 7: 480-486, 1994, Pediatr Res 38: 851-856, 1995, Am J Respir Cell Biol 20: 914-923, 1999). By inhibiting them, events such as delayed repair of respiratory wounds are expected, but adverse drug reactions associated with delayed repair of respiratory wounds have not been observed in the clinical trials (refer to the separate section on interstitial pneumonia with relevancy to gefitinib that cannot be ruled out).

In the human urinary system, a presence of EGFR in the kidney and bladder has been confirmed and they are thought to be involved in maintenances of the kidney and bladder's functions through stimulating epithelial cell growth in the renal tubule, collecting duct, urinary passage, etc. (Int J Cancer 43: 1029-1033, 1989, Nippon Rinsho 50: 2931-2936, 1992, J Urol 138: 1329-1335, 1987). Its inhibition is thought to cause general reductions in kidney functions by reducing functions of the renal tubule, the collecting duct and the glomerulus, but in the clinical studies so far, haematuria was the commonest adverse event of the urinary system (8.6% (18/209) in Study 0016) and most of them are mild, NSC-CTC Grade 1.

Expression of EGFR in other systems in humans such as the central nervous system (brain), circulatory system (heart) and immune system (lymph nodes, spleen) are thought to be rare and no adverse events associated with gefitinib were observed in the clinical studies. With regard to the heart, a dose-dependent inhibition of the delayed rectifier potassium current (Ikr) was observed in a non-clinical study (the general pharmacology study in dogs), but in over 7000 subjects recruited in all clinical studies so far (including studies which were not submitted, such as a combination study with chemotherapy), only one subject reported prolongation of the QTc intervals (a subject in Study 0014, xxxx who received combination therapy with a chemotherapy agent), and a possibility of causing prolongation of the QTc intervals at the clinical dose was thought to be very low. However, the applicant thinks that a possibility of gefitinib causing QTc interval prolongation needs to be investigated more carefully and it is planning to carry out an

investigation of ECG after treatment with gefitinib alone by cardiologists and submit an additional report at the end of June 2002. In the international phase II study, a subject in the 250 mg group showed NCI-CTC Grade 3 bundle branch block (case no. 0259/0007 (overseas patient)), but as a relationship of Ikr inhibition and bundle branch block is not clear and considering the background factor of the patient (6x years old, bodyweight of 112 kg, height of 182 cm) and the patient might have had cardiopathy risk factors, relevancy to gefitinib was considered to be low.
The Evaluation Centre accepted the above applicant's reply.
Furthermore, the Evaluation Centre asked the effect of gefitinib on foetuses, as involvements of epidermal growth factors in proliferation and differentiation of the nerves and angiogenesis in foetuses are reported. The applicant replied as follows.
In rats, gefitinib and the metabolites are known to migrate to the placenta and milk and distributions to the brain and spinal code are confirmed although they are low (refer to section F), and effects of gefitinib at the clinical dose level to development and differentiations in the nerves of foetuses and during the nursing period cannot be ruled out. Gefitinib also has inhibitory actions on VEGFR-TK (KDR and Flt-1) and FGFR-TK, which are know to be involved in angiogenesis, although they are weaker than the EGFRTK inhibitory action, and possibilities to affect development and differentiation and angiogenesis in foetuses are suspected (Nature 367:62-66, 1995, Nature 376: 66-70, 1995). Therefore, the applicant is planning to state in Precautions for Use in the package insert that gefitinib should only be administered to pregnant, parturient and nursing women or women with childbearing potential, if clinical benefit outweighs the risks.
The Evaluation Centre accepted the above response of the applicant, but believes that the actual statements on the package inserts require more discussion.

[Effects on cornea]

The Evaluation Centre asked the applicant's view on safety of gefitinib on the eyes, as non-clinical studies suggested gefitinib's effects on the cornea and subjects who wear contact lenses, etc., were excluded from the phase I studies (Study 0015 and Study V-15-11) and phase I/II studies (Study 0011 and Study 0012) but such exclusion criteria

were not used in the international phase II study (Study 0016) started in October 2000 and the subsequent studies. The applicant replied as follows.

As findings associated with the cornea were observed (corneal granulation, diffused corneal opacity, corneal atrophy, etc.,) in the non-clinical studies of gefitinib (repeated dose toxicity studies in rats and dogs (refer to Section D)), several exclusion criteria concerning the eyes were established and frequent eye tests were conducted during the treatment period in the phase I studies and the phase I/II studies. In June 2000, an advisory board meeting consists of 4 external eye specialists was held in Wilmington (the US) and results of slit lamp microscope examinations of over 800 cases were reviewed. No toxicity consistent with gefitinib was observed and many of ophthalmologic findings and adverse events associated with the eyes were within a range found in normal subjects. In the phase I studies with multiple dose (5 studies including Study 0005), in total of 270 subjects, 85 subjects (36.3%) showed adverse events associated with the eyes. Common adverse events included conjunctivitis in 14.4% (39/270), dry eyes in 7.4% (20/270) and amblyopia in 5.2% (14/270), but none of the findings expected from the results of the non-clinical studies (the above-mentioned corneal granulation, etc.,) were observed. Therefore, the phase II studies were carried out with less frequent assessments on the eye. In the phase II studies (Study 0016 and Study 0039), 102 out of 425 subjects (24.0%) showed adverse events associated with the eyes (22.9% (47/205) in the 250 mg group and 25.0% (50/220) in the 500 mg group). Common adverse events included conjunctivitis in 8.2% (35/425), dry eyes in 4.0% (17/425) and blepharitis in 3.3% (14/425), and the types and incidences of the adverse events were similar to those observed in the phase I studies. The most of the adverse events were NCI-CTC Grade 1 or 2, and only 2 out of 102 subject had Grade 3 events (cataract and corneal erosion). Corneal erosion occurred on day 13 of the treatment (in the 500 mg group, case no. xxx), but it was due to external injury (poked the eye with a tree leaf during gardening) and the investigator assessed it was “not relevant” to gefitinib.

Based on the above results, although we cannot rule out the possibility of developing corneal adverse drug reactions in clinical practice, it is not likely to cause large clinical issues as cautions are raised in “Precautions for Use (draft), Other Adverse Drug Reactions” by stating “if an eye symptom appears, appropriate actions should be taken immediately, for example, conduct opthalmic examinations.”

The Evaluation Centre judged that, as the applicant claims, serious corneal disorders associated with gefitinib have not been observed in clinical studies so far. However, the centre believes that the effect of gefitinib on the cornea needs more deliberations in future, taking results of long-term studies, etc., into account.

[Relevancy to interstitial pneumonia]

The Evaluation Centre asked the applicant's view on the relationships of gefitinib with occurrences of interstitial pneumonia in two Japanese subjects (case no.xxx, case no.xxx) and one Japanese subject (case no.xxx) who were enrolled in Study 0016 and Study 0026 (the extension study of gefitinib treatment in patients enrolled in Study V-15-11 and Study 0016), respectively (as of April 2002, 4 non-Japanese subject with interstitial pneumonia were reported). The applicant replied as follows.

The onsets of three cases of interstitial pneumonia observed in Japan were on day 17, day 87 (in a withdrawal period starting from day 85) and day 10 (this subject was in Study 0016 before enrolled in this study and had received 500 mg gefitinib for 219 days), respectively, and improvements with steroid treatment were seen. As these episodes were during gefitinib treatment, we cannot rule out the possibility that interstitial pneumonia in those patients are related to gefitinib. However, autopsy of case no.xxx presented findings associated with progress of the original disease, such as carcinomatous lymphangitis and carcinomatous pleurisy and autopsy of case no.xxx did not show findings associated with interstitial pneumonia (no autopsy was carried out on case no.xxx). As at this moment, we do not have a direct evidence of gefitinib inducing interstitial pneumonia, we think that these reported interstitial pneumonia are associated with progress of the original disease and a possibility of gefitinib inducing interstitial pneumonia is low.

The Evaluation Centre checked clinical progress of 3 subjects reported with interstitial pneumonia in Japan. In the autopsy of case no.xxx, findings of interstitial pneumonia, such as interstitial oedema and lymphocyte cellular infiltration were observed independent of the distribution of carcinomatous lymphangitis, which the applicant claimed to be the cause of interstitial pneumonia and the investigator also judged it as drug-induced interstitial pneumonia with gefitinib. Although the applicant stated that the

autopsy of case no.xxxx did not have findings associated with interstitial pneumonia, this patient died about 2 months after clinical symptoms of interstitial pneumonia were improved; therefore, it would be very difficult to speculate on observations of whether the patient had interstitial pneumonia from the result of the autopsy. The Evaluation Centre judged that investigations so far do not rule out the possibility of gefitinib being involved in the onsets of interstitial pneumonia and relationships of gefitinib and interstitial pneumonia require more careful future investigations, taking post-marketing surveillance, etc., into account.

[Differences in incidences of adverse events in Japan and abroad]

The Evaluation Centre asked the applicant's opinion on what made differences in types and incidences of adverse events in Japan and abroad in the international phase II study. The applicant replied as follows.

The following differences in incidences of adverse events in Japan and abroad were observed in the international phase II study. Adverse events more common to Japanese were rash (72.5% in Japanese: 45.8% in non-Japanese), diarrhoea (67.6%: 48.6), pruritus (53.9%: 15.0%), dry skin (38.2%: 20.6%), pharyngitis (34.3%: 8.4%), increased ALT (33.3%: 8.4%), increased ASR (32.4%: 6.5%), anorexia (29.4%: 16.8%) and pain (26.5%: 12.1%), and in non-Japanese, asthenia (16.7%: 29.9%) were more common. However, if we only look at adverse drug reactions of NCI-CTC Grade 3 or 4, diarrhoea was 3.9% in Japanese and 2.8% in non-Japanese and increased ALT was 6.9% in Japanese and 0.9% in non-Japanese and rash was 2.9% in Japanese and 4.6% in non-Japanese, showing no large differences. One of the reasons for a higher number of mild to moderate adverse events (NCI-CTC Grade 2 or lower) in Japan may be a difference in the treatment style in Japan and abroad (mainly inpatients and mainly outpatients, respectively). Adverse events with gefitinib tended to occur at an early stage of treatment (for example, incidences of diarrhoea and rash in this study in the first course of the treatment (28 days per course) were 51.5% of Japanese and 39.5% of non-Japanese with diarrhoea, and 68.3% of Japanese and 39.4% of non-Japanese with rash, whereas incidences in the second course were 32.5% in Japanese and 25.4% in non-Japanese with diarrhoea and 10.0% in Japanese and 20.6% in non-Japanese with rash). This may be because that in Japan where more patients were likely to receive inpatient

treatment at an early stage of treatment, more information on adverse events was collected than abroad. Although incidences of adverse events were higher in Japan than abroad, tolerability, which was assessed from duration of gefitinib treatment, ratio of patients required dose reductions, a number of serious adverse events, etc., was good in Japanese. This may be related to good general status of Japanese subjects at the time of enrolment. Considering the effect from those background factors, the applicant considers safety profiles in Japanese and non-Japanese to be not largely different.
The Evaluation Centre judged that the applicant's claim that the difference in medical care environment in Japan and abroad (mainly out-patient and mainly in-patient) was the cause of finding more of the minor adverse events in Japan was a mere speculation, although it is possible. Although the view that tolerance was high in Japanese despite a higher number of adverse events because general status of the Japanese subjects at enrolment was good seemed appraisable, the applicant's claim that safety profiles in Japan and abroad are not largely different on the basis of that is completely irrelevant. The Evaluation Centre believes that it is difficult to compare and study the safety of two groups with such different background factors on physical status of the patients. That is to say, similar to the efficacy assessment, this study cannot be positioned as a bridging study for safety. The Evaluation Centre thinks similarities of safety profiles in Japan and abroad need to be reviewed in full in the new bridging study, which has been planned for implementation in future, taking differences in healthcare environment into account. As a result of full review of the safety profile (types, incidences and severities of adverse events) in Japanese clinical studies, the Evaluation Centre judged that it did not hinder clinical usefulness of gefitinib for treating intractable patients with NSCLC who had previous chemotherapy.

3. Result of document conformity audit by the Organisation for Pharmaceutical Safety and Research and the decision by the Evaluation Centre

Omitted

4. Overall Assessment

Omitted

Evaluation Report (2)

9th May 2002

1. Filed Articles

Omitted

2. Evaluation Details

1) On Physical and Chemical Properties, Specifications and Test Methods

Omitted

2) On Toxicity

Omitted

3) On Absorption, Distribution, Metabolism and Elimination

Omitted

4) On Clinical Studies

(1) On indication of gefitinib

For reasons such as 1) advanced (inoperable) NSCLC after prior treatment with a platinum agent is the only disease for which gefitinib showed efficacy and safety according to the submitted data, 2) outcomes of two large-sale comparative studies abroad will reveal efficacy and safety of gefitinib as the first-line therapy in advanced NSCLC in August 2002 and 3) pathology after surgical removal is clearly different from the above mentioned cancer-bearing state and corneal and other safety of post-operative adjuvant therapy, which is expected to last several years, has not been established, the expert committee members supported the Evaluation Centre's judgement that the filed indication of gefitinib, 'non-small cell lung cancer' should be changed to 'non-small cell lung cancer (inoperative or recurrent)' and 'Precaution for Use concerning Indication' should state '(1) Efficacy and safety of gefitinib in chemotherapy-naïve patients have not be established' and '(2) Efficacy and safety of gefitinib as post-operative adjuvant therapy have not been established'.

(2) On safety of gefitinib

Although no serious adverse events on the cornea have been observed in the clinical studies of gefitinib, the long-term safety is unknown. In addition, a relationship of gefitinib with interstitial pneumonia, which has been observed in Japan and abroad, has not been ruled out. Therefore, the expert committee members supported the Evaluation Centre's judgement that full investigations on those adverse events should continue based on post-marketing surveillance and other studies. Furthermore, the Evaluation Centre presented their view that interstitial pneumonia, from which some deaths have been reported in Japan and aboard, should be warned as an "important adverse drug reaction" in the prescribing information of gefitinib. The applicant replied that they were going to mention it in the prescribing information.

(3) On necessity of post-market special investigation in patients with hepatic dysfunction and renal dysfunction

Clinical experience in Japanese subjects is very small, only about 150 patients in phase I and II studies combined. The expert committee presented an opinion that post-market special investigation is required in order to investigate safety of gefitinib in patients with hepatic and renal dysfunctions. The Evaluation Centre requested the applicant to submit a plan for gefitinib post-market special investigation in those patients.

(4) Raw data check on efficacy

The Evaluation Centre asked the applicant to submit films used for efficacy assessment in the international study (Study 0016, xxxx) and carried out their own investigation. Furthermore, in order to investigate appropriateness of assessment in more detail, the Evaluation Centre requested raw data on several subjects who showed PR in anti-tumour effect according to the submitted application data (case nos. xxxxxxxxxxxxxx), including chronological measurements of tumours and schemata of directions of the measurements of specific lesions when necessary. The following is the judgement on main cases made by the Evaluation Centre.

(i) With case no. xxx, the edge of the right hilar tumour where the measurements are taken was unclear and it was not sure if the measurements were appropriate. The schema the applicant submitted was checked and the Evaluation Centre judged that there is no large difference in the assessment result.

(ii) With case no. xxx, as the measurements of the mediastinal lymph node determined by the Evaluation Centre were largely different from those submitted by the applicant, the applicant was told to review the treatment results on this lesion. The applicant asked the investigator to measure the lesion again and this resulted in very different values from the original. The applicant stated that the anti-tumour effect seen in this case was changed from PR to SD. Based on this, the Evaluation Centre believes that the efficacy rate in non-Japanese subjects in the 500 mg group in the international study was amended to 9.1% (5/55) from 10.9% (6/55), which was the filed value in the Evaluation Report (1).

(iii) With case no. xxxx, according to the schema submitted by the applicant, the measurements were not taken from where they should be taken at left hilar tumour, where the diameter was the biggest, but at the upper border of the tumour. However, the Evaluation Centre judged that would cause no large difference in the efficacy assessment of this case, after studying the effect on the tumour as a whole.

As above (ii) showed, although the efficacy rate in the international study has changed after the raw data check, the Evaluation Centre judged this difference would not affect the judgement on the approval of gefitinib.

3. Overall Assessment

As a result of the above evaluation, the Evaluation Centre judged that the filed article is approvable without changing the filed dosage and administration, providing that the filed indication is amended as below and the following precautions for use concerning indication and the approval conditions are added. The Evaluation Centre believes that this article should be discussed at the 2nd Committee on Drugs.

As this is an approval application of a medicinal product containing a new active ingredient, the re-examination period should be set at 6 years.
The Evaluation Centre sees gefitinib drug substance and formulated products to correspond to a powerful drug.

[Indication] Non-small cell lung cancer (inoperative or recurrent)

<Precaution for use concerning indication>

(1) Efficacy and safety of gefitinib in chemotherapy naïve patients have not been established.

(2) Efficacy and safety of gefitinib as a post-operative adjuvant therapy have not been established.

[Approval Conditions]

Implement a randomised comparative study of a sufficient sample size in Japan in order to establish efficacy and safety of gefitinib in non-small cell cancer (inoperative or recurrent patients) further.

24th May 2002

Evaluation Division, Pharmaceutical and Food Safety Bureau

EVALUATION REPORT (2)

Omitted

NIHS 2781

28th May 2002

EVALUATION REPORT (3)

Omitted

28th June 2002

Evaluation Division, Pharmaceutical and Food Safety Bureau

EVALUATION REPORT (4)

Omitted