25 July 2013
EMA/491185/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Giotrif

International non-proprietary name: afatinib

Procedure No. EMEA/H/C/002280

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Boehringer Ingelheim International GmbH submitted on 28 August 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Giotrif, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 January 2010.

The applicant applied for the following indication:

GIOTRIF is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s).

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that afatinib was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision on the granting of a class waiver (CW-1-2011).

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance afatinib contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Licensing status

Giotrif has been given a Marketing Authorisation in the USA on 12 July 2013.

1.2. Manufacturers

Manufacturer responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
55216 Ingelheim am Rhein
GERMANY

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Arantxa Sancho-Lopez

- The application was received by the EMA on 28 August 2012.
- The procedure started on 19 September 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 December 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 December 2012.
- PRAC RMP Advice and assessment overview adopted by the PRAC on 10 January 2013
- During the meeting on 17 January 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 January 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 26 March 2013.
- The summary report of the inspection carried out at the following site Boehringer Ingelheim Pharma GmbH & Co. KG was issued on 18 April 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 April 2013.
- PRAC RMP Advice and assessment overview adopted by the PRAC on 16 May 2013
- During the CHMP meeting on 30 May 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 June 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 18 July 2013.
- During a SAG-Oncology meeting on 11 July 2013, experts were convened to address questions raised by the CHMP.
- During the meeting on 25 July 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Giotrif.

2. Scientific discussion

2.1. Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide with an estimated 1 million newly diagnosed cases and 880 000 deaths each year. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases. Progress has been made in the clinical management of early stage NSCLC by establishing comprehensive, multi-modality treatment regimens; however, the prognosis for advanced disease has not improved substantially. With an overall 5-year survival rate of 9% to 13%, the treatment of NSCLC remains a highly unmet medical need.

According to the European Society for Medical Oncology (ESMO) guidelines, first-line treatment with a tyrosine kinase inhibitor (TKI), erlotinib or gefitinib, should be prescribed to patients with tumours bearing an activating (sensitising) epidermal growth factor receptor (EGFR) mutation because of significantly higher response rate (RR), longer progression free survival (PFS), and better quality of life (QoL) when compared with first-line chemotherapy. Platinum-based combination chemotherapy prolongs survival, improves QoL, and controls symptoms. This platinum chemotherapy is the backbone treatment for patients not candidates to be treated with TKIs. Patients with NSCLC harbouring an anaplastic lymphoma kinase (ALK) rearrangement should be considered for crizotinib.

The frequency of somatic EGFR mutations was reported to be about 10% in patients with NSCLC from the US, Europe or Australia and up to 30% in patients with NSCLC from Japan and Taiwan. The 2 most common mutations account for about 90% of EGFR mutations observed in NSCLC specimens. These are an in-frame deletion in exon 19, leading to loss of amino acids E746 to A750 (Del 19), and a point mutation in exon 21, resulting in an amino acid substitution (L858R). Despite the initial clinical response to reversible EGFR TKIs, patients almost invariably develop resistance to these inhibitors and their tumours relapse.

Giotrif (afatinib) is an irreversible inhibitor of the ErbB family of receptor tyrosine kinases (TKI). It covalently binds to and blocks signalling from all homo- and heterodimers formed by the ErbB family members EGFR (ErbB1), HER 2 (ErbB2), ErbB3 and ErbB4. Aberrant ErbB signalling triggered by receptor mutations, and/or amplification, and/or receptor ligand overexpression contributes to the malignant phenotype. The recommended dose is 40 mg once daily.

The claimed therapeutic indication is:

GIOTRIF is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGFR) mutation(s).

The approved indication is:

Giotrif as monotherapy is indicated for the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).

The Applicant has received Scientific Advice by the CHMP on clinical issues in January 2007, December 2007 and December 2008. The CHMP gave advice in relation to the pivotal trial LUX Lung 3, and the supportive trial LUX lung 1.

2.2. Quality aspects

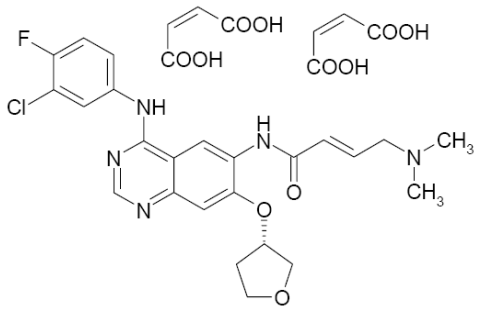
2.2.1. Introduction

The finished product is presented as film-coated tablets containing 20 mg, 30 mg, 40 mg or 50 mg of afatinib (INN) (as dimaleate) as active substance. The other ingredients for the core-tablets are: lactose monohydrate, cellulose microcrystalline, silica colloidal anhydrous, crospovidone and magnesium stearate. The film-coating consists of hypromellose, macrogol 400, titanium dioxide, indigo carmine (except for the 20 mg film-coated tablets) and polysorbate 80.

The film-coated tablets are marketed in perforated blister card consisting of a PVC/PVDC forming sheet and an aluminium lidding foil as described in section 6.5 of the SmPC.

2.2.2. Active substance

The chemical name of afatinib dimaleate is (2E)-*N*-[4-(3-chloro-4-fluoroanilino)-7-{[(3S)-oxolan-3-yl]oxy}quinoxazolin-6-yl]-4-(dimethylamino)but-2-enamide and has the following structure:



Afatinib dimaleate is a white to brownish yellow powder. It exists as a salt (dimaleate) and is highly soluble in water. The highest solubility in organic solvents is observed in DMSO then in methanol. For most of the other organic solvents solubility is less than 1 mg/ml. It is highly soluble in aqueous buffer media with a pH of less than 6. The solubility of afatinib dimaleate is pH-dependent. It was noted that the free base has two ionizable groups due to presence of a dimethylamine and a quinazoline moiety.

Afatinib dimaleate is obtained as the crystalline anhydrous form A. Afatinib contains a chiral center within the furanoyl moiety in the 3S configuration. Furthermore, the 2-buteneamide sub-structure allows for E/Z isomerism. The active substance is manufactured and exists as the E-isomer. The enantiomeric purity of this active substance is controlled routinely by HPLC.
The chemical structure elucidation has been performed by infrared spectroscopy, ultraviolet spectroscopy, ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, X-ray powder diffraction, and mass spectrometry. The data from ^{1}H NMR spectroscopy clearly prove the E configuration of the 2-buteneamide moiety. The results of the elemental analysis are consistent with the proposed molecular formula ($C_{32}H_{33}ClFN_5O_{11}$).

Manufacture

The manufacturing process consists of six main synthetic steps including formation of the dimaleate salt and its crystallisation using well defined starting materials with acceptable specifications.

The designation of the starting materials for the synthesis of the active substance has been justified with respect to their impurity profiles, their potential for a carry-over into the final active substance, their structural complexity and with respect to their proximity to the final intermediate and the drug substance, respectively.

Information provided describes adequately the manufacturing including reactions conditions, quantities of raw materials and yields.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origins and were characterised. The carry-over of impurities, reagents, solvents and catalysts from the starting material into the final active substance has been discussed. Discussion about the impurities confirmed that there is no identified genotoxic risk.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediates, starting materials and reagents have been presented.

The S configuration of afatinib is derived from the stereochemistry of one of the starting materials. The other proposed starting materials contain no chiral centres or olefinic double bonds that could result in stereoisomers. The correct absolute configuration S of the chiral centre for afatinib has been confirmed by the analysis of enantiomeric purity (polarimetry and chiral gas chromatography). Based on the synthetic steps, it has been justified and confirmed that a racemisation or inversion cannot occur.

Regarding polymorphism, Forms A and B are the only under ambient conditions stable forms. Anhydrous form A and form B, do not directly transform into each other, both forms represent two totally independent crystalline modifications. Form A and form B are hygroscopic. Due to its more favourable physicochemical properties form A has been selected for development. Very similar and high solubility of forms A and B was observed under physiological conditions. Differentiation between the different forms is possible by means of differential scanning calorimetry (DSC), microscopy or X-ray powder diffraction.

The active substance is packaged in a closed plastic (low density polyethylene) bag, placed in a moisture-protecting aluminium laminated pouch. This pouch is heat-sealed and finally packaged into a labelled fibre drum prior to storage and shipping. Specifications and description of the methods for polyethylene film and for the seal bags from aluminium laminated have been providedThe materials in contact with the active substance comply with the EC directive 2002/72/EC and EC 10/2011.

Specification

The active substance specification includes tests for: appearance (visual), identification (IR, UV, and HPLC), impurities (HPLC), enantiomeric purity (HPLC), nickel content (atomic absorption

spectroscopy), residual solvents (GC), water (Karl-Fischer), sulphated ash (Ph.Eur.), afatinib assay (HPLC) and maleic acid assay (titration).

A detailed description for all analytical methods was provided. Full method validation data was also provided for the in-house analytical methods in accordance with the relevant ICH Guidelines. The analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data of forty seven batches used in clinical, toxicological and stability studies of the active substance are provided. The results are within the specification and consistent from batch to batch.

Stability

Stability data on three commercial-scale batches of the active substance from the proposed commercial manufacturer and stored in the intended commercial packaging for 24 months under long-term conditions at 25°C/60% RH and 6 months under accelerated conditions at 40°C/75% RH.

The following parameters were tested: appearance (visual), impurities (HPLC), enantiomeric purity (HPLC), water (Karl-Fisher) and afatinib assay (HPLC).

The stability of afatinib in solution as well as in the solid state has been investigated under stress conditions (different pH, oxidative, elevated temperature in dry and humid conditions) in order to identify potential major degradation pathways and to assess the overall chemical stability of this new molecular entity. Degradation was seen under weak acidic to neutral media and oxidation conditions.

Photostability study under ICH Q1B conditions has been performed. Results showed that irradiation of the active substance in the solid state stimulates isomerisation reactions.

The stability results indicate that the active substance is sufficiently stable at controlled room temperature and protected from light and moisture. The results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Pharmaceutical development

The primary goal was to develop the finished product as a solid oral dosage form, combined with the clinical requirement for a reliable drug release as well as patient acceptability (easy-to-swallow dosage form that disintegrates only in the gastric environment) and safe handling of the drug by caregivers. Based on those requirements and the physicochemical properties of the active substances, a film-coated tablet formulation was developed.

As already mentioned the active substance is soluble in water and aqueous media throughout the physiological pH range from pH 1-7.5. In the development and manufacture of the finished product, the anhydrous form (Form A) has been selected. Form A is the preferred form over form

B since it can be better processed and has better physical stability especially with regard to hygroscopicity.

The rationale for the choice of excipients is sufficiently detailed. The excipients selected are commonly used in oral commercial pharmaceutical dosage forms. All the excipients are compendial except for the colorant indigo carmine which complies with EC directive 95/45 as amended.

Compatibility between the active substance and the excipients was extensively studied. The drug product stability data demonstrate compatibility between the active substance and the chosen excipients including the colour pigment and support their use in the intended commercial formulation.

The formulation development from the early trial formulations (TF1) to the final formulations (FF) have been described. The final composition was adjusted and optimised for the excipients during the formulation development to reach the best quality for the final film-coated tablets. Downsizing of the tablet dimensions by optimising the drug load of the tablets was made to improve patient acceptability.

The development of the dissolution method has been discussed and the method well described. The dissolution profiles of different dosage strengths have been tested at different pH values. The solubility of afatinib dimaleate is high throughout the physiological pH range from pH 1 to 7.5. Media in this range provided sufficient solubility of the drug substance for sink conditions for the intended commercial dosage strengths 20 mg, 30 mg, 40 mg and 50 mg. The results demonstrate comparable dissolution profiles independent of the dosage strength. All four dosage strengths of the final formulation are deemed equivalent. The discriminatory power of the dissolution method has been demonstrated.

The final formulation was identical to the clinical trial formulation except for the addition of the colorant to the non-functional film-coat of the tablets. The manufacturing process development has been thoroughly discussed, including the evaluation and the optimisation of the main process steps including dry granulation of the active substance, dry blending of the active substance (dry granulate) with the excipients, subsequent compression into tablets and finally film-coating of the tablet cores, including final drying. The tablet cores of the final formulation for all strengths are manufactured from a common blend. Thus, the different dose strengths are proportionally similar to each other. The primary packaging is a blister/pouch packaging. The blister card consists of a polymer bottom foil and a lidding foil. The bottom foil is a laminate double layer foil, with an outer polyvinyl chloride (PVC) film and an inner polyvinylidene chloride (PVDC) film whereas the lidding foil is an aluminium foil. An additional pouch is used as a secondary packing system containing a molecular sieve sachet as desiccant. This pouch consists of a three-ply laminated aluminium foil, with an outer polyester (PE) film, an aluminium foil, and an inner polyethylene (PET) film. The materials comply with the Ph.Eur and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

The only ingredient from animal origin is lactose. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those use to collect milk for human consumption and the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk for Transmitting Animal Spongiform Encephalopathy Via Human and veterinary medicinal products.

Manufacture of the product

The manufacturing process consists of five main steps: dry granulation, blending, tableting, film-coating and packaging. At the end of the process, the tablets are dried to reduce residual moisture so that long-term stability of the drug product is improved. The process is considered to be a standard manufacturing process.

Flow diagrams of the manufacturing process, including in-process controls, are provided in the dossier. A brief narrative description of each manufacturing step is also provided as well as information related to the equipment used.

Major steps of the manufacturing process have been validated by a number of studies on three consecutive full-scale validation batches for each of the four different strengths. The manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

The in-process controls applied are adequate for this pharmaceutical form.

Product specification

The finished product release and end of shelf-life specifications include appropriate tests for this solid oral dosage form: appearance (visual), identification (UV and HPLC), water content (Karl-Fisher), assay (HPLC), uniformity of dosage (Ph.Eur.), impurities (HPLC), dissolution (HPLC), microbiological quality (Ph.Eur.).

Batch analysis data of forty seven batches used in clinical, toxicological and stability studies of the finished product for each strength are provided. The results confirm the consistency of the process and its ability to manufacture a product complying with the product specification.

Stability of the product

Stability data of three production-scale batches of the highest and the lowest dosestrength for the finished product stored under long term conditions for 24 months at 25°C/60 % RH and for 6 months under accelerated conditions at 40°C/75 % RH according to ICH guidelines were provided. The stability study were conducted in accordance with the ICH guideline Q1A(R2) and the ICH Q1D "Bracketing and Matrixing" using a reduced stability design for the intermediate dosage strengths of 30 mg and 40 mg. The bracketing was acceptable since the film-coated

tablets of the four strengths are packaged in identical container closure. The only slightly difference is the colorant in the film-coat. The batches of the medicinal product are identical to those intended for marketing and were packed in the proposed marketed blister pack.

Stress stability studies were performed on one fully representative batch each of film-coated tablets 20 mg and 50 mg to assess the influence of heat and humidity. In addition, two representative batches each of the same strengths were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.
Samples were tested for: appearance (visual), water content (Karl-Fisher), dissolution (HPLC), resistance to crushing, degradation, assay (HPLC), and microbiological purity (Ph.Eur.). The analytical procedures are stability indicating.

All results meet the proposed shelf-life acceptance criteria. Stress studies showed that the finished product is sensitive to excessive heat and humidity, and is sensitive to light exposure therefore needs to be kept in its primary packaging material. The results remained within the specification during the bulk studies.

Based on the available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The potential impurities, by products of the synthesis and degradation products, have been discussed in detail and do not raise any safety concern. The goal of the pharmaceutical development was to obtain film-coated tablets with a good acceptability profile. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the data provided the quality of this medicinal product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3. Non-clinical aspects

2.3.1. Introduction

All pivotal safety pharmacology and toxicology studies were carried out in compliance with GLP regulations. All other studies are considered also to be of sufficient quality.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The in vitro potency and selectivity of afatinib (BIBW 2992) has been determined in enzymatic assays using human recombinant protein kinase domains. Afatinib proved to be a kinase inhibitor with an IC50 of 0.5 nM on EGFR, 14 nM on HER2 and 1 nM on ErbB4.

To assess selectivity, the inhibitory activity of afatinib on related tyrosine kinases was examined. Enzymes from class II, IV and VII receptor tyrosine kinases, represented by BIRK, VEGFR-2 and HGFR, as well as the non-receptor type tyrosine kinases c-src, Lck, Lyn were used for the analysis (see Table 1).

Table 1. Potency and selectivity of afatinib and other small molecule EGFR tyrosine kinase inhibitors in molecular kinase assays.

The numbers in the table are IC_{50} values [nM].

Kinase	afatinib	Gefitinib	Canertinib
EGFR	0.5	1	0.3
HER2	14	1830	30
ErbB4	1	323	1
BIRK	> 100000	> 100000	> 100000
c-src	> 4000	> 100000	1480
Lck	1718	ND	ND
Lyn	1832	ND	ND
VEGFR-2/KDR	> 100000	> 100000	24900
HGFR	13000	> 20000	> 100000

* ND: not determined

Similarly, a set of 27 serine/threonine kinases comprising MKK-1, ERK2, JNK/SAPK1c, SAPK2α/p38α, SAPK2βp38β, SAPK3/p38γ, SAPK4/p38δ, PKBα/AKT, SGL, S6K1, GSK3β, ROCK II, AMPK, CHK1, MAPKAP-K1α, MAPKAP-K2, MSK-1, PRAK, PKA PKCα, PDK1, CK II, PhosK, CSK, CDK2/cyclinA, CK-I and DYRK1α was tested and was essentially unaffected by the presence of 10 µM afatinib in the assay.

In short-term receptor phosphorylation studies, it has been confirmed that afatinib attains the inhibition at low nanomolar concentrations in serum starved cells with: EC50 = 13 nM in A431 EGFR cells and EC50 = 35 nM in BT-474 HER2 cells. In the same way afatinib inhibits proliferation of NCI-N87 and BT-474 cells in a 72-hour cell growth assay with EC50= 4 and EC50=12 nM, respectively.

The pharmacological inhibition of receptor activation by reversible EGFR inhibitors was shown to be more short-lived, with cells recovering after an 8 hour washout period, as compared to cells treated with afatinib or other irreversible inhibitors. After treatment with irreversible inhibitors cells recovered within 48 h. These results support the hypothesis that irreversible binding to the kinase is associated with a more long-lasting inhibitory effect.

The possibility that afatinib might be active on T790M containing EGFR mutants known to be resistant to erlotinib and gefitinib was initially supported in molecular kinase assays. Further in vitro experiments with afatinib using NSCLC cell lines with activating EGFR mutations, including those resistant to first generation inhibitors, such as T790M or exon 20 insertions showed that afatinib is able to inhibit receptor activation and cell proliferation (see Tables 2 and 3).

Table 2. Inhibitory activity of afatinib and other kinase inhibitors in EGF induced EGFR phosphorylation assays using NSCLC cell lines with different EGFR mutant isoforms

Compound	H1666 $EGFR^{WT}$ EC_{50} [nM]	H3255 $EGFR^{L858R}$ EC_{50} [nM]	NCI-H1975 $EGFR^{L858R/T790M}$ EC_{50} [nM]
afatinib	7	6	93
Canertinib	127	5	79
Erlotinib	87	52	> 4000
Gefitinib	72	11	> 4000

Table 3. Inhibitory activity of afatinib and other kinase inhibitors in anchorage-independent proliferation assays using NSCLC cell lines with different EGFR mutant isoforms

Compound	**NCI-H1666 $EGFR^{WT}$ EC_{50} [nM]**	**H3255 $EGFR^{L858R}$ EC_{50} [nM]**	**NCI-H1975 $EGFR^{L858R/T790M}$ EC_{50} [nM]**
afatinib	60	0.7	99
Canertinib	198	1	101
Erlotinib	110	40	> 4000
Gefitinib	157	5	> 4000

Li D. et al Oncogene 2008;27(34):4702-4711

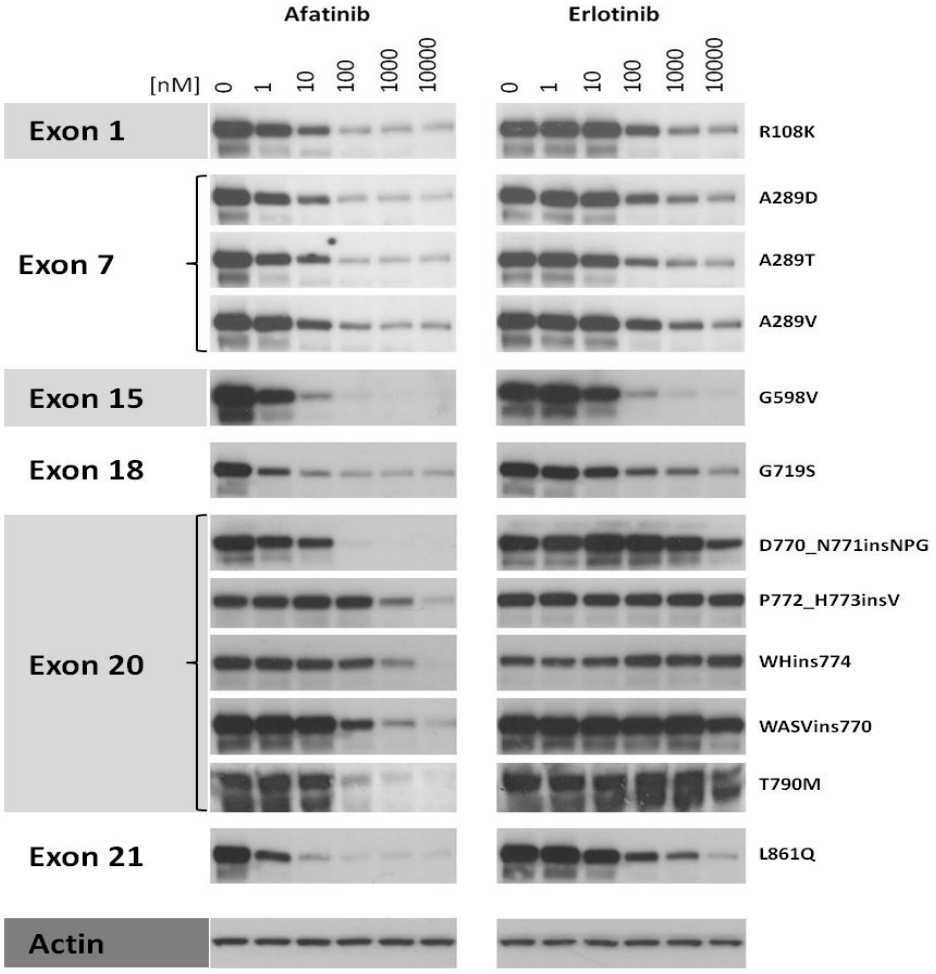
Results when T790M mutants were introduced into an exon 19 deletion mutant background in B-lymphoid mouse Ba/F3 cells are shown in Table 4.

Table 4: Afatinib inhibits survival of Ba/F3 cells ectopically expressing various EGFR Mutants.

	Afatinib EC_{50} (nM)	**Erlotinib EC_{50} (nM)**
L858R	4	16
L858R + T790M	119	>10 000
E746_A750del5	0.9	5
E746_A750del5 + T790M	64	>10 000
S752_I759del8	0.2	33
S752_I759del8 + T790M	103	>10 000
L747_A750del4insP	1	5
L747_A750del4insP + T790M	60	>10 000
L747_P753del7insS	2	0.3
L747_P753del7insS + T790M	49	>10 000
E746_S752del7insV	0.2	25
E746_S752del7insV + T790M	102	>10 000
vIII (variant III deletion)	0.9	144

Additional cellular studies were conducted to assess the inhibitory potency of afatinib and erlotinib on autophosphorylation of several uncommon EGFR mutants expressed in transfected mouse NIH/3T3 fibroblasts (parental NIH/3T3 cells do not express ErbB receptors). These included variants harbouring point mutations in exons 18, 20 and 21 encoding the kinase domain of EGFR (G719S, T790M, L861Q), exon 20 insertions (WASVins770, D770_N771insNPG, P772_H773insV, WHins774) and activating missense mutations in exons 1, 7 and 15 encoding the extracellular domain of EGFR (R108K, A289D, A289T, A289V, G598V) (see Figure 1).

Figure 1. Effect of afatinib and erlotinib treatment on EGFR-Y1068 phosphorylation in NIH/3T3 cells ectopically expressing EGFR mutants



The in vivo activity of afatinib has been assessed in a variety of tumour xenograft models in immunodeficient nude mice.

The NCI H1975 NSCLC cell line carries an activating mutation in the EGFR (L858R) as well as the T790M mutation reported to confer resistance to gefitinib and erlotinib. Growth of established NCI-H1975 tumours in nude mice was fully inhibited by treatment with afatinib. In the NCI-H1781 tumour cell line harbouring activating mutations within the HER2 kinase domain (HER2G776insV G/C) afatinib was shown to have efficacy in this model. Transgenic mice expressing either $HER2^{YVMA}$ or $EGFR^{L858R/T790M}$ in the lung develop massive lung carcinomas within a few weeks after birth and treatment of these tumour-bearing mice with afatinib resulted in partial tumour regressions.

In the MDA-MB-453 breast carcinoma model characterised by HER2 gene amplification and sensitivity to trastuzumab, treatment with afatinib resulted in complete suppression of tumour growth (T/C = 3 %). In the HER2-overexpressing, trastuzumab-resistant breast cancer model SUM 190, afatinib strongly inhibited tumour growth with a T/C value of 11 %, indicating a role for EGFR signaling in trastuzumab resistance. Treatment of mice carrying estrogen dependent MCF-7 xenografts resulted in moderate inhibition of tumour growth (T/C = 48%; [02-04]). In a model of triple-negative breast cancer (SUM 149), afatinib was highly efficacious (T/C = 5%).

In mice carrying EGFR-overexpressing A431 epidermoid carcinoma cells, afatinib was effective (T/C = 2%) and induced tumour regressions. In the ovarian cancer model SKOV 3 (HER2 gene

amplification) as well as the HER2-overexpressing NCI N87 gastric cancer model, treatment with afatinib achieved T/C values of 3 % and 0-4 %, respectively.

A comparison of the anti-tumour efficacies and systemic exposure in xenografted mice treated with various doses of afatinib shows that the necessary maximum plasma concentration in nude mice to reach full antitumour activity (defined as T/C < 10 %) was 80-285 nM and the corresponding AUC(0-24h) was 1.1-3.2 µM·h (see Table 5).

Table 5. Pharmacodynamic and pharmacokinetic correlation analysis for afatinib:
Data are based on the tumour xenograft experiments described above. Afatinib was given orally as a base.

Model	Daily Dose [mg/kg]	T/C [%]	C(max) [nM]	AUC(0-24h) [nM.h]
A431	30	2	587	4007
A431	20	2	285	3198
A431	10	80	87	382
A431	3	100	8	21
MDA-MB-453	20	3	83	972
SKOV-3	20	3	236	2156
SKOV-3	15	13	83	589
NCI-N87	20	4	80	1075
NCI-N87	10	64	66	445

Secondary pharmacodynamic studies

In a battery of binding assays comprising 50 non-peptide receptors, peptide receptors, nuclear receptors, ion channels and amine transporters, afatinib inhibited two receptors by more than 50 % when tested at 5µM; binding of cimetidine to H2 receptors and pirenzepine to M1 receptors which were inhibited by 68 % and 78 %, respectively.

In vivo studies revealed different degrees of effects of afatinib on blood pressure, heart rate, contractility, kidney and liver as well as on gastric emptying, secretion and motility: A small (~10%) but significant increase in systolic blood pressure at 100 mg/kg in rats with a non-significant trend at lower doses (10 and 30 mg/kg). The effect was persistent indicating a long duration of action. Heart rate was slightly and transiently increased at the highest dose. No effects were seen on body temperature, respiration rate, tidal volume and motility. The contractility (LVdP/dt max) was decreased in minipigs after iv administration of afatinib at 6.65 (trend) and 20 mg/kg ($p<0.0001$) and an exposure of ~6 times and ~35 times the C_{maxss} of ~0.2 µM achieved in humans after 50mg/day, respectively (1200 nmol/L and 7110 nmol/L). However, no effects were seen on blood pressure and heart rate or the ECG intervals (QT, PR and QRS interval). Single oral administration of afatinib to rats at 30, 100 and 300 mg/kg, increased urinary glucose excretion after 4h up to 24h, and led to enhanced serum glucose levels at a dose of 300 mg/kg. At this dose increases in serum and urine enzymes were also observed, suggesting liver and renal toxicity. Afatinib reduced gastric emptying in rats at doses of 100 and 300 mg/kg (196% and 430%, respectively). Intraduodenally administration of 30-300 mg/kg BW reduced the gastric secretion parameters juice volume and acid output dose-dependently (significantly different from control only at 300 mg/kg), responses that might indicate effects of afatinib via the H2 receptors at high dose levels.

Safety pharmacology programme

Safety pharmacology studies conducted with afatinib included an assessment of effects of the product on CNS and respiratory system in rats following oral administration, as well as on cardiovascular system in minipigs following repeat oral administration. Also, it was evaluated the in vitro potential of afatinib to inhibit hERG current.

Cardiovascular: In vitro afatinib was shown to have a low potential to inhibit HERG, with an IC50 of 2.4 µM and did not affect the action potential duration (APD) in Isolated Guinea pig papillary muscle at concentrations up to 10 µM. A slight, timedependent, reversible increase of the heart rate that correlated with a shortening of the QT interval was observed in mini pigs at doses of 2.45 and 6 mg/kg (Cmax 35-85 and 70-185 nmol/L, respectively) without any effects on ECG morphology.

Respiratory: No significant effects on respiration rate, tidal volume or minute volume were seen in male or female rats at doses up to 18 mg/kg, except for decrease in minute volume in male rats at 18 mg base/kg, 240 minutes post-dose. This effect is not considered to be relevant for the clinical situation.

CNS: Effects on the nervous system was investigated in rats where no significant changes were seen in the behaviour, physiological state, spontaneous locomotor activity or body temperature after doses up to 18 mg/kg.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies with afatinib have been submitted.

2.3.3. Pharmacokinetics

The pharmacokinetics and drug metabolism of afatinib were studied in male and female mice, male and female rats, female rabbits and male and female minipigs, including excretion balance and biliary excretion as well as investigations on metabolite profiles in plasma, urine, faeces and bile. Afatinib was formulated as a suspension / solution in all animal studies. Aqueous solutions of afatinib were used as oral and intravenous formulations.

Absorption

The absorption in vivo of afatinib was evaluated in rats and minipigs following single oral and intravenous administration and in rabbits following single oral administration. The pharmacokinetics parameters resulted in these studies are given in Table 6.

Table 6. Summary of pharmacokinetics parameters for afatinib from studies in rats, rabbits and minipigs (p: plasma; b: blood)

Species	N	Dose mg/kg	Route	Anal.	Cmax nmol/L	Tmax h	AUC nmol*h/L	t½ h	Vd L/Kg	Clt mL/min *Kg	F %
Rats, Wistar	4 M	8	p.o.	[^{14}C]afatinib MA2 (p)	397	4	2600	4.54	43.6	108	44.5
				[^{14}C]afatinib MA2 (b)	1360	7	101000	62.6	14.2	2.78	-
	4 M	4	i.v.	[^{14}C]afatinib MA2 (p)	1620	-	2920	5.22	16.2	55.3	-
				[^{14}C]afatinib MA2 (b)	3750	-	222000	60.2	3.09	0.624	-

Rabbits, Himalayan	3 F	1.95	p.o.	[^{14}C]afatinib MA2 (p)	34	1	178	2.6	110	467	ND
				[^{14}C]afatinib MA2 (b)	126	1	4060	142	219	17.5	ND
Minipigs Göttingen	2 M/2 F	2	p.o.	afatinib MA2	29.1	4	214	10.8	NA	NA	11.2
	2 M/2 F	2	i.v.	afatinib MA2	1190	0.083	2000	13.8	12.4	35.4	NA

Distribution

Tissue distribution

The distribution of afatinib in the tissues was studied in albino and pigmented male rats by whole body autoradiography after single intravenous or oral dosing of to 4 mg/kg or of 8 mg/kg [^{14}C]afatinib, in male albino rats by tissue dissection after repeated oral dosing of 3 mg/kg [^{14}C]afatinib and in minipigs also by tissue dissection after a single oral dose of 2.46 mg/kg (5.06 µmol/kg) [^{14}C]afatinib.

The results indicated that afatinib was rapidly and well distributed from blood into most of the tissues except for the central nervous system (CNS) since the blood-brain barrier was crossed only to a very small extent.

In rats, the distribution of afatinib after oral administration was qualitatively similar to that after intravenous administration but on a lower level. Also it was similar between pigmented and albino rats. However, in pigmented rats, the concentration of afatinib in the retina of the eye was very high and kept constant over the investigation period.

In Table 7 is shown the tissue distribution of afatinib after repeat oral administration of 3 mg/kg of [^{14}C]afatinib for 13 days to male rats.

Table 7. Tissue distribution of afatinib in rats.

concentration of radioactivity sampling day:	[nmol/kg tissue]**					
	24 h	144 h	192 h	240 h	312 h	accumulation factor*
liver	288	2408	2325	3272	4095	14.2
skin	39	523	504	815	932	23.8
plasma	2	10	14	16	19	7.9
blood	105	992	829	1222	1698	16.1
bone marrow	146	922	813	1126	1733	11.9
brain	8	39	37	51	60	6.7
fat	31	150	123	183	212	7.0
heart	80	661	595	881	1167	14.6
lungs	165	1068	1029	1463	1792	10.9
kidneys	477	3293	3210	4527	5659	11.9
testes	31	259	202	329	412	13.4
muscle	47	350	346	500	698	14.5

*: concentration at 312 h (day 12) divided by concentration at 24 h (day 2). **: calculated from ng-eq/g tissue given in the report using a molecular mass of 485.95 g/mol

In minipigs, at 168 h after oral administration of [^{14}C]afatinib MA2, afatinib was recovered principally in the livers, spleen and testis in both males and females. Similar to findings in the rat, afatinib was found in the retina of the minipigs at 168 h after dosing.

Protein binding and distribution in blood cells.
The mean plasma protein binding of afatinib, which was not saturable, was 91.8% in rabbits (Himalayan), 92.6% in rat (Wistar), 92.9% in minipig (Göttingen), 94.3% in mouse (NMRI), 94.6% in mouse (CD-1), 92.7% in transgenic CByB6F1rasH2 mice, 94.9% in non-transgenic CByB6F1rasH2 mice and 95% in human, over a concentration range of 0.05-0.5 µM.

In vitro, binding of afatinib MA2 to isolated human serum albumin (45 g/L) was moderate (79.6%) and binding to human alpha-1-acid-glycoprotein (AGP) increased with the protein concentration from 11.6 % (0.1 g/L AGP) to 90.6 % (10 g/L AGP).

Distribution of afatinib between blood cells and plasma (CC/CP) was evaluated *in vitro* by incubation of [^{14}C]afatinib in blood of rats, minipigs and human. Afatinib was distributed predominantly into blood cells, as indicated by a CC/CP higher than 1. A species difference in the extent of this distribution was observe, with CC/CP between 4.95 and 6.38 in rat, 5.07 and 2.98 in minipigs or 2.21 and 1.02 in human blood, (CC/CP values 2 min and 3 hours after spiking, respectively).

In other ADME studies, for all investigated species, a time-dependent increase of distribution of [^{14}C]afatinib into blood cells has been found. In rats, the mean CC/CP increased from 7.6 at time point 0.5 h after dosing to 193 at 24 h. In minipigs, CC/CP increased from 5 at time point 6 h after dosing to 28 at 168 h. For rabbits, the respective data are 2.5 at 1 h increasing to 7.4 at 96 h.

Covalent binding to protein
X-ray structure analysis of EGFR in complex with afatinib has revealed that afatinib exhibits the structure of anα,β-unsaturated ketone and covalently binds to Cys^{797} in EGFR.

This covalent binding of [14C]afatinib resulted in the formation of covalent adducts to protein, like haemoglobin, as has been demonstrated *in vitro* in plasma and whole blood of rats, as well *in vivo* studies in plasma protein of rats, minipigs, rabbits, mice and human.

The covalently bound protein adducts are formed by Michael acceptors because of theα,β-unsaturated ketone structural moiety. Since the adduct formation via Michael addition is a chemical equilibrium, covalent protein adducts can decay under release of the α,β-unsaturated ketone-structured parent compound, as has been demonstrated in incubation experiments at 37°C using an aqueous solution of adduct of [^{14}C]afatinib to human serum albumin.

Placenta transfer studies
In pregnant rats was studied the tissue distribution and elimination kinetics of [^{14}C]afatinib after oral administration, showing that the absorption, distribution and elimination kinetics was independent of stage of gestation. Afatinib was widely distributed in tissues and organs, except the brain and, in placenta, the concentration was approx. 2-fold higher than blood, also independent of the gestation stage.
No relevant levels of [^{14}C]afatinib were found in embryos and foetuses except very low concentrations in foetal liver.

Metabolism

In vivo metabolism was studied in rats, mice, minipigs, rabbits and healthy human subjects after oral administration of [^{14}C]afatinib and in bile and urine samples of rats after i.v. dosing.

Metabolism as excretion pathway was of subordinate importance in all species when compared to the excretion of the unchanged parent compound that accounted for > 50%, > 60 %, > 72%, > 87% and > 88% in the rat, mouse, minipig, rabbit and human, respectively. Likewise, the total number of metabolites (ten) that were observed in the excreta of all species at amounts > 1% of the administered dose was relatively small. There were only minor differences in the metabolite pattern between the investigated species, excreta metabolism pattern, and plasma metabolism pattern.

Based on in vitro and in vivo studies, the metabolism of afatinib can be subdivided into three reactions: conjugate formation via Michael addition, enzymatic phase I metabolism (oxidation: *N*-oxide formation (dimethylamino moiety) by FMO3, oxidative *N*-demethylation, by CYP3A4, oxidative *O*-dealkylation (tetrahydrofuran ring), oxidative side-chain *N*-dealkylation (dimethylamino moiety) followed by oxidation, side-chain (amide bond) cleavage and oxidative defluorination) and conjugation of phase I metabolites (*O*-glucuronidation after oxidative *O*-dealkylation of the tetrahydrofuran ring and formation of the carbamoyl glucuronide subsequent to oxidative *N*-demethylation).

Excretion

The excretion of afatinib has been evaluated in mice, rats, rabbits and minipigs using radio-labelled [^{14}C]BIBW. The results of these studies are given in Table 8.

Table 8. Species comparison of excretion data of [^{14}C]afatinib after single oral or intravenous administration, and after repeat oral dosing for 13 days.

Species / N / Sex	Dose (mg/kg)	Route	Anal.	Urine (% dose)	Faeces (% dose)	Bile (% dose)	Recovery (% dose)	Time (h)
CD-1 mice / 10 / M-F	8.5	p.o.	[^{14}C]afatinib MA2	1.2	95.4	10.1	96.8	96[1]
Albino Wistar rats / 4 / M	8	p.o.	[^{14}C]afatinib MA2	2.7	93.6	14.6	96.5	96[2]
Albino Wistar rats / 4 / M	4	i.v.	[^{14}C]afatinib MA2	5.5	90.8	28.3	96.7	96[2]
Wistar rats / 4 / M	3	p.o.	[^{14}C]afatinib MA2	0.7	85.0	11.7	91.3	312
Himalayan rabbits / 3 / F	1.95	p.o	[^{14}C]afatinib MA2	0.8	95.4	22.8[3]	96.8	96[4]
Göttingen minipigs / 4 / M-F	2.46	p.o	[^{14}C]afatinib MA2	2.2	92.9	ND[*]	95.7	168

[1]: 6 h for biliary excretion; [2]: 4 h for biliary excretion and 192 h for urine; [3]: following intraduodenal administration; [4]: 168 h for faeces excretion; [5]: 192 h for urine excretion; [*]: in minipig only spot samples of bile were taken that provide no meaningful data for excretion balance

Excretion in milk of the lactating rats

Female Wistar were administered a single oral dose of 4 mg/kg [^{14}C]afatinib on Day 11 of lactation. The concentrations of total radioactivity in plasma and in the milk of the dams were followed up to 48 h post administration.

The average afatinib concentrations in milk at time points 1 h and 6 h post dose (1220 and 2130 nmol/L, respectively) were approximately 80 and 150-fold above the respective concentration in plasma (15.6 and 14.3 nmol/L), indicating a rapid and pronounced transfer to milk. At 24 h and 48 h post dose, mean afatinib concentrations were 84.7 and 10.9 nmol/L in milk whereas the concentrations in plasma were below the limit of detection.
The individual AUC0-24h of radioactivity in milk ranged from 17700 to 40100 nmol*h/L, which was more than 100-fold above the individual estimated plasma AUC_{0-24h} (118 to 284 nmol*h/L). The estimated amount of total radioactivity secreted into milk within 24 h was about 2.4 to 5.0% of the dose administered to the dams.

Pharmacokinetic drug interactions

Inhibition of cytochrome P-450 enzymes

Concentrations up to 100 µM of afatinib did not show potent inhibition of the most relevant cytochrome P450 isoenzymes for drug metabolism in human, CYP1A1/2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 CYP3A4 and CYP4A11.

Inhibition of UDP-glucuronosyltransferase (UGT) enzymes

The glucuronidation of ß-estradiol was investigated by using human liver microsomes or expressed UDP-glucuronosyltransferase (UGT) 1A1. In this way, ß-estradiol was incubated with human liver microsomes (50 µM) in the presence of potential inhibitors of UGT enzymes at different concentrations (0-200 µM). The 3-glucuronidation of ß-estradiol is mediated selectively by UGT1A1, whereas the formation of the 17-glucuronide of ß-estradiol is catalysed predominantly but not exclusively by UGT2B7. Consequently, expressed UDP-glucuronosyltransferase 1A1 catalysed the formation of ß-estradiol-3-glucuronide.

The quantitative data of the formation of ß-estradiol 3- and 17-glucuronide formation were used for the calculation of IC_{50} data for the inhibitors, as it shown in Table 9.

Table 9. Inhibition data of potential inhibitors of UGT enzymes.

Inhibitor	IC_{50} [µM]	
	ß-estradiol 3-glucuronidation	ß-estradiol 17-glucuronidation
BI 7325	1.3	52.6
Docetaxel	13.6	32.5
Paclitaxel	18.7	32.4
BI 2536	21.7	72.5
Tipranavir	22.7	72
BIBW 2992	24.2	73.7
BIBF 1120	24.5	77.6
Simvastatin	60.2	43.8
Domperidone	74.9	48.2

Enzyme induction study in rats

The administration of afatinib, at dose levels of 4 and 8.5 mg/kg, orally to five male Wistar rats once daily for 4 days caused no induction of CYPIA, CYP2B, CYP3A, CYP2E1 and CYP4A activities and also had no effect on the liver to body weight ratios, total amount of microsomal protein or total amount of hepatic cytochrome P450.

In vitro enzyme induction study in human hepatocytes

A study was conducted to evaluate the *in vitro* induction potential of afatinib MA2 on six major human cytochrome P450 enzymes in cultured primary human hepatocytes from three different donors. In situ enzyme activities were assessed using selective test substrates and mRNA levels were determined by semi-quantitative real-time PCR for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4. Induction of *in vitro* enzyme activity was not found for any of the P450 enzymes tested following treatment with up to 5 µM afatinib for 48 h. No relevant induction of mRNA levels was observed for the respective enzymes upon treatment with afatinib.

Active uptake of afatinib by OATP, OAT and OCT transporters and inhibition of OATP, OAT and OCT mediated transport

In transfected HEK293 cell lines, that expressed the different drug transporters, was evaluated the active transport of afatinib by OATP, OAT and OCT drug transporters. Afatinib exhibited a high passive permeability. No a relevant effect of inhibitors on afatinib was observed. Therefore, afatinib was most likely not a substrate of OATP2, OATP8, OATP-B, OAT1, OAT3, OCT1, OCT2, and OCT3 or it was transported only to such a small extent that its passive permeability markedly exceeds the active, carrier-mediated uptake. Thus, active transport of afatinib by OATP, OAT and OCT drug transporters is not expected to be of relevance for the pharmacokinetics of afatinib.

Also in these studies was evaluated the potential of afatinib, at concentration range of 0-100 µM, to inhibit drug transport that is mediated by OATP2, OATP8, OATP-B, OAT1, OAT3, OCT1, OCT2, and OCT3. The results are shown in Table 10.

Table 10. Inhibition of uptake transport of test substrates by afatinib into HEK293 cell lines that express OATP2, OATP8, OATP-B, OAT1, OAT3, OCT1, OCT2, and OCT3.

Transporter and test substrate (in brackets)	Inhibition by BIBW 2992 IC_{50} [µM]
OATP2 (estradiol 17ß-glucuronide)	82.8
OATP8 (estradiol 17ß-glucuronide)	71.2
OATP-B (estrone 3-sulfate)	6.05
OAT1 (para-aminohippuric acid)	> 100
OAT3 (estrone 3-sulfate)	> 100
OCT1 (N-methyl-4-phenyl pyridinium)	20
OCT2 (N-methyl-4-phenyl pyridinium)	> 100
OCT3 (N-methyl-4-phenyl pyridinium)	11.8

Passive permeability through CaCo-2 cell monolayers, P-gp transport profiling and inhibition of P-gp mediated transport

The passive permeability of afatinib in CaCo-2 cell monolayers, its potential transport by P-gp (ABCB1) and the potential inhibition of P-gp by afatinib were assessed. Afatinib MA2 had a high intrinsic passive permeability (75-120 nm/s) and was also shown to be both a substrate (K_m 10-30 µM) and a medium-potent inhibitor for the drug efflux pump P-gp. Also it was determined that afatinib inhibited the P-gp mediated digoxin transport by CaCo-2 cells with an estimated IC_{50} of 24 µM.

In transcellular transport studies using human P-gp expressing LLC-PK1 cells, the Km for P-gp transport was estimated to be 9.3 µM.

In another study using P-gp expressing LLC-PK1 cells and digoxin as test substrate, the IC_{50} of afatinib on P-gp-mediated transport was 1.6 µM. Due to the different IC_{50} obtained with CaCo-2

cells and LLC-PK1, additional experiments using a range of afatinib and digoxin concentrations were performed. A Ki of 3.4 µM was obtained.

2.3.4. Toxicology

Single dose toxicity

Summary of single dose toxicity studies performed:

Species / Sex / Number / Group Study ID	Dose / Route	Approx. lethal dose / observed max non-lethal dose (mg/kg)	Major findings
Mouse/Crl:NMRI N=6/group (3 males/3 females) for 191 mg/kg; N=3/group (3 males for 382 mg/kg, 3 females for 763 mg/kg) 02B182 / U03-1089	191, 382 and 763 mg/kg oral gavage (demineralized water)	763 / 382	One animal affected at 763 mg/kg - reduced activity, abdominal breathing, reduced body temperature, increased abdominal girth and reddish yellowish crust around the oronasal region. Macroscopic changes indicate that the gastrointestinal tract was the target organ system.
Rat/CrlGlxBrl Han:WI N=6/group (3 males/3 females) for 191 mg/kg; N=3/group (3 males for 382 mg/kg, 3 females for 763 mg/kg) 02B181 / U03-1088	191, 382 and 763 mg/kg oral gavage (demineralized water)	191-382 / 191	Major adverse clinical effects occurring with a delay of up to 7 days; piloerection, soiled anogenital region, reduced body temperature and emaciation. Macroscopic changes were mostly seen in the gastrointestinal tract and included reddened or necrotic mucosa, and the gastro-intestinal tract distended and filled with gas or with redbrownish or whitish fluid. At 382 and 763 mg/kg two animals per group were killed in moribund state, one animal was found dead in each group.

Repeat dose toxicity (with toxicokinetics)

Summary of repeat dose toxicity studies performed:

Study ID / Duration	Species / Sex / Number / Group	Route / Dose (mg free base / day / kg)	Major findings
GLP 4 weeks + 2 week recovery	Rat CrlGlxBrlHan: WI 10/sex/grou	Oral (gavage); batch no. 8260090; solution in demineralised water	**NOAEL 4 mg/kg** Mortality or premature sacrifice: HD: 12/25M and 4/25F (>D16) Clinical: HD: Diarrhoea (>D5), emaciation, exsiccosis; skin alterations MD: Reddened/thickened lips in 1 M only (>D20) Body weight: ↓bwt and food consumption HD (more pronounced in M, males lost weight whereas F had a ↓bwt gain) Organ wt: prostate and ovaries, dose-dependent ↓abs.&rel. wt

Study ID/Duration	Species/Sex/Number/ Group	Route/Dose (mg free base/day/kg)	Major findings
	p (20 in control and HD) +5/sex/gr for TK (Another 10 F in control and LD added on Day 13, treated for 29 days. D6: 4 females were erroneously administered an additional MD dose. Histology not ana-lysed – no alterations present in main study LD)	0, 4, 8.5, 18	already starting at LD, axillary lymph node ↑abs&rel wt (HD/M) ↑rel wt (HD/F) (MD – trend) - considered secondary to the skin lesions, thymus ↓abs.&rel. wt (HD/M) spleen ↓abs wt. & trend rel wt (HD/M) Histology: *Kidney;* Papillary necrosis in kidneys (HD/M>F, MD/1M), basophilic, dilated or PAS-positive tubuli (HD, MD/1M+ 1F) *Skin;* moderate to severe folliculitis and dermatitis (HD>MD) *GI;* epithelial atrophy in oesophagus, stomach, small and large intestine; atrophy of endometrial epithelium (HD>MD) *Prostate and/or seminal vesicles;* atrophic (HD) *Seminiferous tubules of the testes* ↑apoptosis *Endometrial* (HD/MD)*/vaginal epithelium* (HD); atrophy *Thymus & Spleen*; minimal to severe atrophy (HD, M>F) Ophtamology: no test substance related findings Hematology: Rblc no relevant changes, WBC ↑ WBCct ↑%neutrophils ↓% lymphocytes – dose dependent and more pronounced effect in HD, ↑ platelet ct (HD) Bone marrow: : ↑ neutrophil precursors (HD/M+F, MD/F); ↓ erythrocyte precursors (HD/M+F), ↑%plasma cells and macrophages (dose-response in M, F only HD) Clin. Chem: ↑AST +85% HD/M, ↑BUN HD/M+F, minor ↑plasma globulin conc, minor ↓alb and albumin/globulin ratio Urine: ↓ urine vol. HD/M+F, MD/M, ↑ β-NAG HD, ↑ creatinine (HD), ↑ microprotein HD, ↑ protein in urine HD/M and WBC in urinary sediment HD/M Imunotox: *peripheral;* ↓% analyzed cells (↓% MNC) MD+HD, ↑%monocytes and ↓% B-lymphocytes HD, *spleen;* ↓number of analysed cells (HD) ↓% B-lymphocytes (HD+MD) ↓natural killer cell activity (HD) Recovery: clinical changes were reduced in incidence and severity, bw reached almost control values, the neutrophilia had diminished and bone marrow parameters were normalised. Histology changes were reversible except for changes in kidney and skin.
GLP 13 weeks + 6 week recovery	Rat CrlGlx BrlHan:WI 10/sex/group (20 in control and HD) + 5/sex/gr for TK	Oral (gavage); batch no. 8360110; solution in demineralised water 0, 2, 5, 10	**NOAEL 2 mg/kg** Mortality: 2M, 1F (HD) prematurely sacrificed between D39-D82 (microscopic findings in these animals were related to the skin and the kidneys) Clinical: wavy/rough or dull fur (HD & MD8/20M), hair loss, swollen muzzle with skin alterations (HD>D28/M>F) Body weight: ↓ bwt +slight ↓food consumption (HD/M) Organ wt: ↑ axillary lymph nodes (HD) – regarded as secondary to inflammatory skin lesions, ↑ pituitary (F/HD+MD) Histology: *Kidney;* unilateral or bilateral necrosis of the renal papilla in 6/19 (HD, including prematurely sacrificed) *Skin;* Minimal to severe folliculitis, prominent in the facial area and on the tail (19/19/HD; 8/10M+1/10F/MD) Ophtamology: no test substance related findings Hematology: Rblc no relevant changes, ↑WBC and neutrophil ct. (HD/M+F, MD/M; ↑ platelet ct (HD+21%, D86) prothrombin unchanged Bone marrow: slight changes (HD) regarded to be without biological relevance (MD+LD not analysed) Clin. Chem: ↑aldolase activity (2.2fold HD, 1.5fold MD), ↑GLDH activity (1.7fold HD/F) ↑globulin (HD, MD), ↓alb and albumin/globulin ratio (HD D86/87)

Study ID/Duration	Species/Sex/Number/ Group	Route/Dose (mg free base/day/kg)	Major findings
			Urine: ↓ urine volume (HD/M); ↑ protein concentration, ↑ WBC ct and RBC ct seen in some animals (9HD, 1LD, 1 ctrl) Recovery: renal papillary necrosis in 4/18 recovery animals; skin lesions were still present at recovery end in 15/18 animals.
GLP 26 weeks + 8 week recovery	Rat CrI:WI (Han) 20/sex/group (30 in control and HD)	Oral (gavage); batch no. 8430191; solution in demineralised water 0, 1.5, 3, 6	**NOAEL 1.5 mg/kg.** Mortality: 1M (HDrecov/D220) poor general condition (congestion of the liver), 1F(MD/D87) anesthesia related – Not considered test-item related Clinical: slight wavy/rough fur and slight swelling of the paws (LD) swelling of the muzzle, wavy/rough fur, swollen/encrusted paws (MD+HD) + encrusted muzzle and scaly skin on the tail (HD) Body weight: ↓bw gain & bw D182 +slight ↓food cons. (HD/M) Organ wt: ↑ axillary (HD/M) and mesenteric (HD/F) lymph nodes Histology: changes in skin (folliculitis, inflammatory infiltration; M>F), regional lymph nodes (reactive hyperplasia, histiocytosis, plasmocytosis; M>F), spleen (extramedullary haemopoiesis), kidney (papillary necrosis in 8/20 HD/M and 1/20 HD/F; unilateral (2M, 1F) or bilateral (6M)), nasal cavity (inflam. infiltration) HD. Ophtamology: There were no test item related findings. Hematology: RBlc no relevant changes, ↑ WBC ct (HD/1.45x) and neutrophil ct (HD/M 2.7x, HD/F 1.5x), ↑ platelet ct (HD/M) Bone marrow: bone marrow smears were not evaluated. Clin. Chem: ↑globulin ↓ albumin and A/G ratio (M>F) (Minor changes in ALT and G-GT) Urine: (HD/M); ↓ urine volume ↑ total protein (1.5x) ↑ WBC Recovery: Almost all changes had ameliorated or were absent at recovery end except for some alterations in skin (M>F) and kidneys (M).
GLP 4 weeks + 2 week recovery	Minipig Goettingen 4/sex/group (6 in control and HD)	Oral (gavage); batch no. 8260090; solution in demineralised water 0, 1, 2.45, 6	**NOAEL 1 mg/kg.** Minimal to slight atrophy of oesophagus epithelium (4/4 M), squamous stomach mucosa (1/4 M) and in the seminal vesicle (1/4 M) considered as tolerable pharmaco-dynamic drug effects. Mortality: None of the animals died prior to scheduled necropsy Clinical: soft or loose stool seen temporarily (2/8 MD 4/12 HD); slight to moderate, dose-dependent, reversible increase in heart rate which correlated with a shortening in QT-interval (MD, HD) no treatment related changes in ECG morphology Body weight: On a group basis, bw was not affected (1HD/M ↓bw gain and food consumption) Organ wt: No treatment-related changes in absolute or relative wt Histology: MD+HD; atrophy of the surface epithelia of the digestive and upper respiratory tract, on mucinous glands (HD; atrophy of intestinal villi) and atrophy of corneal epithelium (1 HD/F) atrophy of seminal vesicle (2HD/M) Ophtamology: No test substance-related findings Hematology: RBlc No relevant findings, ↑ ct+% neutrophilic cells (MD/M+HD/M) Bone marrow: not assessed (staining difficulties) Clin. Chem: no changes in clinical chemistry parameters considered to be drug-related [slight ↑BUN (HD+MD) [mild vs pre-test]), minor ↑globulin + ↓alb. & A/G ratio (-10%)] Urine: No changes Recovery: All alterations resolved.

Study ID/Duration	Species/Sex/Number/ Group	Route/Dose (mg free base/day/kg)	Major findings
GLP 13 weeks + 6 week recovery	Minipig Goettingen 6/sex/group (4 in LD)	Oral (gavage); batch no. 8360110; solution in demineralised water 2 mL/kg 0, 0.5, 2, 7/5.5 (dose reduced from 7 to 5.5 mg/kg on D32-42, D45, and >D77)	**NOAEL 0.5 mg/kg.** Minimal hyperkeratosis of the non-glandular stomach (1/4 M) and hypertrophy of serous acinar cells in the sublingual gl (1/4 M) considered as tolerable pharmacodynamic drug effects. Mortality: No mortalities Clinical: soft feces/loose stool (HD/M>F @7mg/kg), Positive test for occult blood in 2HD/M (D9+D77) No relevant, dose dependent, consistent effects on PR-, QT-interval, QRS-complex width, heart rate or ECG morphology. Body weight: slight decrease (HD/M) Organ wt: No drug-treatment related changes of absolute or relative organ weights (↓ovaries in drug-treated groups considered a sequel of the unusually high weight of the ovaries in control D92 7±2.5g [ctrl D134 3.5±1.1g – similar to treated groups]) Histology: atrophic dose-dependent changes in the digestive tract, mucous portions of the (sub)mandibular and sublingual glands, larynx, trachea, prostate and seminal vesicle and corneal epithelium; activation of erythro- and myelopoiesis in bone marrow. Ophtamology: No drug-treatment related findings Hematology: RBlc no relevant changes, ↑ ct+% neutrophilic cells and slight ↑ WBC ct (HD) Bone marrow: Activation of erythro- and myelopoiesis Clin. Chem: slight ↑BUN (HD/M>F), ↓albumin/globulin ratio (HD/up to -29%) Urine: No relevant changes (non-consistent changes in ß-NAG, creat. and prot.) Recovery: During recovery changes regressed completely or ameliorated (increased hematopoiesis) at 2.0 mg/kg and almost all changes (i.e. except for a very mildly increased hematopoiesis in 3 animals and a mild hypertrophy of the serous portion of the sublingual gland in one animal) had regressed at 7.0/5.5 mg/kg. *[The observation of loose stool on one or several days was the reason for reducing the dose from 7.0 to 5.5 mg/kg on Day 32.]*
GLP 52 weeks + 6 week recovery	Minipig Goettingen 4/sex/group (8 in control and HD)	Oral (gavage); batch no. 8430191; solution in demineralised water 0, 0.5, 1.5, 5	**NOAEL 0.5 mg/kg.** Minimal to slight atrophy/vacuolation of epithelium/stratum corneum or squamous epithelium in oesophagus (2/4 M) and non-glandular stomach (4/4 M) considered as tolerable pharmacodynamic drug effects. Mortality: No mortalities Clinical: soft or liquid faeces during brief periods HD/3M+3F. No dose-related effect of the test item on HR and QRS, QT and QTf durations. PQ duration tended to increase – not dose-related and did not lead to second degree-auricular-ventricular block. Body weight: no drug related effects Organ wt: No drug-treatment related changes of absolute or relative organ weights (lower weight of the ovaries at 0.5 and 1.5 mg/kg at the end of the treatment period (D365) were not detectable in HD and are considered as a sequel of the unusually high weight of the ovaries in the Control Group, probably due to the individual stages of the estrous cycle) Histology: atrophic squamous epithelium of the esophagus and gastric pars proventricularis (LD/M>F, MD/M>F, HD), larynx glandular atrophy (MD/2M3F, HD/1M2F) atrophy of the corneal epithelium of the eyes (MD/1M2F, HD/4M4F). The opacities of the

Study ID / Duration	Species / Sex / Number / Group	Route / Dose (mg free base / day / kg)	Major findings
			subcapsular ocular lens seen at the ophthalmological examination were confirmed histopathologically. Ophtamology: Opacities of the subcapsular lens (1LD+2HD) considered incidental Hematology: slightly ↑neutrophil cell ct (HD/M) Bone marrow: bone marrow smears were not evaluated since there were no toxicologically meaningful changes of hematological parameters Clin. Chem: minimal ↑BUN (HD/M), ↑globulin+↓alb.&A/G ratio (HD/M-19%F-26%) Urine: No relevant group differences were seen Recovery: All alterations resolved during the recovery period except for minimal atrophy of the esophageal squamous epithelium and minimal vacuolation of the squamous epithelium of the gastric pars proventricularis in 1/4 males each.

The toxicokinetic studies to obtain the exposure to afatinib, have been conducted as part of the repeat-dose toxicity studies performed in rats, mouse and minipigs and from embryo-fetal development studies performed in rats and rabbits.
In rats, toxicokinetic monitoring revealed that the exposure (AUC_{0-24h}) increased more than proportionally to dose and the plasma concentrations of afatinib were higher in males than in females. Additionally, accumulation of drug was observed. This accumulation of the drug could explain the more toxicity of afatinib in the repeat-dose toxicity studies performed in rats.
In pregnant rats, AUC_{0-24h} increased slightly more than proportionally to dose but no accumulation was observed.

In mice and minipigs, no drug accumulation was observed, although at higher doses a more than proportional increase in systemic exposure was observed in minipigs, and no sex difference in exposure was noted. In pregnant rabbits, also a slight increase in the exposure more than proportionally with dose was found but there was no drug accumulation

As shown it Table 11 the exposure was compared in the repeat-dose toxicity studies performed in rats and minipigs, and the exposure in embryo-fetal development studies, performed in rats and in rabbits, with the clinical exposure.

Table 11. Safety margins derived from repeat-dose toxicity studies and from embryo-fetal development studies on afatinib compared with the clinical situation.

Species / treatment duration	NOAEL of animal study (mg / kg)	HED at NOAEL (mg / m²)	Mean C_{max} at NOAEL (nmol/L)	Mean AUC_{0-24h} at NOAEL (nmol·h/L)	Animal to Human Safety Margin#		
					Based on HED (mg / m²)	Based§ on multiples of C_{max}	Based§ on multiples of AUC_{0-24h}
Rats/26 W	1.5	9	♂: 37.9 ♀: 17.2	♂: 303 ♀: 97.7	0.3	♂: 0.36 ♀: 0.16	♂: 0.19 ♀: 0.06
Minipigs/52 W	0.5	17.5	♂: 2.35 ♀: 1.34	♂: 26.2 ♀: 19.5	0.6	♂: 0.02 ♀: 0.01	♂: 0.02 ♀: 0.01
Rats	16	96	342	3540	3.1	3.2	2.2

Rabbit	5	60	116	425	1.9	1.2	0.30

[#]: For comparison, data derived from a meta-analysis of clinical studies at steady state are used: 50 mg/day afatinib, equivalent to 0.83 mg/kg or 31 mg/m^2 for 60 kg individual. Mean C_{max} = 158 nmol/L, mean $AUC_{\tau,SS}$ = 2330 nmol·h/L. Note: 1 nmol/L afatinib corresponds to 0.486 ng/mL afatinib. [§]: Protein binding was taken into account: 7.4 % unbound fraction for rat, 7.1% unbound fraction for minipig, 8.2 % unbound fraction for rabbit, 5 % unbound fraction for human.

Genotoxicity

The summary of these studies is given in Table 12.

Table 12. Pivotal (GLP) genotoxicity studies performed with afatinib

Assay	**Indicator cells**	**Concentrations or dose levels (free base)**	**Main Results**	
in vitro				
Ames Bacterial Reversion	*S. typhimurium* TA98, 100, 102, 1535, 1537 with and without metabolic activation	afatinib 5-1000 µg/plate	Weak positive response in TA 98 (up to 2.2-fold increase at 30 µg/plate with and without metabolic activation; using plate incorporation)	POSITIVE
Chromosomal aberration	Human lymphocytes	afatinib 1-30 µg/mL (for chromosomal analysis)	No induction of chromosomal aberrations at non-cytotoxic concentrations	NEGATIVE
in vivo				
Mutation study in male Muta™Mice	Liver, duodenum, skin	0, 24, 47, 70 mg/kg administered daily orally (gavage) for 4 weeks	Life-threatening dose achieved at 70 mg/kg (not evaluated). No mutation induction at 24 and 47 mg/kg	NEGATIVE
Bone marrow micronucleus test in Wistar rats	Bone marrow	0, 4, 8.5, 18 mg/kg administered daily for 4 weeks	Life-threatening dose achieved at high-dose level. Marginal bone marrow toxicity. No micronucleus induction	NEGATIVE
Comet assay in Wistar rats	Liver, kidney and jejunum	0, 2, 16, 200 mg/kg, 2 x treatment at 24 h interval	No induction of DNA damage up to the MTD	NEGATIVE

Carcinogenicity

No studies assessing the carcinogenic potential of afatinib have been performed.

Reproduction Toxicity

The influence of afatinib on fertility and early embryonic development was investigated in a pivotal study in rats together with effects on pre- and postnatal development in rats performed in parallel. Embryo foetal developmental toxicity of afatinib was investigated in pregnant rats (a non GLP dose range finding study and a pivotal (GLP) study) and in rabbits (a dose range finding study as well as a pivotal (GLP) study). The results are summarised in Tables 13-15:

Table 13. Pertinent findings in the pivotal (GLP) oral fertility and early embryonic development study with afatinib in rats

Species; dosing period; daily dose [mg/kg]	**Pertinent findings**
Rat M: minimum 5 weeks (from 4 weeks before pairing) F: from 2 weeks before pairing until GD 7 0, 4, 6, 8	<u>All groups:</u> No effects on oestrus cycles, mating performance and fertility (assessed by pre-coital interval, percentage mating, conception rate and fertility index). <u>4 mg/kg:</u> No adverse effects. <u>6 mg/kg:</u> No adverse effects. Clinical signs (loose faeces, encrustations, reddening of muzzle) at low frequency in M and rarely in F. ↓ BW gain in M (0.72x Control). <u>8 mg/kg:</u> No adverse effects. One satellite M sacrificed on D19. Clinical signs (loose faeces, encrustations, reddening of muzzle) at low frequency in M and rarely in F. ↓ BW gain in M (0.55x) and F (0.69x prior to pairing, 0.8x early in gestation). ↓ no. of live embryos (0.82x); ↓ no. of corpora lutea (0.91x). ↓ Implantation counts (0.88x) and ↑ post implantation loss (2.3x).

Table 14. Pertinent findings in the pivotal (GLP) embryo-foetal development toxicity studies with afatinib in rats and rabbits

Species; dosing period; daily dose [mg/kg]	**Pertinent findings**
Rat GD 6-17; 0, 4, 8, 16	<u>All groups:</u> All dams were pregnant. No effects on litter data. Foetal pathology: incidence of major and minor abnormalities and skeletal variants showed no relationship to treatment. Neither type nor distribution of malformations suggested any association with treatment. <u>8 mg/kg:</u> maternal NOAEL. No adverse effects on embryo-foetal development. <u>16 mg/kg:</u> 1 F sacrificed on GD15 (↓ BW anal fluid discharge, hunched posture). Survivors: piloerection, loose and/or liquid faeces > GD 12, encrustations around muzzle/nose, ↓ BW and ↓ FC during treatment period. Embryo-foetal NOAEL.
Rabbit GD 6-18; 0, 2.5, 5, 10	<u>All groups:</u> Malformations equally distributed between Control and dose groups, without dose relationship or within normal limits. <u>2.5 mg/kg:</u> maternal NOAEL. No adverse effects on embryo-foetal development. <u>5 mg/kg:</u> ↓/absent faecal output in 2/21 F, 1/21 F with diarrhoea or liquid faeces. 1 F with complete abortion. Embryo-foetal NOAEL. <u>10 mg/kg:</u> 2 F found dead on GD 17/19, 2 F sacrificed GD 22. 3 F with abortion. ↓ BW, ↓ FC during treatment period, ↓ or absent faecal output. ↓ Foetal wt., 3.1% of foetuses were runts (<65% of control wt.). Variations: flexure of extremities, less integument at forelimbs, 1 additional vessel at the aortic arch, 1 additional vessel at the right or left A. carotis, thin wall of

	stomach, small testis, lumbar rib, isolated lumbar rib (flying rib), changed curvature of rib (unilateral) and humerus distally partly not ossified (bilateral).

Table 15. Pertinent findings in the pivotal (GLP) oral pre- and postnatal development study with afatinib in rats

Species; dosing period; daily dose [mg/kg]	**Pertinent findings**
Rat GD 6 to Day 20 of lactation 0, 4, 6, 8	All groups: No effects on the ability of animals to give birth to a live litter or rear that litter to weaning. Maternal treatment with afatinib did not affect F1 mating performance or fertility of the offspring nor any functional developmental landmarks or behavioural assessments, including learning and memory assessments. 4 mg/kg: No adverse effects on pre- and postnatal development. 6 and 8 mg/kg: No adverse effects on pre- and postnatal development. Birth wt. and BW gains of offspring before weaning were low (0.91x Control in M and F at 8 mg/kg). ↓ BW of animals derived from females at 6 or 8 mg/kg at start of the F1 generation and weights remained below Control through most of the F1 generation (F1 males 0.91x and 0.94x Control on Day 74 at 6 and 8 mg/kg, respectively; F1 females generally >0.9x Control prior to pairing, and no difference to Control during the gestation period). Toxicokinetics: No relevant difference of systemic exposure to afatinib between dose groups of 6 and 8 mg/kg.

↑, ↓: increase, decrease BW: body weight M, F: males, females GD: gestation day wt.: weight

Local Tolerance

The local tolerance of afatinib has been tested in rabbits for its when applied dermally or ocularly.

Dermal tolerance study in rabbits

The local dermal tolerance of afatinib MA2 has been evaluated in 4 female Chbb:NZW rabbits applied with a single dose of 100 mg for up to 4 h. No noteworthy findings have been found, only two areas of very slight erythema were observed in 1 animal immediately and 4 h after a 1 h exposure to the test article. Afatinib was classified as non-irritant and non-corrosive.

Acute eye irritation study in rabbits

The potential effects of afatinib in eyes were investigated in a single female Crl:KBL(NZW) rabbit treated with a single dose of 20 mg afatinib MA2, applied into the conjunctival sac. Immediately following application, marked ocular side effects (chemosis, swelling of the eye lids, hyperaemic iris and conjunctivae) were observed, some of them persisting up to Day 17 of the observation period. Although no additional animal was tested due to the marked adverse effects observed, additional slit lamp examinations revealed no findings on Day 3 and Day 18, but on Day 12 dilated blood vessels of the sclera as well as sprouting of vessels were noted.

Whereas no changes were observed macroscopically or histopathologically in the control right eye, macroscopic evaluation of the treated eye at necropsy revealed a red discolouration of the third eyelid. In addition, histopathological examinations revealed changes of local conjunctival irritation. Afatinib was classified as an eye irritant.

Other toxicity studies

Immunotoxicity

The potential effects of afatinib on the immune system were investigated within the 4-week oral rat toxicity study. The animals were dosed with 0, 4, 8.5, and 18 mg/kg (0, 24, 51 and 108 mg/m^2) of afatinib. Samples from blood and spleen were taken at treatment, at necropsy and recovery termination and analysed by flow cytometry for subsets of various leukocyte cell populations. Natural killer cell activity was determined for spleen cells by lysis of radiolabeled target cells.

Dose-dependent changes in peripheral blood and bone marrow, indicative of neutrophilia, were seen in both sexes at 8.5 and 18 mg/kg. The percentage of analysed peripheral blood cells was reduced at 8.5 and 18 mg/kg. The percentage of monocytes was marginally increased and that of B-lymphocytes was decreased at 18 mg/kg. In addition, the percentage of B-lymphocytes was significantly lower in the spleen of all drug-treated groups, (statistically significant at 8.5 and 18 mg/kg). Activity of natural killer cells was mainly unaffected except for a minimally reduced activity at 18 mg/kg. Absolute and relative thymus weight and absolute spleen weight were significantly lower in males at 18 mg/kg.

The described differences to vehicle control were largely also seen at the end of the 2-week recovery period. In view of the marked and life-threatening toxicity observed in high-dose animals at 18 mg/kg, along with numerous premature sacrifices/deaths, the observed immunological low-grade changes may be an unspecific response caused by the exaggerated toxicity and, therefore, are not regarded to be of relevance for humans.

Studies on impurities

Specified impurities present at and above the ICHQ 3A/3B levels in afatinib drug substance and/or drug product were adequately qualified in GLP safety studies by in vitro and in vivo genotoxicity tests and a 13-week oral repeat-dose toxicity study in rats.

Photosafety

In Vitro 3T3 NRU phototoxicity test with afatinib

The phototoxic potential of afatinib for phototoxicity was investigated *in vitro*, using the 3T3 Neutral Red Uptake (NRU) phototoxicity test. Afatinib, as dimaleate salt, was dissolved and diluted in EBSS at neutral pH and concentrations of 4 mg/mL, 3 mg/ml and 1 mg/mL. UV/VIS light absorption of afatinib was determined under irradiation (Irr) over a spectrum from about 250 nm to 750 nm wavelength. Thereafter, BALB/c 3T3 cells were treated for 1 h with different concentrations of the test solution and, in the presence of the test item, for a further 50 min in the absence (-Irr) or in the presence (+Irr) of a nontoxic dose of UVA light. 1 Day after treatment, cellular uptake of the vital dye Neutral Red (NR) was determined. Reduced cellular NR uptake was regarded as parameter for cytotoxicity. A second experiment was performed in the same way, but with a modified concentration range of the test item to confirm the results. To clarify the contradictory results from the first and the second experiment, a third experiment was performed with adjusted concentration range.

In three independent experiments, afatinib exerted cytotoxic effects on BALB/c 3T3 murine fibroblast in the absence and in the presence of irradiation. In the first experiment, EC_{50} was calculated as 12.22 µg/mL (-Irr) and as 2.31 µg/mL (+Irr). In the second experiment, EC_{50} was calculated as 18.98 µg/mL (-Irr) and extrapolated as 10.5 µg/mL (+ Irr), since no reduction of cell viability to 50% was obtained within the modified concentration range. In the third experiment, EC_{50} was calculated as 17.86 µg/mL (- Irr) and as 8.74 µg/mL (+ Irr). The Photo-Irritation Factor (PIF) was calculated as 5.3 (first experiment), as 1.87 (second experiment, using the extrapolated EC_{50} value) and as 2.04 in the final third experiment.

Thus, according to the OECD guidance, the test item was classified as "probably phototoxic".

Maleic acid

Maleic acid anion is the counter ion to afatinib in drug substance. Maleic acid has been reported to be associated with renal side effects. Because no data from repeat dose studies in the minipig were available, a 4 week study (32 days of treatment) was initiated with maleic acid with a single dose group of 3 mg/kg, equivalent to the amount of maleic acid anion administered as afatinib in the respective 4 week toxicity study in minipigs which was run in parallel. For this purpose maleic acid was dissolved in demineralised water and administered orally (gavage) to four Goettingen minipigs per sex (ca. 4 5 months old, body weight 9 12 kg).

Daily oral administration of 3 mg/kg maleic acid for four weeks was not associated with any changes in clinical signs, clinical pathology, gross or histopathology in minipigs.

2.3.5. Ecotoxicity / environmental risk assessment

Summary of main study results

Substance (INN / Invented Name): Afatinib / Giotrif			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Determined by potentiometric titration	log D (pH7.4) = 3.8	Potential PBT: (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log D (pH7.4) = 3.8	not B
	BCF Fish	9.2 – 9.7	not B
Persistence	DT50 or ready biodegradability	0% in 28 days (OECD 301B)	P
Toxicity	NOEC Fish	32 µg/L	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.25	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	covalent binding to proteins via the α,ß-unsaturated ketone moiety and Michael addition		(Y) might affect accumulation studies
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Mean of 3 soils: K_{oc} = 245970 Kd = 3076 Mean of 2 sludges: K_{oc} = 5624 Kd = 1885	Suggested Kd-trigger for sludge of 3700 L/kg No terrestrial risk assessment peformed.
Ready Biodegradability Test	OECD 301B Hydrolysis as a function of pH	Not ready biodegradable (0% in 28 days) Decomposition after 8 weeks 25°C/pH4: 6% /pH7: 39%	

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ =0.8 day/river; 1.1 day/pond $DT_{50, sediment}$ =dissipation half-lives not reached $DT_{50, whole system}$ =6.8 days/river; 2.3 days/pond % shifting to sediment = 48.1%/river; 62.5%/pond (at day 99)			The amount of non-extracted radioactivity continuously increased with time. Non-extracted residues accounted for 7.0% and 6.3% of applied radioactivity at time 0.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	1200	µg/L	Pseudo-kirchneriella subcapitata
Daphnia sp. Reproduction Test	OECD 211	NOEC	2700	µg/L	Daphnia magna
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	32	µg/L	Brachydanio rerio
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	9000	µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF Fish low dose / high dose	9.2/ 9.7 *unit*	L/kg	
Sediment dwelling organism	OECD 218	NOEC	80	mg/kg	*Chironomus riparius*

2.3.6. Discussion on non-clinical aspects

Afatinib is a small molecule tyrosine kinase inhibitor that belongs to the ErbB-family of blockers. In vitro, afatinib has been shown to be a potent and selective inhibitor of EGFR/ErbB1, HER2/ErbB2 and HER4/ErbB4, it has also been shown active against EGFR-mutations known to be resistant towards other EGFR TK inhibitors. In vivo activity and inhibition of ErbB-dependent processes was shown in tumour xenograft models as well as in transgenic mice.

The secondary pharmacology findings were in line what would be expected from an EGFR TK inhibitor and are not expected to have any adverse clinical consequences at the recommended use.

No adverse safety pharmacology findings were identified in investigations on afatinib. The cardiovascular signals seen in the secondary pharmacology and safety studies performed are neither considered to be adverse and the proposal not to conduct a thorough QT-study was considered acceptable by the CHMP.

No pharmacodynamic drug interactions studies with afatinib have been carried out. This was agreed as the applied indication is in monotherapy.

Pharmacokinetics of afatinib has been sufficiently studied and showed that the species used in the toxicological studies (rat and minipig) are relevant to use. The rat was selected as the rodent species for toxicology testing on afatinib due to its widely accepted use in toxicology investigations. The minipig was selected as the non-rodent species due to the poor gastrointestinal tolerance of dogs observed in early pharmacology investigations, because it had shown a metabolite pattern comparable to humans in liver microsome in vitro investigations and its ability for quinazoline metabolism by aldehyde oxidase.

The most prominent feature of afatinib is the covalent binding to proteins which were shown to result in an almost linear tissue accumulation over time.

Oral administration of single doses to mice and rats indicated a low acute toxic potential of afatinib. In oral repeated-dose studies for up to 26 weeks in rats or 52 weeks in minipigs the main effects were identified in the skin (dermal changes, epithelial atrophy and folliculitis in rats), the gastrointestinal tract (diarrhoea, erosions in the stomach, epithelial atrophy in rats and minipigs) and the kidneys (papillary necrosis in rats). Depending on the finding, these changes occurred at exposures below, in the range of or above clinically relevant levels. Additionally, in various organs pharmacodynamically mediated atrophy of epithelia was observed in both species. This information has been adequately communicated in section 5.3 of the SmPC.

No genotoxicity has been found in three in vivo studies and in the in vitro chromosomal aberration assay. No long-term studies to assess the carcinogenic potential of afatinib have been perforemed. This is in line with the ICH Harmonised Tripartite Guideline S9 (Nonclinical evaluation for anticancer pharmaceuticals) and was considered acceptable by the CHMP.

Afatinib has been evaluated regarding potential reproductive and developmental toxicity according to ICH guidance. The embryo-foetal development studies performed on afatinib revealed no indication of teratogenicity. The respective total systemic exposure (AUC) was either slightly above (2.2 times in rats) or below (0.3 times in rabbits) compared with levels in patients. A fertility study in male and female rats up to the maximum tolerated dose revealed no significant impact on fertility. The total systemic exposure (AUC0-24) in male and female rats was in the range or less than that observed in patients (1.3 times and 0.51 times, respectively). A study in rats up to the maximum tolerated doses revealed no significant impact on pre-/postnatal development. The highest total systemic exposure (AUC0-24) in female rats was less than that observed in patients (0.23 times). No studies have been performed in juvenile animals. Since the proposed indication of afatinib is for adults, the lack of studies in juvenile animals is acceptable. In addition radiolabelled afatinib administered orally to rats on Day 11 of lactation was excreted in the breast milk of the dams. The non-clinical findings on reproductive toxicity have been adequately communicated in section 5.3 of the SmPC.

Specified impurities present at and above the ICHQ 3A/3B levels in afatinib drug substance and/or drug product were adequately qualified in GLP safety studies by in vitro and in vivo genotoxicity tests and a 13-week oral repeat-dose toxicity study in rats.

An in vitro 3T3 test showed that afatinib may have phototoxicity potential. The majority of patients treated with afatinib are expected to develop some signs of skin adverse events, which are related to the pharmacodynamic activity of the drug and which also have been observed for patients treated with other EGFR inhibitors (gefitinib, erlotinib, lapatinib). Precautionary

measures against these skin related adverse events include avoidance of direct sun exposure, use of protective clothing and appropriate sun screen (see section 4.4 of the SmPC and package leaflet).

Afatinib is not a PBT substance. Considering the data provided, afatinib does not pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

Based on the nonclinical safety data afatinib has been adequately characterised in terms of its pharmacodynamics activity, pharmacokinetic properties and side effect profile in the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies in patients with NSCLC

Trial number	Trial description	Trial design	Number of patients [1]
	A. Trials in EGFR TKI-naïve patients with NSCLC with EGFR mutations		
1200.22	Phase II trial with afatinib monotherapy	Non-randomised, open-label, uncontrolled	129 (actual)
1200.32	Phase III trial with afatinib monotherapy vs. chemotherapy (pemetrexed/cisplatin)	Randomised, open-label, active-controlled	345 (actual)
1200.34	Phase III trial with afatinib monotherapy vs. chemotherapy (gemcitabine/cisplatin)	Randomised, open-label, active-controlled	364 (actual)
1200.123	Phase IIb trial with afatinib monotherapy vs. gefitinib	Randomised, open-label, active-controlled	264 (planned)
	B. Trials in EGFR TKI pre-treated patients with NSCLC with clinical enrichment for EGFR mutations		
1200.23	Phase IIb/III trial with afatinib monotherapy vs. placebo	Randomised, double-blind, placebo-controlled	585 (actual)
1200.33	Phase I/II trial with afatinib monotherapy [2]	Non-randomised, open-label, uncontrolled	74 (actual)
1200.42	Phase III trial with afatinib monotherapy / afatinib plus weekly paclitaxel vs. chemotherapy [3]	Non- randomised/ randomised, open-label, uncontrolled / active-controlled [3]	1154 (actual)
1200.70	Phase Ib dose escalation trial with afatinib plus sirolimus	Non-randomised, open-label, uncontrolled	up to 42 (planned)
1200.71	Phase Ib dose escalation trial with afatinib plus cetuximab	Non-randomised, open-label, uncontrolled	240 (planned)
C. Other trials in patients with NSCLC			
1200.40	Phase II trial with afatinib monotherapy in EGFR FISH positive patients	Non-randomised, open-label, uncontrolled	70 (actual)
1200.41	Phase II trial with afatinib monotherapy in EGFR FISH positive patients or patients with EGFR- or HER2-mutation [4]	Non-randomised, open-label, uncontrolled	41 (actual)
1200.72	Phase II trial with afatinib monotherapy in patients without EGFR mutation	Non-randomised, open-label, uncontrolled	43 (actual)

2.4.2. Pharmacokinetics

Clinical pharmacokinetic (PK) data are provided from in total of 31 clinical studies: 12 basic PK studies, 10 plasma monitoring/sparse PK sampling studies and 9 PK studies of afatinib in combination therapy. In addition, 6 reports on PK meta-analysis, PKPD and population PK analysis of afatinib have been provided. The clinical pharmacology profile was investigated in studies performed in cancer patients but also in healthy volunteers.

Absorption

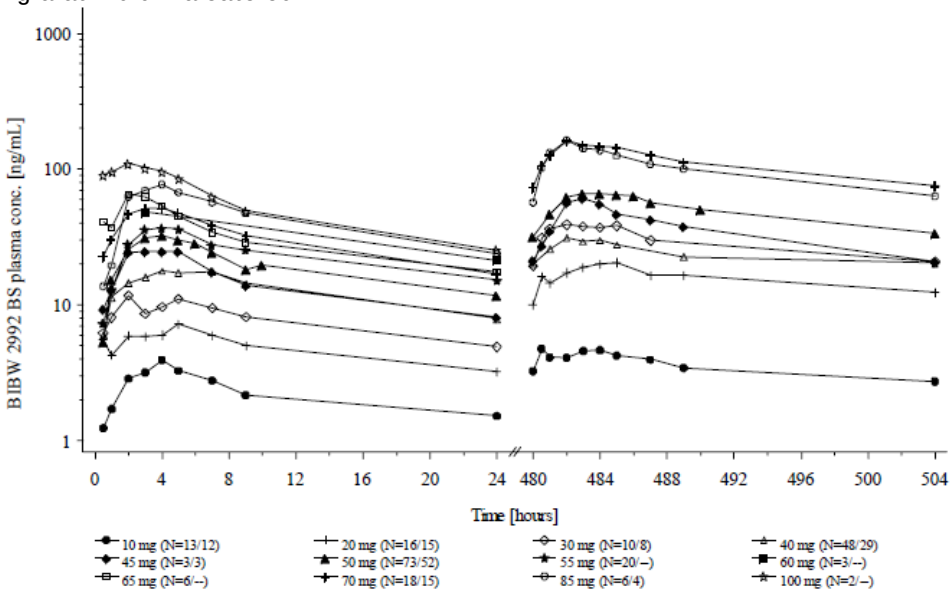
Following oral administration C_{max} of afatinib were observed 2-5 hours post-dose following a single dose as well as at steady state, *i.e.* an intermediate t_{max} (see Table 16).

Table 16. Summary of t_{max} of afitinib, as an indication of absorption rate, after a single dose as well as at steady state

Description	Formulation	Dose (mg)	Single dose t_{max} (h)	$t_{1/2}$ (h)	Steady state t_{max} (h)	$t_{1/2}$ (h)
MTD	TF1	10 - 100	2 (0.5 – 7)	17 (8 – 101)	2 (0.5 – 5)	38 (25 – 97)
MTD	TF1	10 - 65	4 (0.5 – 24)	22 (12 – 65)	3 (0.5 – 9)	38 (25 -78)
MTD	TF2	10 - 50	3 (1 -9)	23 (10 – 147)	3 (0.5 - 7)	36 (16 – 125)
MTD	TF2	10 - 60	-	-	5 (1 – 24)	37 (18 – 153)
Dose propor	FF	20 - 50	5 (1 – 8)	30 (23 – 45)	-	-
QTc	FF	50	3 (1-6)	23 (10 – 27)	3 (1 – 7)	-

In Figure 2, the plasma concentration-time curves shows quite flat C_{max} profiles, particularly at steady state which may indicate ongoing absorption over period of hours.

Figure 2. Geometric mean plasma concentration-time profiles of afatinib after doses of 10 100 mg afatinib dimaleate od



- **Bioavailability**

Following oral administration of afatinib, Cmax were observed approximately 2 to 5 hours post dose. Cmax and AUC0-∞ values increased slightly more than proportionally in the dose range from 20 mg to 50 mg afatinib.

No absolute bioavailability of afatinib in man has been determined. Following an oral dose of 15 mg (2.25 MBq) [^{14}C]afatinib dimaleate, the total recovery of radioactivity was 89% with 85% recovered in faeces. 8% was recovered in faeces during the first 24h *post* dosing and 70% within 72h.

Based on a number of factors such as the solubility and permeability of afatinib, the bioavailability observed in animal species and the limited effect of a Pgp inhibitor on afatinib exposure, the applicant has stated that absolute bioavailability of afatinib is likely high.

In a scenario with high bioavailability, parent compound in faeces represents absorbed and then excreted drug. Thus, in this case the greatest concern in terms of drug-drug interaction would be interactions that involve hepatic and intestinal transport proteins. Afatinib has been shown to be a substrate to the efflux transporters BCRP and Pgp, but not to MRP2. The studies with uptake transporters (e.g. OATPs) were inconclusive due to a high background uptake in control cells, likely due to the high permeability of afatinib. The available *in vivo* studies with the BCRP and Pgp inhibitor ritonavir indicated that inhibition of intestinal efflux transporters had a limited effect on afatinib exposure.

In the possibly less likely scenario of low bioavailability, the parent compound recovered in faeces would represent unabsorbed drug, and the major elimination pathway for *absorbed* afatinib would be metabolism. *In vitro*, enzyme-dependent metabolism was catalysed by FMO3 and CYP3A4. Furthermore, conjugates formed by Michael addition, which is not dependent on metabolising enzymes, were observed *in vitro*. The *in vivo* mass-balance confirmed presence of conjugates formed by Michael addition in faeces. The metabolite m15, formed by FMO3, was recovered in urine but to a lesser degree than the conjugated metabolites, while the CYP3A4-mediated metabolite was not detectable in excreta. Thereby, even if metabolism would be the major elimination pathway this would be primarily non-enzymatic and the risk for metabolic drug-drug interactions would be low.

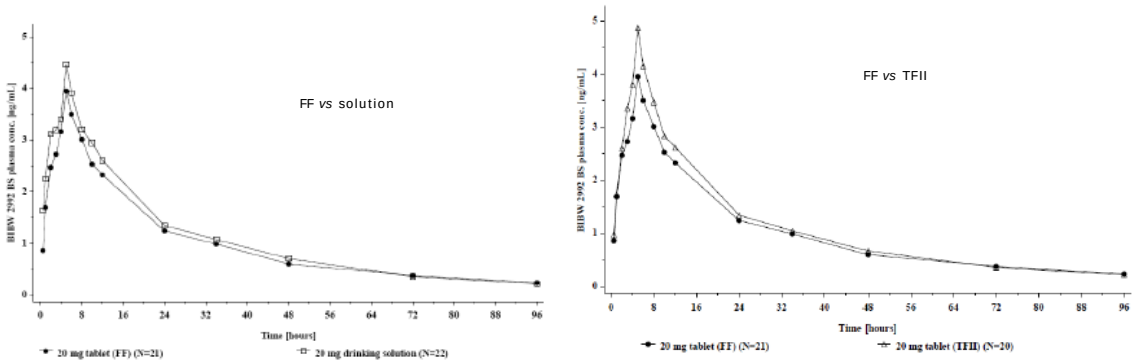
Regardless of whether the bioavailability is low or high, mass-balance data indicate that urinary excretion of parent compound is a minor route of elimination.

- **Bioequivalence**

In a relative bioavailability study, the final formulation (FF) was compared to the test immediate release film coated tablet from which the final tablet was further developed.

The relative bioavailability study was a single dose study with randomised, 3-way crossover design in healthy male subjects (n=22). The treatments were separated by at least three weeks and blood samples were collected for 96h. The plasma concentration-time profiles of afatinib following the three different formulations are shown in Figure 3.

Figure 3. Geometric mean plasma concentration-time profiles of afatinib following an oral dose of 20 mg as the final tablet (FF) and a solution (left panel); and as the final tablet (FF) and a test film coated tablet (TFII; right panel)



The statistical analysis of relative bioavailability between the final formulation and the test film coated tablet is shown in Table 17.

Table 17. Adjusted by-treatment gMean and relative bioavailability comparison of final tablet (FF) and an oral solution; and final tablet and test film coated tablet (TFII)

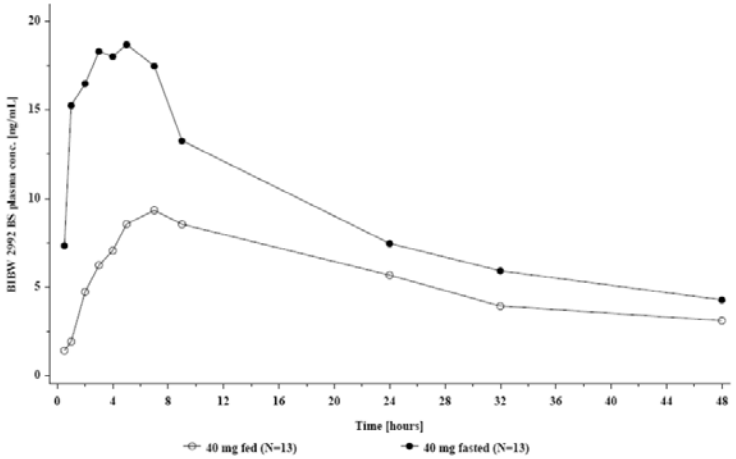
	Adjusted gmean		**Ratio (%)**	**Two sided 90 % CI**	
				Lower limit	**Upper limit**
	Tablet FF	**Solution**	**FF/Solution**		
C_{max} (ng/ml)	4.2	5.0	85	69	109
$AUC_{0-\infty}$ (ng.h/ml)	106	115	92	76	112
	Tablet FF	**TFII**	**FF/TFII**		
C_{max} (ng/ml)	4.2	5.3	80	65	100
$AUC_{0-\infty}$ (ng.h/ml)	105	121	87	70	107

- **Influence of food**

The food effect on the absorption/systemic exposure of afatinib was studied as a secondary objective in one of the MTD studies. Thirteen patients were evaluated in that part of the study, which was a randomized, two-way crossover design with a single dose of 40 mg afatinib dimaleate with or without a high fat/high caloric meal. The test film coated tablet TFII was used and blood samples were collected during 48h *post* dose.

As seen in Figure 4 the absorption was delayed and decreased when afatinib dimaleate was dosed under fed condition.

Figure 4. Geometric mean plasma concentration-time profile of afatinib after single oral dose of 40 mg (tablet TFII) without or with food.



The absorption rate was slowed down, t_{max} 3-8h, in the fed state the exposure of afatinib decreased with about 50% and 40% for C_{max} and $AUC_{0-\infty}$, respectively, (see Table 18).

Table 18. Geometric mean and (CV%) pharmacokinetic parameters of afatinib following an oral single dose of 40 mg afatinib dimaleate (tablet TFII) with or without food

	Fed	Fasted	$Ratio_{fed/fasted}$ (%)	90% CI (%) Lower limit	Upper limit
C_{max} (ng/ml)	12.2 (83)	24.9 (51)	50	36	68
$AUC_{0-\infty}$ (ng.h/ml)	414 (63)	676 (62)	61	50	75
t_{max}[a] (h)	6.9 [3.1-8.1]	3.0 [1.0-6.9]	–	–	–

[a] Median and range

Systemic exposure to afatinib is decreased by 50% (C_{max}) and 39% ($AUC_{0-\infty}$), when administered with a high-fat meal compared to administration in the fasted state. Based on population pharmacokinetic data derived from clinical trials in various tumour types, an average decrease of 26% in $AUC_{T,SS}$ was observed when food was consumed within 3 hours before or 1 hour after taking afatinib.

Distribution

Following oral dosing with afatinib dimaleate a bi-exponential decay could be seen after the first dose but with a change in the plasma concentration-time profile after repeated dosing towards a more mono-exponential decrease which might indicate a distribution phase reaching equilibrium.

In vitro protein binding of [^{14}C]afatinib was determined by equilibrium dialysis at 50-500 nM and the unbound fraction (f_u) was calculated to be 5.0% independently of concentration. The f_b of [^{14}C]afatinib to isolated human serum albumin (HSA ; 45 g/L) was 80%. The binding to alpha-1-acid-glycoprotein (AGP) increased with protein concentration with a f_b of 12% at 0.1 g/L AGP to 91% bound at 10 g/L AGP.

The distribution into blood cells was studied and the blood/plasma ratio was determined to 2.2 and 1.0 at 2min and 3h (after spiking), respectively. The change ratio with time may be attributed to the covalent binding (CVB) process.

The apparent volume of distribution has not been determined since afatinib has only been dosed orally to man. High V_z/F was calculated and increased from 1940 L following a single dose to 2770 L at steady state.

Afatinib was distributed into blood cells, as indicated by a concentration ratio of blood cells to plasma that decreased from 2.21 at 2 min after spiking to 1.02 at 3 hours after spiking and was equal until 48 hours after spiking. Binding of afatinib to human serum albumin (45 g/L) was moderate (79.6 %). Binding of 150 nM afatinib to human alpha-1-acid-glycoprotein (AGP) increased with the protein concentration from 11.6 % at 0.1 g/L AGP to 90.6 % at 10 g/L AGP. The apparent volume of distribution (Vz/F) was high with 1940 L for single dose treatment and 2770 L at steady state.

Elimination

Generally a longer $t_{1/2}$ was calculated, about 37h, following the last dose at steady state compared to the $t_{1/2}$ determined after the first dose, about 23h. The $t_{1/2}$ of afatinib calculated following an oral dose of [^{14}C]afatinib dimaleate in the ADME study was 34h.

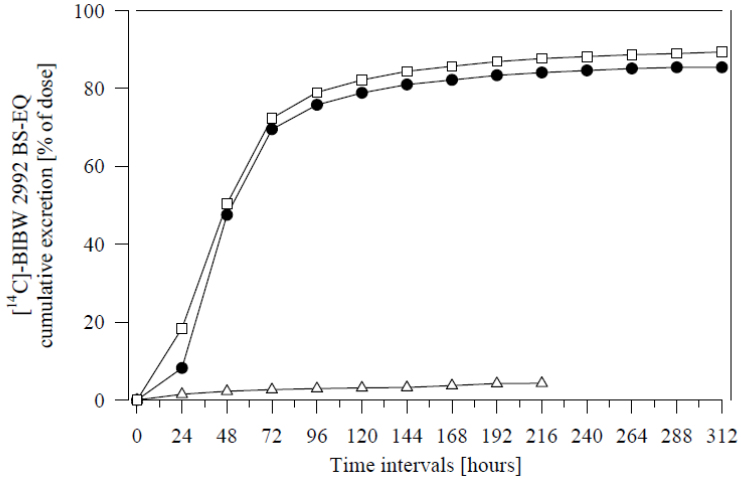
Clearance has not been determined since afatinib has only been dosed orally to man. CL/F was calculated to 1050 ml/min following a single dose to 898 ml/min at steady state.

Excretion

The mass-balance of excretion was studied in 8 healthy volunteers following a single dose 15 mg (2.25 MBq) [^{14}C]afatinib dimaleate administered as an oral solution. Blood samples were drawn at regular intervals during 96h *post* dose and urine and faeces samples were planned to be collected up to 120h after dosing, however, depending on ongoing excretion at 120h the sampling period was prolonged. Urine samples collected 0-72h *post* dosing where pooled across subjects, as were the faeces samples, (proportionally according to the weight of the single fraction samples) for determination of excretion pattern.

Most of the radioactivity was excreted within four days, 79% (range 65-88%) of the dose, with most of it excreted in faeces (Figure 5). The total recovery was 89% (range 84-95%) within 13 days with 4.3% (range 3.4-6.0%) of the dose excreted in urine and 85% (range 77-93%) in faeces.

Figure 5. Geometric mean cumulative excretion of [14C]afatinib equivalent in percent of radioactive dose in urine (Δ), faeces (●) and total recovery until 312 h (13 days; □) following an oral dose of 15 mg (2.25 MBq) [14C]afatinib dimaleate



The most prevalent component in excreta was parent compound accounting for almost 90% of the recovered radioactivity (Table 19). Only small amounts of metabolites were observed in excreta.

Table 19. Overview of excretion pattern in urine and faeces, 0-72h samples pooled across subjects, following an oral dose of 15 mg (2.25 MBq) [^{14}C]afatinib dimaleate

	Percentage of radioactive dose (%)		
	Urine	**Faeces**	**Total recovery**
parent	1.8	62.3	64.1
m4	0.6	4.3	4.9
m13	0.01	2.7	2.7
m15	0.3	–	0.3
minor metabolites	0.03	0.74	0.77
Sum	2.7	70.0	72.7

Metabolism

Afatinib was metabolised only to a minor extent in humans, which was consistent with in vitro studies and studies in animals. Metabolic patterns in plasma, urine and faeces were investigated after single oral administration of [14C]-afatinib to healthy male subjects. In addition, metabolism of afatinib was qualitatively investigated in cancer patients with various solid tumours. Urine and plasma samples on Day 14 following multiple oral administrations of 70 mg tablets once daily were selected for metabolic profiling. The metabolism was mainly governed by non enzyme-catalysed Michael adduct formation with proteins or nucleophilic small molecules. Other metabolism of afatinib proceeds via the following reactions: conjugate formation with electron-rich small molecules such as cysteine (m4), N-acetylcysteine (m13), glutathione and their breakdown products (Michael addition); and N-oxide formation (dimethylamino moiety) yielding m15 (FMO3). Due to the low amounts formed in vivo all metabolites can be classified as trace / minor pathways.

In plasma, [14C]-afatinib was the predominant radioactive compound that was detected by radioactivity detection (97.4 % of total extracted sample radioactivity at 1 h after dosing, 97.7 % at 4 h and 100 % at 6 h). Only a few trace metabolites of afatinib were detected. Non-extractable radioactivity was found in all plasma samples following oral [14C]–afatinib administration, considered as being covalently bound to plasma protein, which was expected due to the chemical structure of afatinib.

Afatinib was also found to be the major analyte in plasma of cancer patients after multiple administration of 70 mg afatinib. In addition, the metabolite m3 was detected in low amounts, but no other metabolite was detected with this qualitative investigation in plasma samples of cancer patients.

The most prevalent component in the excreta was the parent compound (88 % of the excreted radioactivity, 64.1 % of the dose), followed by m4 (6.7 % of the radioactivity in the excreta, 4.9 % of the dose), m13 (3.7 % of the excreted radioactivity, 2.7 % of the dose), and m15 (0.4 % of the excreted radioactivity, 0.3 % of the dose).

Additional qualitative information on the metabolism of afatinib in cancer patients was obtained by LC-MS analyses of urine samples taken on Day 14 after multiple administration of 70 mg afatinib once daily.

Dose proportionality and time dependencies

Dose proportionality, in the clinical dose range, was studied in healthy subjects. Healthy male volunteers received an oral dose of afatinib dimaleate in a single rising, sequential study design. Doses of 20, 30, 40 or 50 mg were administered using the final tablet formulation. There was a non-proportional increase in exposure with increase in dose in the studied dose range.

In a phase II MTD study, patients received a single oral dose of afatinib dimaleate, the day after they were dosed with docetaxel (60-75 mg/m^2), in a dose range of 10-160 mg. An over-proportional increase in exposure, with dose, was seen between 10 mg and 40 mg and then becoming proportional up to 160 mg.

The observed over-proportional increase of concentrations with increasing doses were characterized in the population PK analysis using a non-linear function for relative bioavailability (F1). F1 increased with increasing dose according to a power function with a power of 0.485 up to an estimated maximum dose of 70 mg from which F1 remained constant.

Steady state was reached at least within eight days following once daily dosing, which is in agreement with a terminal $t_{1/2}$ of about 35h. The exposure at steady state was about 2-3 times higher compared to a single dose. The overall accumulation ratio was 2.8 when based on total exposure and 2.1 when based on maximum plasma levels.

Afatinib did not induce CYP450 *in vitro* and was only metabolised to a minor extent by conventional metabolism *i.e.* enzyme catalyzed metabolism by that minimizing the risk for time dependency.

Target and Special populations

Target population

A population pharmacokinetic (PPK) analysis was conducted by the use of nonlinear mixed effects modelling in NONMEM to characterise the PK of afatinib and to evaluated the effect of intrinsic

and extrinsic factors. The analysis included data from studies in patients with different solid tumours, in total 927 patients (4460 observations).

The PK was described by a two-compartment disposition model with first order absorption and elimination. Absorption was characterized by a non-linear function for relative bioavailability (F). F increased according to a power function with a power of 0.49 up to 70 mg, followed by a proportional increase with dose. Significant covariates were ECOG (Eastern Cooperative Oncology Group) performance score, lactate dehydrogenase (LDH) and alkaline phosphatase (AP) influencing the afatinib exposure by affecting F. The exposure increased with increasing ECOG, LDH and AP levels. Furthermore, head & neck squamous cell carcinoma (HNSCC) patients had a significantly higher F than NSCLC or breast cancer patients. Weight (incorporated according to allometry), creatinine clearance (CRCL), sex and total protein (TPRO) were found to be statistically significant covariates on CL/F. CL/F increased with increasing WT. When CRCL was greater than 120 mL/min, CL/F was assumed to be constant, and otherwise it declined linearly with decreasing CRCL. Female patients had a slightly lower CL/F as compared to male patients and CL/F decreased with increasing TPRO. Lastly, increase in V2/F with increasing WT was also statistically significant. Age, smoking history, alcohol consumption and presence of liver metastases had no statistically significant impact on the PK of afatinib.

Renal impairment: Afatinib has not been studied in a dedicated trial in subjects with renal impairment. The effect of impaired renal function was explored in the population PK analysis using creatinine clearance (CRCL) (according to Cockcroft Gault formula) as a surrogate marker. CRCL was found to be a statistical significant covariate for CL/F, with exposure to afatinib moderately increased with decreasing CRCL. Compared with a patient with a CRCL of 79 mL/min (median in population), exposure to afatinib was predicted to increase by 13% and 42% for a patient with a CRCL of 60 mg/mL and 30mg/ml respectively and to decrease by 20% for a patient with a CRCL of 120 mL/min.

Hepatic impairment

A dedicated hepatic impairment study (single dose) indicated no relevant effect of mild (Child Pugh A, score 5-6) to moderate hepatic impairment (Child Pugh B, score 7-9) on afatinib exposure.

Gender, weight, race and age

The effect of gender, weight (range 31.4 to 134 kg), race and age (range 28 to 87 years) on the pharmacokinetics of afatinib was evaluated in the population pharmacokinetic analysis. No clinically relevant effects were observed. Gender was a statistically significant covariate for CL/F where female patients were predicted to a 15% higher plasma exposure ($AUC_{T,SS}$) than male patients. Weight was incorporated into the model according allometry on CL/F and V2/F and $AUC_{T,SS}$ was predicted to increase by 26% for a patient weighing 42 kg and to decreased by 22% for a patient weighing 95 kg compared to the average patient (62.5 kg). The PK was found not to be significantly different between Asian and Caucasian patients and age was not a significant covariate.

The exposure of afatinib in Japanese patients was evaluated in a MTD part of a phase I/II study with twelve patients included. The variability in PK was moderate to high. There was a slight tendency to higher exposure in the Japanese compared to the Caucasian patients at steady state

but the study concludes that the PK is comparable between the two groups. 50 mg afatinib dimaleate was chosen as the starting dose in the phase II step in the study. A 55 mg dose has been determined as the MTD in Caucasian patients.

Pharmacokinetic interaction studies

Effects of afatinib on other substances

Competitive and mechanism-based inhibition of cytochrome (CYP) P450 isoforms by afatinib maleate was investigated in human liver microsomes using specific probe substrates. For CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP4A11, competitive inhibition was low or absent at afatinib concentrations up to 100 µM. For CYP2C9 an IC50 value of 79.3 µM was determined. There was no indication of mechanism-based inhibition of CYP3A4 by afatinib up to 100 µM.

In primary human hepatocytes, afatinib up to 5 µM caused no relevant induction of enzyme activity or mRNA levels for CYP1A2, 2B6, 2C8, 2C9, 2C19 or 3A4.

In human liver microsomes, afatinib showed some inhibition of UGT1A1-mediated glucuronidation of estradiol and BIBF1202 (a metabolite to the experimental tyrosine kinase inhibitor nintedanib) with an IC50 value of 24.3 µM and a Ki of 10.9 µM, respectively.

In two different studies, afatinib concentration-dependently inhibited the transport of the known Pgp substrate digoxin over Caco-2 cell monolayers with a mean IC50 value of 24 µM or a Ki value of 3.4 µM, respectively. The interaction of afatinib with Pgp was also evaluated using monolayers of Pgp-expressing LLC-PK1 cells. In this study, afatinib inhibited digoxin transport with an IC50 value of 1.59 µM.

Afatinib showed concentration-dependent inhibition of the BCRP-mediated efflux of estrone-3-sulfate over Caco-2 cell monolayers. At the highest afatinib concentration (30 µM) the inhibition was of the same degree as for the known BCRP inhibitor fumitremorgin C. The mean IC50 value for afatinib BCRP inhibition was 0.75 µM.

Afatinib as inhibitor of human organic anion transporting-polypeptide (OATP) isoforms was investigated using HEK293 cells expressing OATP1B1, OATP1B3, or OATP2B1. Afatinib inhibited OATP1B1- and OATP1B3-mediated estradiol 17β-D-glucuronide uptake and OATP2B1-mediated estrone-3-sulfate uptake in a concentration-dependent manner with IC50 values of 82.8, 71.2, and 6.05 µM, respectively.

Inhibition of human organic cation transporter (OCT) isoforms was investigated using HEK293 cells expressing OCT1, OCT2 or OCT3. Afatinib inhibited OCT1 and OCT3-mediated transport of the probe substrate MPP+ in a concentration-dependent manner with IC50 values of 20.0 and 11.8 µM, respectively, while OCT2-mediated MPP+ transport was not relevantly inhibited by afatinib up to 100 µM.

Inhibition of the human organic anion transporter (OAT) isoforms by afatinib was evaluated using HEK293 cells expressing OAT1 or OAT3. Afatinib did not show strong inhibition of OAT1-mediated PAH uptake or OAT3-mediated E-sul uptake and the IC50 values were >100 µM.

Effects of other substances on afatinib

Afatinib has been shown to be a CYP3A4 and Pgp substrate *in vitro*. Three *in vivo* interaction studies have been performed. Two studies evaluated the interaction between afatinib and the CYP3A4/Pgp inhibitor ritonavir administered at different timepoints in relation to afatinib. The third study evaluated the effect of the strong inducer rifampicin on afatinib.

When the CYP3A4/Pgp inhibitor ritonavir was administered 1 hr before a 20 mg dose of afatinib AUC_{inf} and C_{max} increased by 48% and 38%, respectively, as compared with administration of afatinib alone. Median Tmax was unchanged, and afatinib distribution and elimination phases, including terminal $t_{1/2}$ and mean residence time (MRT), appeared to be similar with and without ritonavir, indicating that ritonavir affected bioavailability rather than elimination of afatinib. When administered simultaneously with or 6 hr after a 40 mg dose of afatinib, ritonavir had only a minor effect on afatinib AUC (20% and 10% increase, respectively) and basically no effect on Cmax.

Seven days of pre-treatment with rifampicin led to about 34% and 22% decreases in afatinib AUC_{inf} and C_{max}, respectively. Other pharmacokinetic parameters, such as Tmax, $t_{1/2}$ and mean residence time (MRT) were similar between the two treatments, indicating that the effect was primarily on bioavailability and not on elimination.

2.4.3. Pharmacodynamics

Mechanism of action

No specific clinical pharmacology studies have been submitted.

Primary and Secondary pharmacology

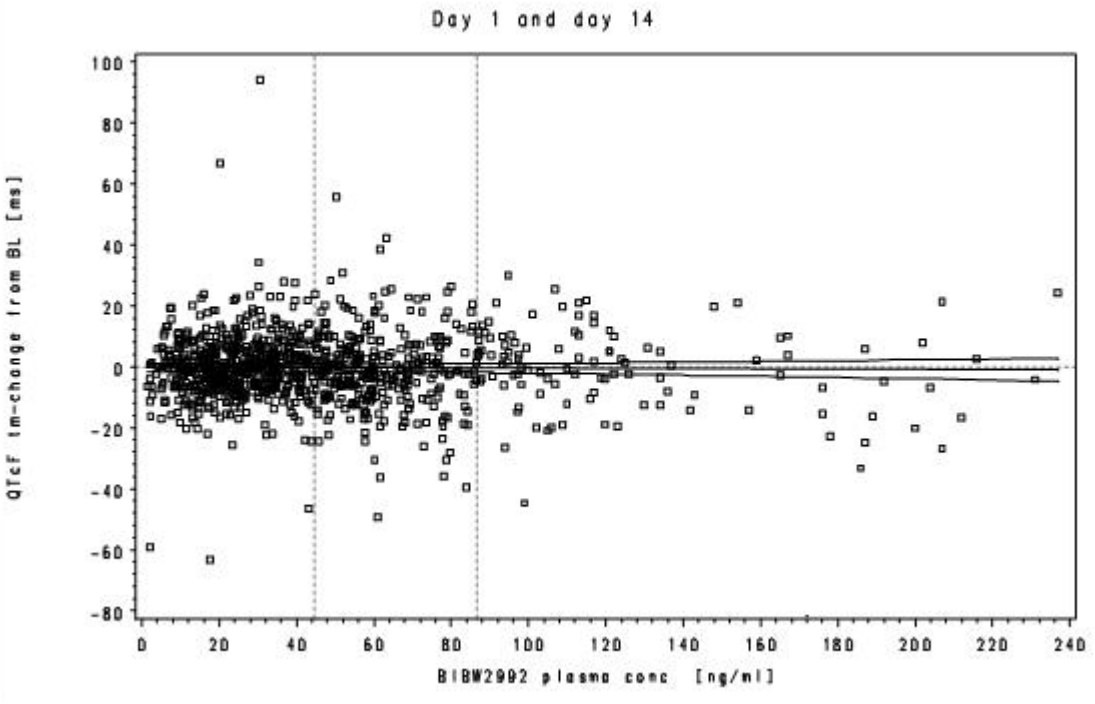
In the pivotal study 1200.32, no correlation between PK and efficacy could be established, although there was a weak trend towards a relationship between partial response and higher pre-dose concentrations at week 2 and 4.The relationship between AEs and trough afatinib plasma concentration was explored on Day 15 (Course 1). It was shown that median afatinib trough levels increased with the severity of diarrhea and rash/acne.

In the pivotal Trial 1200.32, NSCLC patients were dosed with 40 mg afatinib, but were dose-escalated to 50 mg afatinib in case of good tolerability and sequentially dose reduced to 30 mg and 20 mg afatinib in case of non-tolerated adverse events. Individual trough plasma concentrations suggested that patients who were dose reduced had originally higher plasma exposure and patients who were escalated to 50 mg had originally lower plasma exposure at 40 mg afatinib in comparison to the average exposure in the 40 mg dose group. After dose adjustments, plasma exposure was similar for all dose groups at Day 43 of afatinib treatment, the Day of the last PK observation. In addition, the variability decreased in the 40 mg dose group from 85 % (Day 22) to 66.5 % (Day 43).

Trial 1200.24 was designed to assess a potential impact on QTcF of continuous oral treatment with afatinib at a daily dose of 50 mg. Dose reductions to 40 mg/day or 30 mg/day were allowed in patients with drug-related toxicity.

Individual values for time-matched changes in QTcF from baseline and mean afatinib plasma concentrations are shown for Days 1 and 14 combined in Figure 6. Within the observed concentration range there was no signs of a QT prolonging effect.

Figure 6. Individual values for time-matched changes in QTcF from baseline and mean afatinib plasma concentrations for Days 1 and 14.



2.4.4. Discussion on clinical pharmacology

Definite conclusions on the relative importance of different elimination pathways, such as biliary excretion, metabolism and renal elimination, cannot be drawn from mass-balance data. However, taking all available data into account (e.g. *in vitro* permeability and transport data, mass-balance data, pharmacokinetics in renal and hepatic impairment, interaction data) and possible clinical consequences of different scenarios, the CHMP was of the opinion that conclusions on the interaction risk can be drawn based on already available data and that an absolute bioavailability study was not required.

Bioequivalence could not be shown between the final tablet and the test tablet used in the clinical program. However, the FF tablet has been used in the phase III studies, and the lack of demonstrated bioequivalence for the formulations used in certain exploratory studies is not considered to be critical for the interpretation of results.

Afatinib is for oral use. The tablets should be swallowed whole with water. If swallowing of whole tablets is not possible, these can be dispersed in approximately 100 ml of noncarbonated drinking water. No other liquids should be used. The tablet should be dropped into the water without crushing it, and stirred occasionally for up to 15 min until it is broken up into very small particles. The dispersion should be consumed immediately. The glass should be rinsed with

approximately 100 ml of water which should also be consumed. The dispersion can also be administered through a gastric tube.

An important feature of afatinib is the covalent binding to lysine residues on proteins. This property is desirable from a pharmacodynamic point of view, but as the binding increases over time and causes a very long retention time of the drug in the body, concerns were raised regarding the long-term safety of afatinib treatment. These concerns have been adequately addressed in the RMP and further data will be provided post-authorisation by the applicant to determine the time needed to complete washout of afatinib: a PK sampling for non-covalently bound afatinib after cessation of treatment in patients who have been treated long-term with afatinib.

As the time needed for complete elimination of afatinib is unknown and there are no or limited amount of data from the use of this medicinal product in pregnant women, the risk for humans is thus unknown. Therefore, if used during pregnancy or if the patient becomes pregnant while or after receiving afatinib, she should be informed of the potential hazard to the foetus. In addition, as a precautionary measure, women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with afatinib. Adequate contraceptive methods should be used during therapy and for at least 1 month after the last dose. This information has been adequately highlighted in section 4.6 of the SmPC.

In vivo afatinib was metabolised only to a minor extent and the metabolism was governed by Michael adduct formation to proteins or nucleophilic small molecules. It was found that metabolism generally is of subordinate role for afatinib and that specifically enzyme-catalyzed oxidative metabolic reactions play a negligible role for the metabolism of afatinib in vivo.

Higher exposure to afatinib has been observed in female patients, patients with lower body weight and those with underlying renal impairment. This could result in a higher risk of developing adverse reactions in particular diarrhoea, rash/acne and stomatitis. Closer monitoring is recommended in patients with these risk factors. This has been adequately highlighted in section 4.4 of the SmPC.

It appears that moderate differences in afatinib exposure can be adequately handled by dose adjustments based on tolerability. Therefore, moderate increases in exposure due to intrinsic and extrinsic factors may not need to lead to adjustment of the starting dose. The SmPC includes adequate recommendations in sections 4.2 and 5.2.

In vitro studies have demonstrated that afatinib is a substrate of P-gp and BCRP. When the strong P-gp and BCRP inhibitor ritonavir (200 mg twice a day for 3 days) was administered 1 hour before a single dose of 20 mg afatinib, exposure to afatinib increased by 48% (area under the curve (AUC0-∞)) and 39% (maximum plasma concentration (Cmax)). In contrast, when ritonavir was administered simultaneously or 6 hours after 40 mg afatinib, the relative bioavailability of afatinib was 119% (AUC0-∞) and 104% (Cmax) and 111% (AUC0-∞) and 105% (Cmax), respectively. Therefore, it is recommended to administer strong P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) using staggered dosing, preferably 6 hours or 12 hours apart from afatinib. Adequate information has been included in section 4.5 of the SmPC.

Pre-treatment with rifampicin (600 mg once daily for 7 days), a potent inducer of P-gp, decreased the plasma exposure to afatinib by 34% (AUC0-∞) and 22% (Cmax) after administration of a single dose of 40 mg afatinib. Strong P-gp inducers (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital or St. John's Wort (Hypericum perforatum)) may decrease exposure to afatinib. Adequate information has been included in section 4.5 of the SmPC.

Based on in vitro data, afatinib is a moderate inhibitor of P-gp. However, based on clinical data it is considered unlikely that afatinib will result in changes of the plasma concentrations of other P-gp substrates. Adequate information has been included in sections 4.4 and 4.5 of the SmPC.

In vitro studies indicated that afatinib is a substrate and an inhibitor of the transporter BCRP. Afatinib may increase the bioavailability of orally administered BCRP substrates (including but not limited to rosuvastatin and sulfasalazine). Adequate information has been included in section 4.5 of the SmPC.

In vitro data indicated that drug-drug interactions with afatinib due to inhibition of OATB1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, and OCT3 transporters are considered unlikely. Adequate information has been included in section 5.2 of the SmPC.

In humans it was found that enzyme-catalyzed metabolic reactions play a negligible role for the metabolism of afatinib. Approximately 2% of the afatinib dose was metabolized by FMO3 and the CYP3A4-dependent N-demethylation was too low to be quantitatively detected. Afatinib is not an inhibitor or an inducer of CYP enzymes. Therefore, afatinib is unlikely to interact with other medicines that modulate or are metabolised by CYP enzymes. Adequate information has been included in section 5.2 of the SmPC.

In vitro data indicated that drug-drug interactions with afatinib due to inhibition of UGT1A1 are considered unlikely. Adequate information has been included in section 5.2 of the SmPC.

Importantly, co-administration of a high-fat meal with afatnib resulted in a significant decrease of exposure to afatinib by about 50% in regard to Cmax and 39% in regard to AUC0-∞. The SmPC includes adequate information in sections 4.2, 4.5 and 5.2 indicating that afatinib should be administered without food.

2.4.5. Conclusions on clinical pharmacology

Based on the clinical pharmacology data afatinib has been adequately in the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).

2.5. Clinical efficacy

The proposed indication for afatinib is the treatment of patients with locally advanced or metastatic NSCLC with EGFR mutation(s). The evaluation of efficacy supporting this indication is based on 1 pivotal (1200.32) and 3 supportive trials (1200.22, 1200.23, and 1200.42) in patients with pathologic confirmation of stage IIIB or stage IV NSCLC. An overview of the characteristics of the 4 main trials included in the efficacy evaluation is provided in Table 20.

Table 20. Main trials included in the evaluation of efficacy

Trial	Regions	EGFR mutation status	Line of treatment	Prior EGFR TKI	Afatinib starting dose	Comparator	Number of treated patients per group
Pivotal trial							
1200.32 LUX-Lung 3	Asia, Europe, North America, South America	Positive	First	No	40 mg	Chemo [1]	Afatinib: 229 Chemo: 111
Supportive trials							
1200.22 LUX-Lung 2	Taiwan, USA	Positive	First or second	No	40 mg or 50 mg	None	129 (40 mg: 30; 50 mg: 99)
1200.23 LUX-Lung 1	Asia, Europe, North America	Clinical enrichment [2]	Third or fourth	Yes	50 mg	Placebo	Afatinib: 390 Placebo: 195
1200.42 LUX-Lung 5	Asia, Europe, South America	Clinical enrichment [2]	Second or later	Yes	50 mg	None [3]	1154

[1] Chemotherapy with pemetrexed/cisplatin
[2] Knowledge or testing of EGFR mutation status at study entry was not required.
[3] Only data from the uncontrolled trial Part A are included in the evaluation of efficacy.

In addition study 1200.34/LUX-Lung 6 was provided during the procedure. LUX-Lung 6 was a randomised, open-label, phase III study of afatinib versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR-activating mutation.

2.5.1. Dose response studies

Three dose-escalation trials were undertaken in patients with a variety of solid tumours (1200.2, 1200.3, and 1200.4) in order to define the recommended phase II dose (RPIID). Dose limiting toxicities were found to be diarrhoea (16 of 171 patients), dehydration (7 patients of 171 patients), skin reactions (5 patients of 171 patients) and fatigue (2 patients of 171 patients). Based on these data, the RPIID was found to be 50 mg q.d. Additional data from the Phase I trial 1200.17 (i.e. the extension trial of trials 1200.1 and 1200.2) supported this finding. The frequency of dose-limiting toxicities (DLTs) increased with afatinib dose, as did the frequency and severity of a number of commonly-reported drug-related AEs. DLTs of diarrhoea and dehydration occurred more frequently at daily doses of afatinib 55 mg and above.

Additional data from the supportive study 1200.22 / Lux Lung 2 (see full details in the Supportive Studies section) which included patients receiving both 40 mg and 50 mg afatinib starting dose, showed that efficacy results where comparable, however tolerability of the highest dose (50 mg) was lower than the 40 mg. Any AE leading to dose reduction were 9 (30.0%) vs 63 (63.6%); Serious AEs 5 (16.7%) vs 37 (37.4%) and Investigator defined drug-related serious AEs 2 (6.7%) vs 12 (12.1%) for afatinib 40 mg and 50 mg, respectively. Based on these results the

pivotal trial (study 1200.32) was amended to reduce the starting dose to 40 mg once daily after knowing results from study 1200.22.

2.5.2. Main studies

Title of Study

Study 1200.32/LUX-Lung 3 - A randomised, open-label, phase III study of afatinib versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR-activating mutation.

Methods

Study Participants

Main inclusion criteria:

1. Pathologically confirmed diagnosis of Stage IIIB (with cytologically proven pleural effusion or pericardial effusion) or Stage IV adenocarcinoma of the lung. Patients with mixed histology were eligible if adenocarcinoma was the predominant histology.

2. EGFR mutation detected by central laboratory analysis of tumour biopsy material.

For the tumour tissue samples, DNA extraction and amplification using real-time PCR was performed. Genotyping of the most frequent EGFR mutations was conducted using an established real-time polymerase chain reaction (PCR) protocol together with fluorescence detection (TheraScreen®: EGFR29 Mutation Kit, DxS Product Code EG-51, QIAGEN Manchester Ltd, Manchester, UK). In addition, a central pathology review was performed, including an assessment of the percentage of tumour involvement; the results were not reported to the investigator.

3. Measurable disease according to RECIST version 1.1.

4. Eastern Cooperative Oncology Group (ECOG) score of 0 or 1.

5. Age≥18years.

6. Life expectancy of at least 3 months.

Main exclusion criteria:

1. Prior chemotherapy for relapsed or metastatic NSCLC. Neoadjuvant or adjuvant chemotherapy was permitted if at least 12 months had elapsed between the end of chemotherapy and randomisation.

2. Prior treatment with EGFR-targeting small molecules or antibodies.

3. Radiotherapy or surgery (other than biopsy) within 4 weeks prior to randomisation.

4. Active brain metastases (defined as stable for <4 weeks and/or symptomatic and/or requiring treatment with anticonvulsants or steroids and/or leptomeningeal disease).

5. Any other current malignancy or malignancy diagnosed within the past 5 years (other than non-melanomatous skin cancer and in situ cervical cancer).

6. History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3, unstable angina or poorly controlled arrhythmia. Myocardial infarction within 6 months prior to randomisation.

7. Cardiac left ventricular function with resting ejection fraction of less than 50%.

Treatments

In the afatinib arm the starting dose was 40 mg once daily. Afatinib was to be taken once daily at approximately the same time each day at least 1 hour before food intake and at least 3 hours after food intake. Patients with pre-specified AEs during Course 1, i.e., diarrhoea or skin-related AEs or mucositis of any CTCAE Grade, or any drug-related AE of CTCAE Grade ≥2 were to continue afatinib at 40 mg once daily unless dose reduction was necessary. Patients with limited side effects during Course 1 (i.e., none of the above events occurred) were to increase the afatinib dose to 50 mg once daily from Course 2 onwards. The afatinib dose for these patients was 50 mg once daily for subsequent courses unless dose reduction was necessary.

In the chemotherapy arm, patients were to receive pemetrexed (500 mg/m2) followed by cisplatin (75 mg/m2) on Day 1 of each 21-day treatment course. Patients were to receive 6 treatment courses unless they developed documented disease progression, experienced unacceptable side effects, or the patient or the investigator requested permanent discontinuation of the study medication. Haematology assessment was to be performed before each new treatment course and the next treatment course was to be delayed for patients with a platelet count <100,000 /mm3 or ANC <1500 /mm3.

Patients were to receive supportive care with anti-emetics, hydration, and vitamin supplements during chemotherapy in accordance with the current SmPC of the supplied medication and institutional guidelines.

Objectives

The trial objective was to compare the efficacy and safety of afatinib monotherapy with pemetrexed / cisplatin chemotherapy as first-line treatment for these patients.

Outcomes/endpoints

The primary endpoint was progression-free survival (PFS) as assessed by central independent review according to RECIST version 1.1.

PFS was defined as the time from randomisation to disease progression (or death if the patient died before progression).

The key secondary endpoints of this trial were:

- Objective response (defined as complete response [CR], or partial response [PR]) according to RECIST version 1.1 (time to objective response, duration of objective response)

- Disease control (defined as a patient with objective response or stable disease [SD]) according to RECIST version 1.1 (duration of disease control)

- Overall survival (OS)

Other secondary endpoints were

- Tumour shrinkage (as specified in the trial statistical analysis plan [TSAP])

- Change from baseline in body weight (as specified in the TSAP)

- Change from baseline in Eastern Cooperative Oncology Group (ECOG) performance status (as specified in the TSAP)

- Health-Related Quality of Life (HRQOL) as measured by standardised questionnaires (European Organisation for Research and Treatment of Cancer [EORTC] quality of life questionnaires C30 [QLQ-C30] and lung cancer module [QLQ-LC13], with the pre-specified endpoints cough (QLQ-LC13 question 1), dyspnoea (composite of QLQ-LC13 questions 3-5; individual item from QLQ-C30 question 8), and pain (composite of QLQ-C30 questions 9 and 19; individual items from QLQ-LC13 questions 10, 11, 12)

- Pharmacokinetics of afatinib

- Safety of afatinib as indicated by the incidence and severity of adverse events, graded according to the US NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and changes in safety laboratory parameters.

Sample size

It was estimated that 217 PFS events would provide 90% power for the log-rank test, presuming a hazard ratio of 0.64 for afatinib relative to pemetrexed / cisplatin chemotherapy.

It was planned to enter 330 patients, i.e., 220 patients in the afatinib arm and 110 patients in the pemetrexed / cisplatin chemotherapy arm.

Randomisation

Patients were randomised (ratio 2:1) to receive either afatinib or pemetrexed / cisplatin. The randomisation was stratified according to EGFR mutation category (L858R vs. Del 19 vs. Other) and race (Asian vs. Non-Asian).

Blinding (masking)

This was an open-label trial due to the inherent differences between the 2 treatment arms (patients randomised to the afatinib arm received oral tablets while patients randomised to the chemotherapy arm received an intravenous infusion).

Statistical methods

Planned analyses

For this trial, 2 analysis data sets were defined; these were the randomised set (RS) and the treated set (TS). The randomised set included all patients who were randomised to receive treatment, whether treated or not. The RS was used for tables about demographic and other baseline characteristics as well as for the primary evaluation of efficacy.

The treated set included all randomised patients who were documented to have taken at least 1 dose of study medication (i.e., afatinib or pemetrexed / cisplatin). Patients were allocated according to the treatment actually received. The TS was used for the safety analyses.

Primary analyses

The primary endpoint was progression-free survival (PFS) as assessed by central independent review according to the modified RECIST version 1.1 criteria.

A stratified log-rank test (2-sided, α = 0.05) was used to test for the effect of afatinib on PFS compared with pemetrexed / cisplatin chemotherapy. The test included the 2 stratification factors used at randomisation, i.e., EGFR mutation category (L858R vs. Del 19 vs. Other) and race (Asian vs. Non-Asian).

Overall survival

Overall Survival (months), defined as the time from randomisation to death, was formally analysed twice. The first analysis was the analysis at the time of the primary PFS analysis and the second was performed at a time when more complete information is available on OS. To preserve the overall 1-sided α-level of 0.025, a Haybittle-Peto stopping boundary was used (p-value <0.0001) for the first analysis. A stratified log-rank test was used to test the effect of afatinib on OS compared with pemetrexed / cisplatin chemotherapy. The test included the 2 stratification factors used at randomisation, i.e., EGFR mutation category and race. A Cox proportional hazards model, also stratified by EGFR mutation category and race, was used to estimate the hazard ratio and 95% CI between the 2 treatment arms. Additional summaries were produced to explore the potential impact of subsequent anti-cancer therapy on OS.

Interim analyses

A decision of whether to proceed to full accrual was to be performed based on the first 40 patients randomised to treatment with afatinib, using all radiological imaging data recorded up to and including the planned Week 6 imaging data of the 40th patient. The trial was to proceed to full accrual after the DMC had certified that at least 16 of the first 40 patients randomised to treatment with afatinib had responded. Otherwise accrual was to be paused and the DMC was to perform a general risk/benefit assessment of whether to resume accrual or stop recruitment into the trial. The determination of the best overall response for each patient was based on investigator assessment. This trial was not stopped and preceded to full accrual. Note: Protocol amendment 2 specified this analysis of the response of the first 40 patients randomised to treatment with afatinib.
The DMC was to review the safety data of all patients approximately every 6 months. During these regular meetings, the DMC could examine PFS and OS to completely assess the risk-benefit advantage of afatinib. The significance level for the primary analysis of PFS was not to be adjusted for possible interim looks by the DMC.

Health related Quality of Life (HRQL)

The EORTC QLQ-C30 comprises 30 questions, using both multi-item scales and single-item measures. These include a global health status / HRQOL scale, 5 functional scales, 3 symptoms scales, and 6 single items to assess dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties. Each of the multi-item scales includes a different set of items; no item occurs in more than 1 scale. The EORTC QLQ-LC13 module comprises 13 questions. The module was designed for use in patients receiving treatment with chemotherapy or radiotherapy. The EORTC QLQ-LC13 incorporates 1 multi-item scale to assess dyspnoea, and a series of single items to assess pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and haemoptysis. The pre-specified HRQOL endpoints were the time to deterioration for cough (QLQ-LC13 question 1), dyspnoea (composite of QLQ-LC13 questions 3-5), and pain (composite of QLQ-C30 questions 9 and 19). In addition, the 3 alternative measures of pain (QLQ-LC13 questions 10, 11, 12) were examined descriptively for consistency with the composite of QLQ-C30 questions 9 and 19, as well as the measure of dyspnoea (QLQ-C30 question 8) was compared with the composite of QLQ-LC13 questions 3-5. The EQ-5D questionnaire consists of the EQ-5D descriptive system and a visual analogue scale. The EQ-5D descriptive system comprises the 5 dimensions of mobility, self-care, usual activities, pain / discomfort, and anxiety / depression, with 3 levels per each dimension (levels: no problems; some problems; severe problems). The patients indicate their health state by ticking the box against the most appropriate statement in each of the 5 dimensions. The visual analogue scale records the patient's self-rated health status on a vertical, graduated (0 - 100) scale.

HRQOL was assessed at the time points specified in the flow chart below:

	Screening [1]		Courses 1 to 2 [2]		Course ≥3 [2]	EOT [3]	FU [4]	OP [5]
	Visit 1	Visit 2	Visit 1	Visit 2				
Days	≤6 weeks before treatment start	≤28 days before treatment start	Day 1 (±2 days)	Day 8 (±2 days)	Day 1 (±2 days)			
HRQOL, caregiver support assessment			X		X	X	X	

The respective questionnaires were to be completed by the patients at the site before they saw the investigator, prior to clinical assessment, prior to any treatment at the clinic, and before the patients were provided with any new information about their disease status, in order to avoid influencing the responses.

Results

Participant flow and Recruitment

The first patient was enrolled in the trial on 17 August 2009; the last patient was entered into the trial on 28 February 2011. Overall, 1269 patients were screened in 133 centres in 25 countries; and 345 patients were randomised. About two thirds of randomised patients were from Asia, about one fifth of randomised patients were from Europe.

About 30% of the enrolled patients were eligible for the trial. Altogether 924 patients were not randomised; 817 of those patients had a tumour sample that was EGFR mutation negative (see Table 21). Of the remaining 452 patients with an EGFR mutation positive tumour sample, 58 patients did not meet the inclusion or exclusion criteria; 24 patients withdrew their consent; 5 patients were not randomised due to AEs; 5 patients were lost to follow-up; and 15 patients were not randomised due to other reasons.

Table 21. Disposition of patients/all patients

	Afatinib N (%)	Chemotherapy N (%)	Total N (%)
Patients enrolled			1269
Patients not randomised			924
Patients randomised	230	115	345
Patients not treated	1	4	5
Patients treated[1]	229 (100.0)	111 (100.0)	340 (100.0)
Treatment discontinued	164 (71.6)	111 (100.0)	275 (80.9)
Completed 6 courses of chemotherapy[2]	n.a.	60 (54.1)	60 (17.6)
Progressive disease[3]	133 (58.1)	19 (17.1)	152 (44.7)
Other AE	23 (10.0)	17 (15.3)	40 (11.8)
Non-compliance with protocol[4]	1 (0.4)	4 (3.6)	5 (1.5)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Refusal to continue intake of study medication	6 (2.6)	11 (9.9)	17 (5.0)
Other[5]	1 (0.4)	0 (0.0)	1 (0.3)
On treatment at the cut-off date	65 (28.4)	0 (0.0)	65 (19.1)

Abbreviations: n.a. = not applicable.

1 Patients who received at least 1 dose of study medication (i.e., afatinib or pemetrexed / cisplatin).

2 Includes patients who progressed after 6 courses of chemotherapy.

3 On treatment.

4 The principal investigator considered the chemotherapy complete after 4 courses (3 patients in the chemotherapy arm; based on ASCO guidelines); radiation therapy was needed (1 patient in the afatinib arm); or the patient preferred treatment in another hospital (1 patient in the chemotherapy arm; see Appendix 16.2.1, Listing 1).

5 Patient 3502005 took the last dose of study medication on 19 October 2010; on 21 October 2010 the patient experienced a sepsis that was fatal on 22 October 2010 ((Appendix 16.2.7, Listing 2.1)). The investigator recorded that the treatment was discontinued due to 'Other' reason = patient died (Appendix 16.2.1, Listing 1).

Important protocol violations

More patients randomised to the afatinib arm (28.3%) than patients in the chemotherapy arm (15.7%) were reported to have important protocol violations. The most frequent protocol violations were intake of incorrect trial medication (mainly not following the protocol pre-specified dose modification scheme; afatinib 15.2% of patients; chemotherapy 1.7%), violations of the entrance criteria (afatinib 7.0%; chemotherapy 10.4%), and non-adherence to safety-related withdrawal criteria (patient continued in the study after PD according to RECIST 1.1; afatinib 6.1%; chemotherapy 0.9%). No patients with a protocol violation have been excluded from the primary analysis.

Conduct of the study

There were two amendments to the protocol:

Amendment 1:

Exclusion criterion 21 was changed; it originally referred to patients randomised to treatment with chemotherapy only. As the consent process took place before randomisation, it was necessary to cover both treatment arms with this exclusion criterion.

The restricted medications during treatment with afatinib were changed. It was specified that the list of restricted medications refers to all patients randomised. An additional explanatory paragraph was added that the concomitant use of potent P-gp inhibitors and inducers was to be avoided during treatment with afatinib. The background was that a trial (1200.79) in healthy volunteers indicated that co-administration of these drugs affected the pharmacokinetics of afatinib.

Amendment 2:

Several changes and corrections were introduced with the second amendment to the protocol; major changes are presented below.

It was specified that the trial had 2 screening visits. During the first screening visit, the patient signed the first informed consent and agreed to the EGFR mutation testing. During the second screening visit only for patients with a positive EGFR mutation testing, patients signed a second informed consent and agreed to participate in the main part of the trial. The original protocol allowed for collection of AEs and concomitant medications as well as collection of demographic information at the first screening visit; this was not covered by the first informed consent. This error was corrected with protocol amendment 2.

The strict time window for afatinib intake was removed to accommodate individual patient's daily schedule preference because afatinib has a long half-life. The old instruction to take afatinib "at the same time each day (±2 hours) at least 1 hour before food intake and at least 3 hours after food intake" was replaced by the information that afatinib was to be taken "at approximately the same time each day at least 1 hour before food intake and at least 3 hours after food intake".

The concomitant medication for patients randomised to treatment with pemetrexed / cisplatin was modified to allow for local variation in the pre-treatment with folic acid. Patients treated with pemetrexed were to receive at least 5 doses of oral folic acid or a multivitamin containing folic acid during the 7 days prior to commencing treatment according to the SPC or local institutional practice.

The length of the observation period of this trial was specified. It was added that the observation period may end earlier depending upon the timing of analyses requested by regulatory authorities.

It was specified that the decision of whether to proceed to full accrual was based on the first 40 patients randomised to treatment with afatinib whether or not they had stopped treatment before the Week 6 assessment. Furthermore, it was emphasised that the DMC could stop the trial if less than 16 of these patients showed a response to treatment.

New information was added to the appendix of the protocol. The appendix was updated with the current SPC of cisplatin provided for the trial. In addition, the RECIST version 1.1 criteria in the appendix were updated to ensure consistency with the imaging charter for the central independent review of radiological imaging.

Baseline data

The baseline demographic and oncological history are summarised in Tables 22a and 22b:

Table 22a: Demographics by treatment

	Afatinib		Chemotherapy		Total	
Patients [N (%)]	230	(100.0)	115	(100.0)	345	(100.0)
Gender [N (%)]						
Male	83	(36.1)	38	(33.0)	121	(35.1)
Female	147	(63.9)	77	(67.0)	224	(64.9)
Age, mean (StD) [years]	60.5 (10.1)		59.9 (10.0)		60.3 (10.1)	
Age categories [N (%)]						
<65 years	140	(60.9)	71	(61.7)	211	(61.2)
≥65 years	90	(39.1)	44	(38.3)	134	(38.8)
Race group [N (%)]						
Caucasian	61	(26.5)	30	(26.1)	91	(26.4)
Eastern Asian	165	(71.7)	83	(72.2)	248	(71.9)
Other Asian	1	(0.4)	0	(0.0)	1	(0.3)
Other	3	(1.3)	2	(1.7)	5	(1.4)
Geographical region [N (%)]						
Europe[1]	47	(20.4)	27	(23.5)	74	(21.4)
North America[2]	2	(0.9)	0	(0.0)	2	(0.6)
Asia[3]	160	(69.6)	83	(72.2)	243	(70.4)
Other[4]	21	(9.1)	5	(4.3)	26	(7.5)
Smoking status [N (%)][5]						
Never smoked	155	(67.4)	81	(70.4)	236	(68.4)
Ex-smoker	70	(30.4)	32	(27.8)	102	(29.6)
Current smoker	5	(2.2)	2	(1.7)	7	(2.0)
Weight, mean (StD) [kg]	61.06 (12.87)		58.53 (12.08)		60.22 (12.65)	
Body mass index, mean (StD) [kg/m²]	23.855 (4.053)		22.963 (3.995)		23.557 (4.050)	
ECOG performance score at baseline [N (%)]						
0	92	(40.0)	41	(35.7)	133	(38.6)
1	138	(60.0)	73	(63.5)	211	(61.2)
2[6]	0	(0.0)	1	(0.9)	1	(0.3)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; StD = standard deviation.

1 Austria, Belgium, France, Germany, Hungary, Ireland, Italy, Romania, Russia, Ukraine, and the United Kingdom.

2 Canada and the United States of America.

3 Hong Kong, Japan, Korea, Malaysia, Philippines, Taiwan, and Thailand.

4 Argentina, Australia, Brazil, Chile, and Peru.

5 As documented in the eCRF. Never smoked was defined as <100 cigarettes/lifetime.

6 At screening, the ECOG performance score was 0 for this patient (patient 4308001), i.e., the patient was eligible for the trial. Before start of treatment, the ECOG performance score worsened to 2.

Table 22b: Oncological history by treatment

	Afatinib		Chemotherapy		Total	
Patients [N (%)]	230	(100.0)	115	(100.0)	345	(100.0)
Time since first diagnosis, median (range) [months]	1.10 (0.0 - 103.1)		1.00 (0.0 - 91.6)		1.00 (0.0 - 103.1)	
Clinical stage at screening [N (%)][1]						
IIIB	20	(8.7)	17	(14.8)	37	(10.7)
IV	210	(91.3)	98	(85.2)	308	(89.3)
Any metastases at screening [N (%)]	229	(99.6)	113	(98.3)	342	(99.1)
Location of metastatic sites [N (%)]						
Pleural effusion	102	(44.3)	49	(42.6)	151	(43.8)
Bone	115	(50.0)	40	(34.8)	155	(44.9)
Brain	27	(11.7)	15	(13.0)	42	(12.2)
Liver	38	(16.5)	13	(11.3)	51	(14.8)
Other	163	(70.9)	79	(68.7)	242	(70.1)

Abbreviations: StD = standard deviation.
[1] Based on the American Joint Committee on Cancer (AJCC) staging system, 6th edition.

Randomisation was stratified by EGFR mutation category (L858R vs. Del 19 vs. Other) and race (Asian vs. Non-Asian) (see Table 23).

Table 23a. Stratification factors at baseline by treatment / RS

	Afatinib N (%)		Chemotherapy N (%)		Total N (%)	
Patients	230	(100.0)	115	(100.0)	345	(100.0)
EGFR mutation category						
L858R[1]	91	(39.6)	47	(40.9)	138	(40.0)
Del 19 alone	113	(49.1)	57	(49.6)	170	(49.3)
Other	26	(11.3)	11	(9.6)	37	(10.7)
Race category						
Asian	166	(72.2)	83	(72.2)	249	(72.2)
Non-Asian	64	(27.8)	32	(27.8)	96	(27.8)

Abbreviations: EGFR = Epidermal Growth Factor Receptor.
Stratification factors as documented in the eCRF.
[1] If both L858R and a deletion in exon 19 were detected in the same sample, the patient was to be allocated to the stratification category 'L858R'; there was no patient with a sample with L858R and Del 19.

The small subgroup of patients with 'Other' EGFR mutations was genetically heterogeneous; altogether 10 different genetic subtypes of 'Other' EGFR mutations were identified (see Table 23b)

Table 23b. Patients with 'Other' EGFR mutations by treatment / RS

	EGFR mutation	Afatinib N (%)		Chemotherapy N (%)		Total N (%)	
Patients		230	(100.0)	115	(100.0)	345	(100.0)
'Other' EGFR mutation							
T790M	T790M only	2	(0.9)	0	(0.0)	2	(0.6)
	Del 19 + T790M	3	(1.3)	0	(0.0)	3	(0.9)
	L858R + T790M	5	(2.2)	2	(1.7)	7	(2.0)
	G719S, G719A, and G719C + T790M	1	(0.4)	0	(0.0)	1	(0.3)
Exon 20 insertions	Exon 20 insertion only	6	(2.6)	3	(2.6)	9	(2.6)
S768I	S768I only	1	(0.4)	0	(0.0)	1	(0.3)
	L858R + S768I	2	(0.9)	0	(0.0)	2	(0.6)
G719X[1]	G719S, G719A, and G719C only	3	(1.3)	1	(0.9)	4	(1.2)
	G719S, G719A, and G719C + S768I	0	(0.0)	2	(1.7)	2	(0.6)
L861Q	L861Q only	3	(1.3)	3	(2.6)	6	(1.7)

Abbreviations: EGFR = Epidermal Growth Factor Receptor.
EGFR mutation category as documented in the eCRF.
[1] G719S, G719A, or G719C.

Numbers analysed

The primary evaluation of efficacy in this trial was based on the randomised set, i.e., all randomised patients, regardless of whether treated or not. Of the 345 patients in the randomised set (afatinib 230 patients; chemotherapy 115 patients), 340 patients (afatinib 229 patients; chemotherapy 111 patients) were documented to have taken at least 1 dose of study medication and were included in the treated set (see Table 24).

Table 24. Patient analysis sets with primary reason for exclusion / RS

	Afatinib 40	Pe500+Cis75	Total
Randomised Set	230 (100.0)	115 (100.0)	345 (100.0)
Treated Set (TS)	229 (99.6)	111 (96.5)	340 (98.6)
Not in TS for following reason:			
Not treated	1 (0.4)	4 (3.5)	5 (1.4)
Reduced Assay Set (ASSAY)#	173 (75.2)	79 (68.7)	252 (73.0)
Not in ASSAY for following reason:			
Mutation not in reduced assay	57 (24.8)	36 (31.3)	93 (27.0)

Outcomes and estimation

Primary endpoint

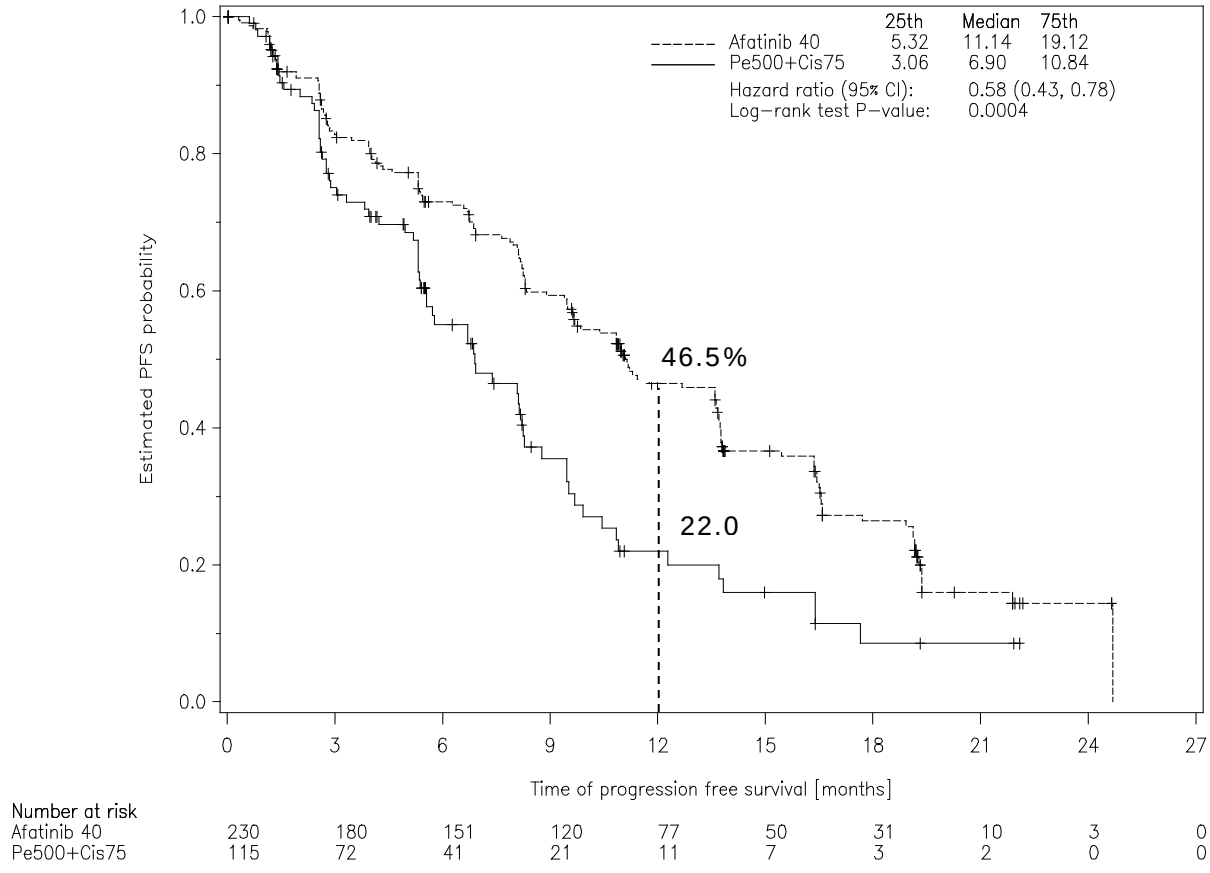
The primary analysis of progression-free survival by central independent review is summarised in Table 25 and Figure 7.

Table 25. PFS based on central independent review (RS).

	Afatinib	Chemotherapy
Patients [N (%)]	230 (100.0)	115 (100.0)
Patients with PFS event [N (%)]	152 (66.1)	69 (60.0)
PFS time [months]		
25th percentile (95% CI)	5.32 (3.98, 6.87)	3.06 (2.56, 5.32)
Median (95% CI)	11.14 (9.63, 13.63)	6.90 (5.39, 8.25)
75th percentile (95% CI)	19.12 (16.49, 19.35)	10.84 (8.77, 16.39)
Hazard ratio vs. chemotherapy[1]	0.577	
95% CI	(0.425, 0.784)	
p-value (2-sided)[2]	0.0004	

Abbreviations: CI = confidence interval.
[1] Hazard ratio derived from a Cox proportional hazard model stratified by EGFR mutation category and race.
[2] Derived from a log-rank test stratified by EGFR mutation category and race.

Figure 7: Kaplan-Meier estimates of PFS based on central independent review in trial 1200.32 /RS



A total of 78 patients (33.9% of randomised patients) in the afatinib arm and 46 patients (40.0%) in the chemotherapy arm were censored for the primary PFS analysis. The main reasons for censoring differed between the 2 treatment arms: In the afatinib arm, 23.0% of patients were censored because they were alive and progression-free at the cut-off date. In contrast, 28.7% of chemotherapy patients were classified as having been censored due to the start of a new anti-cancer therapy.

Investigators stopped tumour imaging after they judged that a patient had progressed. Most patients then began additional anti-cancer treatment. If the central independent review classified such patients as not having progressed, they are presented in Table 26 as being censored because of the start of new treatment, as no further imaging was available for central independent review.

Table 26: Summary of censoring for PFS based on central independent review

	Afatinib N (%)	Chemotherapy N (%)
Patients	230 (100.0)	115 (100.0)
Patients with PFS event	152 (66.1)	69 (60.0)
Disease progression	150 (65.2)	69 (60.0)
Death	2 (0.9)	0 (0.0)
Patients censored	78 (33.9)	46 (40.0)
Alive and no progression at the cut-off date	53 (23.0)	5 (4.3)
New anti-cancer therapy	20 (8.7)	33 (28.7)
No post-baseline imaging, alive, and no progression during the trial	3 (1.3)	8 (7.0)
No post-baseline imaging, death or progression after the second scheduled imaging	1 (0.4)	0 (0.0)
2 or more consecutively missed images immediately prior to death	1 (0.4)	0 (0.0)

Source data: Tables 15.2.1.1: 4, 15.2.1.1: 3, 15.2.1.2.2: 13

Secondary endpoints

- Objective response and disease control

Results on objective response and disease control are shown in Table 27.

Table 27. Objective response and disease control based on central independent review/RS

	Afatinib	Chemotherapy
Patients [N (%)]	230 (100.0)	115 (100.0)
Objective response [N (%)]	129 (56.1)	26 (22.6)
95% CI[1]	(49.4, 62.6)	(15.3, 31.3)
Odds ratio vs. chemotherapy[2]	4.660	
95% CI	(2.774, 7.828)	
p-value (2-sided)	<0.0001	
Disease control [N (%)]	207 (90.0)	93 (80.9)
95% CI[1]	(85.4, 93.6)	(72.5, 87.6)
Odds ratio vs. chemotherapy[2]	2.140	
95% CI	(1.134, 4.037)	
p-value (2-sided)	0.0189	

[1] Exact 95% confidence interval by Clopper and Pearson.
[2] Odds ratio, 95% confidence interval, and p-value derived from a logistic regression model stratified by EGFR mutation category and race.

- Overall survival

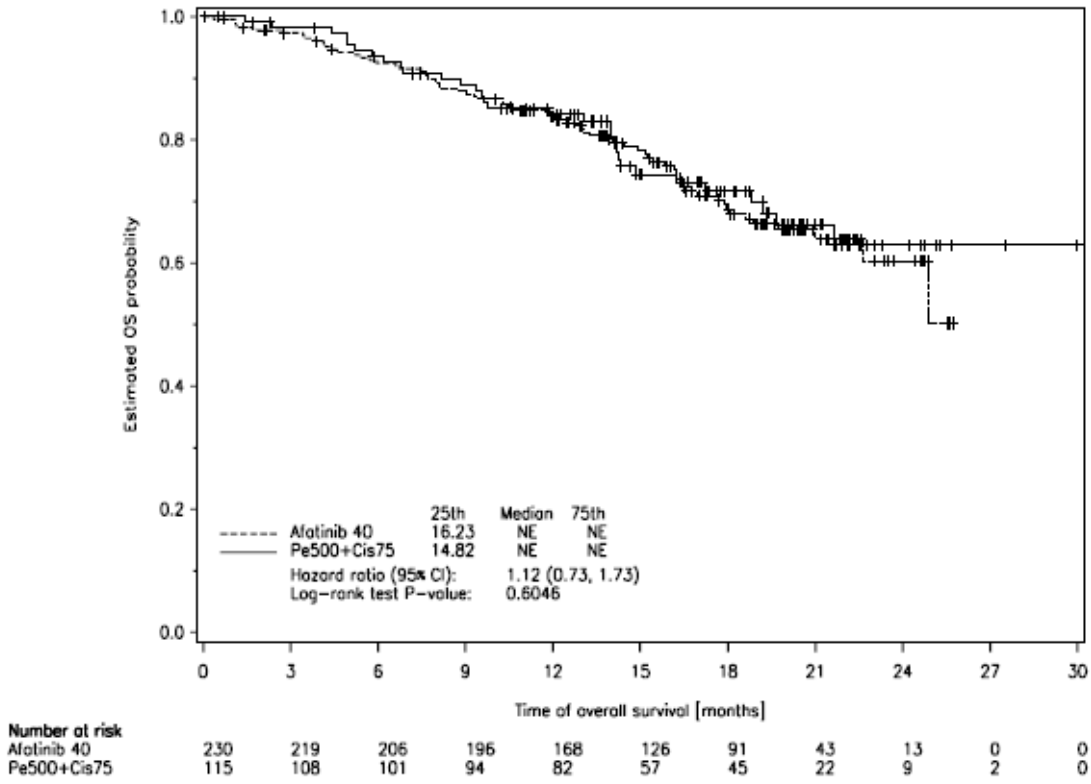
The overall survival data were not mature by the cut-off date for the primary analysis. Only 67 patients (29.1%) in the afatinib arm and 31 patients (27.0%) in the chemotherapy arm had died by the cut-off date. Hence, the median OS time was not estimable (see Table 28 and Figure 8). The final analysis of OS will be performed when approximately 209 patients have died.

Table 28. Overall survival

	Afatinib	Chemotherapy
Patients [N (%)]	230 (100.0)	115 (100.0)
Deaths [N (%)]	67 (29.1)	31 (27.0)
Survival time [months]		
25th percentile (95% CI)	16.23 (13.24, 17.94)	14.82 (13.04, 21.62)
Median (95% CI)	NE (22.64, NE)	NE (21.62, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Hazard ratio vs. chemotherapy[1]	1.121	
95% CI	(0.727, 1.728)	
p-value (2-sided)[2]	0.6046	

Abbreviations: CI = confidence interval; NE = not estimable.
1 Hazard ratio derived from a Cox proportional hazard model stratified by EGFR mutation category and race.
2 Derived from a log-rank test stratified by EGFR mutation category and race.

Figure 8. Probability of overall survival/RS



Updated results provided with a cut-off on January 2013 showed a HR of 0.907 (CI 95%, 0.660-1.246, p=0.5457)

A summary of subsequent anti-cancer therapy after discontinuation of study medication by treatment is shown in Table 29.

Table 29. Summary of subsequent anti-cancer therapy after discontinuation of study medication by treatment (all lines of therapy)

	Afatinib N (%)	Chemotherapy N (%)
Patients	230	115
Discontinued study treatment	164 (100.0)	111 (100.0)
Any new anti-cancer therapy	118 (72.0)	89 (80.2)
Systemic anti-cancer therapy	114 (69.5)	89 (80.2)
Chemotherapy (or chemotherapy-based combination)	102 (62.2)	36 (32.4)
Platinum-based	80 (48.8)	7 (6.3)
Single agent chemotherapy	39 (23.8)	29 (26.1)
Platinum-based + bevacizumab	15 (9.1)	0 (0.0)
Single agent + bevacizumab	4 (2.4)	1 (0.9)
Other chemotherapy combinations	3 (1.8)	3 (2.7)
EGFR TKI	39 (23.8)	72 (64.9)
Erlotinib	24 (14.6)	39 (35.1)
Gefitinib	15 (9.1)	40 (36.0)
Afatinib	0 (0.0)	3 (2.7)[1]
Other	5 (3.0)	4 (3.6)
EGFR TKI-containing combination	2 (1.2)	8 (7.2)
Erlotinib in combination	2 (1.2)	6 (5.4)
Gefitinib in combination	0 (0.0)	2 (1.8)
Radiotherapy	18 (11.0)	9 (8.1)

[1] These patients (patients 3601006, 4105006, and 4107002) received afatinib in named-patient use programs.

- Patient reported outcome

The analyses of symptom control and HRQOL for this report focused on the pre-specified NSCLC-related symptoms of cough, dyspnoea, and pain measured by the EORTC QLQ-C30 and QLQ-LC13 questionnaires. High compliance rates for HRQOL questionnaire completion on treatment were observed (87% to 99%) and were found to be similar for both treatment arms. Results are shown in Table 30.

Table 30. Improvement, stabilisation, and worsening of cough, dyspnoea, and pain-related items of QLQ-C30 and QLQ-LC13.

	Afatinib				Chemotherapy			
	N[1]	Improved %	Stable %	Worsened %	N[1]	Improved %	Stable %	Worsened %
Cough	218	67.0	12.0	21.0	105	60.0	12.0	28.0
Dyspnoea*	218	64.0	9.0	27.0	107	50.0	8.0	42.0
Dyspnoea, rested	217	24.0	46.0	30.0	107	23.0	43.0	34.0
Dyspnoea, walked	218	46.0	26.0	28.0	107	40.0	22.0	37.0
Dyspnoea, climbed stairs*	218	52.0	18.0	30.0	107	37.0	21.0	41.0
Short of breath*	218	57.0	18.0	24.0	107	36.0	21.0	42.0
Pain	218	59.0	5.0	36.0	107	48.0	13.0	39.0
Have pain*	218	56.0	8.0	36.0	107	40.0	21.0	39.0
Pain affecting daily activities	218	42.0	12.0	46.0	107	33.0	22.0	45.0
Pain in the chest*	218	51.0	25.0	24.0	107	37.0	28.0	35.0
Pain in arm or shoulder*	218	41.0	23.0	36.0	107	26.0	42.0	32.0
Pain in other parts of the body	207	42.0	12.0	47.0	98	34.0	24.0	42.0

Cough: QLQ-LC13, Q1; dyspnoea: QLQ-LC13, Q3-Q5 (Q3: dyspnoea, rested; Q4: dyspnoea, walked; Q5: dyspnoea, climbed stairs); short of breath: QLQ-C30, Q8; pain: QLQ-C30, Q9 and Q19 (Q9: have pain; Q19: pain affecting daily activities); pain in the chest: QLQ-LC13, Q10; pain in arm or shoulder: QLQ-LC13, Q11; pain in other parts of the body: QLQ-LC13, Q12.

* p <0.05 (2-sided) in favour of afatinib, for odds ratio from a logistic regression analysis of 'improved / not improved' stratified by EGFR mutation category and race.

[1] Patients with baseline assessment and at least 1 post-baseline assessment.

In addition, compared with chemotherapy, afatinib statistically significantly delayed the time to deterioration for cough (HR 0.595; 95% CI 0.406, 0.872; p = 0.0072) and dyspnoea (HR 0.682; 95% CI 0.501, 0.928; p = 0.0145). A trend towards a delayed deterioration of pain was also observed (HR 0.825; 95% CI 0.618, 1.101; p = 0.1913).

Ancillary analyses

Sensitivity analyses

- PFS based on investigator assessment

Progression-free survival was also analysed based on investigator assessment, using the same censoring rules as for the primary PFS analysis (see Table 31).

Table 31: PFS based on investigator assessment

	Afatinib	Chemotherapy
Patients [N (%)]	230 (100.0)	115 (100.0)
Patients with PFS event [N (%)]	155 (67.4)	83 (72.2)
PFS time [months]		
Median (95% CI)	11.07 (9.66, 13.60)	6.70 (5.42, 8.11)
Hazard ratio vs. chemotherapy[1]	0.488	
95% CI	(0.367, 0.649)	
p-value (2-sided)[2]	<0.0001	

Abbreviations: CI = confidence interval.

[1] Hazard ratio derived from a Cox proportional hazard model stratified by EGFR mutation category and race.

[2] Derived from a log-rank test stratified by EGFR mutation category and race.

The differences between the central independent review and the investigator assessment were analysed in more detail (see Table 32).

Table 32. Concordance in identifying PFS events.

		PFS event based on investigator assessment			
		Afatinib N (%)		Chemotherapy N (%)	
		No	Yes	No	Yes
PFS event based on central independent review	No	54 (23.5)	24 (10.4)	23 (20.0)	23 (20.0)
	Yes	21 (9.1)	131 (57.0)	9 (7.8)	60 (52.2)

The denominator used for this table is the total of patients randomised to the respective treatment arm, i.e., 230 patients for the afatinib arm and 115 patients for the chemotherapy arm.

- PFS in patients with NSCLC with 'Common' EGFR mutations

Based on central independent review, a statistically significant interaction between treatment and subgroup was observed for the subgroups defined by EGFR mutation category (p = 0.0012 for the EGFR mutation subgroup Common vs. Other; p = 0.0002 for the EGFR mutation subgroup L858R vs. Del 19 vs. Other). The pre- specified category 'Common' EGFR mutation comprised L858R and Del 19.

The treatment effect of afatinib on PFS was stronger in the subgroup of patients with 'Common' EGFR mutations compared with chemotherapy (see Table 33):

Table 33: PFS in patients with NSCLC with EGFR mutations of the category 'common', based on central independent review.

EGFR mutation category	Afatinib	Chemotherapy
Common		
Patients [N (%)]	204 (100.0)	104 (100.0)
Patients with PFS event [N (%)]	130 (63.7)	61 (58.7)
PFS time [months]		
Median (95% CI)	13.60 (10.84, 13.77)	6.90 (5.39, 8.25)
Hazard ratio vs. chemotherapy[1]	0.471	
95% CI	(0.344, 0.646)	
p-value (2-sided)[2]	<0.0001	
Del 19		
Patients [N (%)]	113 (100.0)	57 (100.0)
Patients with PFS event [N (%)]	67 (59.3)	35 (61.4)
PFS time [months]		
Median (95% CI)	13.70 (11.14, 16.36)	5.55 (3.06, 8.15)
Hazard ratio vs. chemotherapy[1]	0.278	
95% CI	(0.176, 0.441)	
p-value (2-sided)[2]	<0.0001	
L858R		
Patients [N (%)]	91 (100.0)	47 (100.0)
Patients with PFS event [N (%)]	63 (69.2)	26 (55.3)
PFS time [months]		
Median (95% CI)	10.84 (8.25, 13.77)	8.11 (5.72, 9.69)
Hazard ratio vs. chemotherapy[1]	0.733	
95% CI	(0.461, 1.165)	
p-value (2-sided)[2]	0.1871	

Abbreviations: CI = confidence interval.
[1] Hazard ratio derived from a Cox proportional hazard model with treatment fitted as the only factor.
[2] Derived from a log-rank test (2-sided).

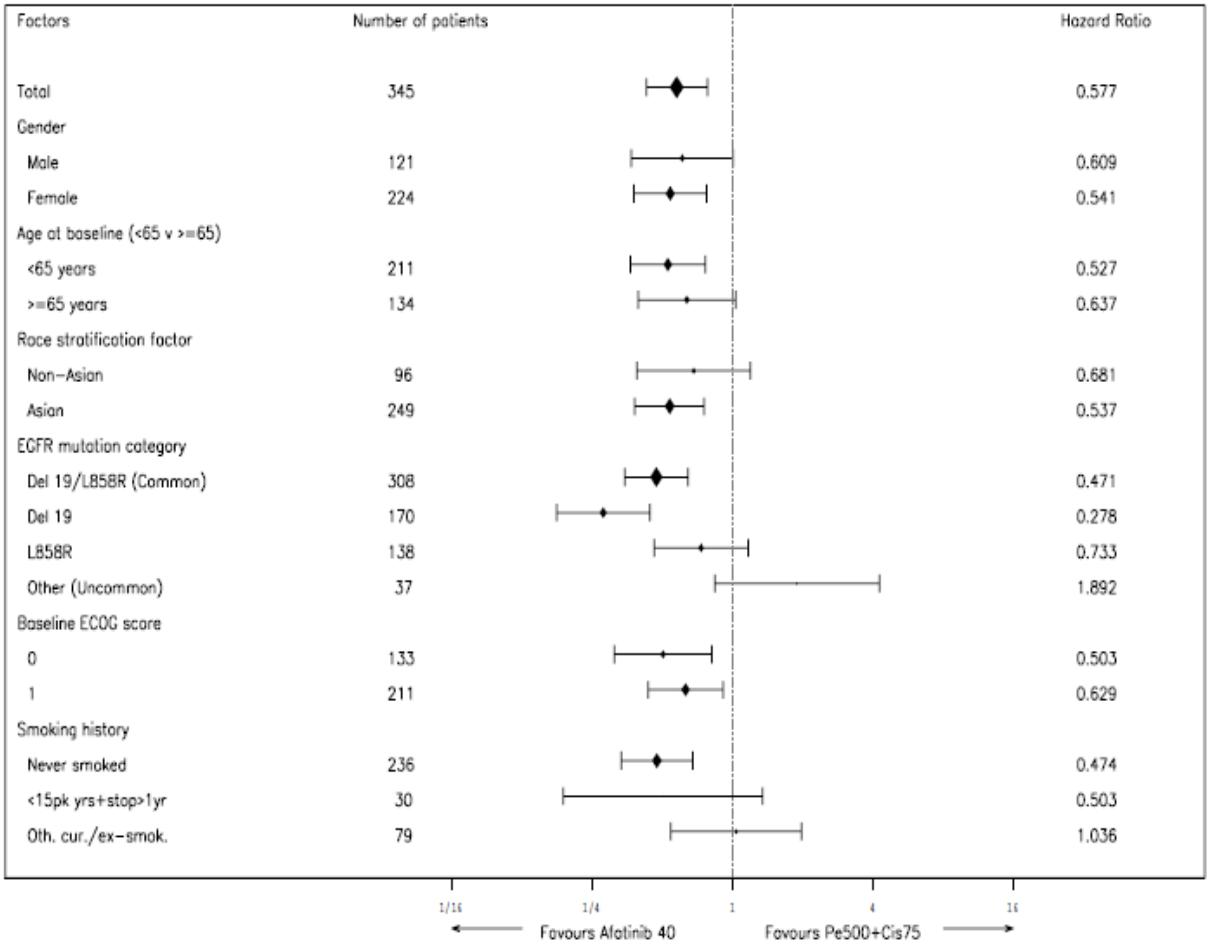
Subgroup analyses

The consistency of the treatment effect of afatinib vs. pemetrexed / cisplatin on PFS by central independent review was investigated for the following demographic and baseline characteristics: ECOG performance score at baseline, gender, age, size of target lesions at baseline, race, EGFR mutation category, geographical region, smoking history, and presence of brain metastases at baseline. The results of these subgroup analyses were substantially consistent with the primary analysis of PFS (see Figure 9).

The treatment effect of afatinib was similar in relevant subgroups defined by gender, age, race, geographical region, and ECOG performance score at baseline.

The treatment effect of afatinib vs. pemetrexed / cisplatin on PFS in relevant subgroups was also analysed based on investigator assessment.

Figure 9. Comparison of the treatment effect of afatinib vs. pemetrexed / cisplatin on the primary endpoint PFS in pre-defined subgroups, based on central independent review



Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial 1200.32/LUX-Lung 3

Title: LUX-Lung 3; A randomised, open-label, phase III study of afatinib versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR-activating mutation		
Study identifier	1200.32 / U12-1199-01	
Design	Randomised, open-label, phase III study	
	Duration of main phase:	17 AUG 2009 – 09 FEB 2012
Hypothesis	Superiority	

Treatments groups	Afatinib (film-coated tablets)		40 mg once daily (q.d.) with possible dose escalation to 50 mg q.d. and dose reduction to 40 mg q.d. (if applicable), 30 mg q.d., or 20 mg q.d. (according to the protocol-defined dose escalation and dose reduction scheme), if required. No dose increase was allowed after a dose reduction. For afatinib, patients received continuous daily dosing as long as they did not develop disease progression..
	Pemetrexed (lyophilised powder) / cisplatin (solution for infusion)		Pemetrexed 500 mg/m² as an infusion over 10 minutes followed after 30 minutes by cisplatin 75 mg/m² as an infusion over 2 hours on Day 1 of each 21-day treatment course. The treatment with chemotherapy could be delayed or the dose could be reduced in accordance with the guidance in the current summary of product characteristics. Each treatment course was planned to be 21 days. For pemetrexed / cisplatin, patients were to receive a maximum of 6 treatment courses unless they developed disease progression
Endpoints and definitions	Primary endpoint	PFS	The primary endpoint was progression-free survival (PFS) as assessed by central independent review according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1
	Secondary endpoint	Objective response; Disease control; OS	Objective response (defined as complete response [CR], or partial response[PR]) according to RECIST version 1.1 (time to objective response, duration of objective response) Disease control (defined as a patient with objective response or stable disease [SD]) according to RECIST version 1.1 (duration of disease control) Overall survival (OS)
Database lock	Date of statistical analysis plan: 23 January 2012 Revised		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Afatinib	Chemotherapy
	Number of subject	230	115

	median PFS (IRC)	11.14 months	6.90 months
	95% CI	(9.63, 13.63)	(5.39, 8.25)
	median PFS (investigators)	11.07 months	6.70 months
	95% CI	(9.66, 13.60)	(5.42, 8.11)
	Objective response	129 (56.1%)	26 (22.6%)
	Disease control	207 (90.0%)	93 (80.9%)

Effect estimate per comparison	Primary endpoint (PFS based on central independent review)	Comparison groups	Afatinib/Chemotherapy
		Log-rank test stratified by EGFR mutation category and race.	point estimate
		P-value	0.0004
		Hazard ratio vs. chemotherapy	0.577; 95% CI (0.425, 0.784)
	PFS based on investigator assessment	Comparison groups	Afatinib/Chemotherapy
		Hazard ratio vs. chemotherapy	0.488; 95% CI (0.367, 0.649)
		Log-rank test stratified by EGFR mutation category and race	
		P-value	<0.0001
	OS	Comparison groups	Afatinib/Chemotherapy Deaths [N (%)] 67 (29.1)/ 31 (27.0)
		Hazard ratio vs. chemotherapy	1.121
		95% CI	0.727, 1.728
		P-value	<P-value>
Notes	The overall survival data were not mature by the cut-off date for the primary analysis. The median OS time was not estimable. The final analysis of OS will be performed when approximately 209 patients have died		

Supportive studies

- **Study 1200.23/Lux Lung 1**: An international, multi-centre, randomised, double-blind, Phase IIb/III trial of afatinib plus best supportive care (BSC) versus placebo plus BSC in non-small cell lung cancer patients failing erlotinib or gefitinib.

Methods

Study participants

Patients with confirmed diagnosis of stage IIIB (with pleural effusion) or IV NSCLC with pleural effusion whose disease progressed after at least one, but not more than two, lines of cytotoxic chemotherapy of which one must have been a platinum-containing regimen, and treatment with erlotinib or gefitinib, or both, for at least 12 weeks.

Treatment

50 mg/day afatinib starting dose, with the option to reduce to 40 mg/day or 30 mg/day, according to a pre-specified, protocol defined dose-reduction scheme based on Common Terminology Criteria for Adverse Events (CTCAE) grade (Version 3.0)

The treatment was continuous with repeated treatment courses in the absence of disease progression, as long as patients tolerated therapy, did not meet criteria for treatment withdrawal, and neither the patient nor investigator requested discontinuation of treatment.

Objectives

The primary objective was to investigate the efficacy and safety of afatinib plus best supportive care (BSC) vs. placebo plus best supportive care (BSC) in patients with advanced NSCLC with progressive disease after at least 1 but not more than 2 lines of chemotherapy and at least 12 weeks of treatment with erlotinib or gefitinib.

Outcome/endpoints

Primary endpoint: overall survival (OS)
Secondary Endpoints: progression-free survival (PFS); objective tumour response based on the RECIST, Version 1.0; duration of disease control; time to and duration of objective response; HRQoL, and PK. Safety: Adverse events, according to CTCAE Version 3.0, laboratory investigations, physical exam, Eastern Cooperative Oncology Group (ECOG) performance score, electrocardiogram, left ventricular function, vital signs.

Statistical analysis

The original protocol stated that the primary analysis would be conducted when 309 randomised patients had died; this would have allowed 85% power. Amendment 1 to the protocol, dated 6 April 2009, increased the number of deaths required for the analysis to 359 deaths, providing 90% power for the log-rank test, presuming a hazard ratio of 0.70 for afatinib plus BSC relative to placebo plus BSC. The hypothesized hazard ratio of 0.70 is taken from the erlotinib registration trial, which showed a 4.7 month median survival time for the placebo group and 6.7 months for erlotinib.

An interim analysis on objective response was performed within the framework of a Data Monitoring Committee (DMC) after 40 patients treated with afatinib had undergone tumor imaging at least once during treatment. The independent DMC recommended continuing the trial based on the number of responders observed. The independent DMC was unblinded; however, the trial team and investigators remained blinded to treatment assignments during these interim analyses.

The final analyses of overall survival and secondary endpoints were conducted when 358 deaths were observed among all randomised patients. The log-rank test, stratified by baseline ECOG

performance score (0, 1 vs. 2) and gender (male vs. female), were used to test for the effect of afatinib at the one-sided 0.025 significance level.

The data cut-off for the primary analysis was 8 July 2010. Updated results for OS have been provided on a data cut-off on 13 February 2012.

Results

Recruitment

A total of 697 patients provided signed informed consent at 86 centres, including 432 patients in Asia, 174 patients in Europe, and 91 patients in North America. There were 585 patients who met eligibility criteria and were randomised in the study; all patients randomised received at least one dose of study medication (see Table 34).

Table 34. Overall patient disposition—number (%) of all enrolled patients

	Placebo N (%)	Afatinib N (%)	Total N (%)
Enrolled			697
Randomised	195	390	585
Treated	195 (100.0)	390 (100.0)	585 (100.0)
Continuing on treatment at data cut-off	1 (0.5)	10 (2.6)	11 (1.9)
Treatment discontinued	194 (99.5)	380 (97.4)	574 (98.1)
Progressive disease	178 (91.3)	314 (80.5)	492 (84.1)
Other adverse event	4 (2.1)	51 (13.1)	55 (9.4)
Patient refusal to take study medication	7 (3.6)	8 (2.1)	15 (2.6)
Other[1]	3 (1.5)	4 (1.0)	7 (1.2)
Non-compliant with protocol	2 (1.0)	3 (0.8)	5 (0.9)

[1] Includes the following: cause unknown, patient died at home; repeat biopsy showed NSCLC consistent with squamous cell carcinoma; too ill for follow-up; AE and progressive disease; desire to stop due to AEs and did not want dose reductions; patient decision to change treatment; unknown death.

Conduct of the study

The protocol had two global amendments:
Amendment No. 1 (6 Apr 2009) - The purpose of this amendment was to update the sample size and to add a restriction for patients with known ILD.
Amendment No. 2 (26 Jul 2010) - The purpose of this amendment was to add a restriction for concomitant medications. For safety reasons caution has to be exercised in combining afatinib with potent P-gp inhibitors and inducers.

Important protocol violations are summarised in Table 35:

Table 35. Important protocol violations – randomised set

	Placebo	BIBW 2992	Total
Total randomized	195 (100.0)	390 (100.0)	585 (100.0)
Patients with at least one important protocol violation	19 (9.7)	61 (15.6)	80 (13.7)
Diagnosis of NSCLC questionable (or incorrect disease stage)	4 (2.1)	12 (3.1)	16 (2.7)
Prior treatment with erlotinib or gefitinib does not meet entrance criterion	1 (0.5)	9 (2.3)	10 (1.7)
Prior chemotherapies for NSCLC does not meet entrance criterion	5 (2.6)	17 (4.4)	22 (3.8)
ALT, AST or Tbili exceeds entrance criteria	0 (0.0)	3 (0.8)	3 (0.5)
Other deviation from exclusion criteria	8 (4.1)	14 (3.6)	22 (3.8)
Informed consent	1 (0.5)	1 (0.3)	2 (0.3)
Informed consent not available or after randomization	0 (0.0)	1 (0.3)	1 (0.2)
Informed consent is > 14 days after the visit procedures are performed at screen	0 (0.0)	1 (0.3)	1 (0.2)
Trial medication is not administered according to protocol.	2 (1.0)	6 (1.5)	8 (1.4)

Baseline data

The baseline demographics and disease characteristics are summarised in Tables 36 and 37.

Table 36. Demographics of patients in trial 1200.23/RS

	Placebo		Afatinib 50 mg		Total	
Patients, n (%)	195	(100.0)	390	(100.0)	585	(100.0)
Gender, n (%)						
Male, n (%)	78	(40.0)	159	(40.8)	237	(40.5)
Female, n (%)	117	(60.0)	231	(59.2)	348	(59.5)
Age, mean (StD) [years]	59	(10.4)	58	(10.8)	58	(10.6)
Age category, n (%)						
< 65 years	127	(65.1)	275	(70.5)	402	(68.7)
≥ 65 years	68	(34.9)	115	(29.5)	183	(31.3)
Race/ethnicity, n (%)						
Caucasian	72	(36.9)	121	(31.0)	193	(33.0)
Eastern Asian[1]	110	(56.4)	227	(58.2)	337	(57.6)
Other Asian	12	(6.2)	38	(9.7)	50	(8.5)
Other	1	(0.5)	4	(1.0)	5	(0.9)
Geographic region, n (%)						
Asia	119	(61.0)	242	(62.1)	361	(61.7)
Europe	55	(28.2)	101	(25.9)	156	(26.7)
North America	21	(10.8)	47	(12.1)	68	(11.6)
ECOG performance status at baseline, n (%)						
Score 0	53	(27.2)	92	(23.6)	145	(24.8)
Score 1	127	(65.1)	268	(68.7)	395	(67.5)
Score 2	15	(7.7)	30	(7.7)	45	(7.7)
Smoking history, n (%)						
Never smoked	121	(62.1)	245	(62.8)	366	(62.6)
<15 pack years and stopped >1 year before diagnosis	13	(6.7)	27	(6.9)	40	(6.8)
Current or other ex-smoker	61	(31.3)	118	(30.3)	179	(30.6)

[1] Patients were regarded as Eastern Asian if they were of Asian race and of Japanese, Chinese, Taiwanese, or South Korean ethnicity.

Table 37. Baseline disease characteristics of patients in trial 1200.23/RS

	Placebo		Afatinib 50 mg		Total	
Patients, n (%)	195	(100.0)	390	(100.0)	585	(100.0)
Time since first diagnosis, median [years]	2.0		1.9		1.9	
Clinical stage at screening, n (%)						
IIIB	6	(3.1)	15	(3.8)	21	(3.6)
IV	189	(96.9)	375	(96.2)	564	(96.4)
Number of metastatic sites, n (%)						
0	4	(2.1)	8	(2.1)	12	(2.1)
1	67	(34.4)	131	(33.6)	198	(33.8)
2	56	(28.7)	126	(32.3)	182	(31.1)
≥3	68	(34.9)	125	(32.1)	193	(33.0)
Metastatic site[1], n (%)						
Any	191	(97.9)	382	(97.9)	573	(97.9)
Lung	105	(53.8)	214	(54.9)	319	(54.5)
Bone	93	(47.7)	175	(44.9)	268	(45.8)
Pleural effusion	77	(39.5)	140	(35.9)	217	(37.1)
Brain	45	(23.1)	101	(25.9)	146	(25.0)
Liver	46	(23.6)	79	(20.3)	125	(21.4)
Adrenal glands	15	(7.7)	32	(8.2)	47	(8.0)
Other	29	(14.9)	65	(16.7)	94	(16.1)

[1] Patients with multiple metastatic sites are counted in each category where metastasis existed.

Prior therapies

About 40% of patients were treated with two lines of chemotherapy, 60% with one. Prior EGFR-TK therapy is summarised in Table 38.

Table 38. Prior therapies in trial 1200.23/RS

	Placebo	Afatinib	Total
Total randomised [N (%)]	195 (100.0)	390 (100.0)	585 (100.0)
Prior EGFR TKI [N (%)]			
Erlotinib only	108 (55.4)	215 (55.1)	323 (55.2)
Gefitinib only	79 (40.5)	152 (39.0)	231 (39.5)
Erlotinib and gefitinib	8 (4.1)	23 (5.9)	31 (5.3)
Duration of prior EGFR TKI [N (%)]			
< 12 weeks[1]	1 (0.5)	3 (0.8)	4 (0.7)
12 - <24 weeks	34 (17.4)	75 (19.2)	109 (18.6)
24 - <36 weeks	38 (19.5)	88 (22.6)	126 (21.5)
36 - <48 weeks	30 (15.4)	50 (12.8)	80 (13.7)
48 weeks or more	92 (47.2)	174 (44.6)	266 (45.5)
Duration of prior EGFR TKI [weeks]			
Mean (Std[2])	59 (44.8)	53 (40.8)	55 (42.2)
Median (min, max[3])	44 (9, 311)	42 (9, 370)	43 (9, 370)
Best response to prior EGFR TKI [N (%)]			
CR/PR	85 (43.6)	178 (45.6)	263 (45.0)
Stable disease	97 (49.7)	177 (45.4)	274 (46.8)
Progressive disease	4 (2.1)	15 (3.8)	19 (3.2)
Unknown	9 (4.6)	20 (5.1)	29 (5.0)
Duration between end of prior EGFR TKI and randomization [N (%)]			
< 4 weeks	84 (43.1)	146 (37.4)	230 (39.3)
4 - < 8 weeks	39 (20.0)	78 (20.0)	117 (20.0)
8 - < 12 weeks	15 (7.7)	34 (8.7)	49 (8.4)
12 weeks or more	56 (28.7)	130 (33.3)	186 (31.8)
Missing	1 (0.5)	2 (0.5)	3 (0.5)

This trial was designed to enrol a patient population that was clinically enriched for EGFR mutations by requiring that all patients had undergone at least 12 weeks of prior therapy with erlotinib or gefitinib. Overall, 45.5% of patients had undergone ⩾48 weeks of prior EGFR TKI therapy, and most patients (91.8%) had experienced clinical benefit from the prior EGFR TKI (45.0% had a best response of CR or PR, and 46.8% had experienced SD). Of the 141 patients with evaluable EGFR mutation test results (based on combined results from central and local testing), 96 patients (68%) were EGFR mutation positive.

Numbers analysed

Two analysis data sets were defined. The randomized set (RS) included all 585 randomised patients (390 randomised to afatinib and 195 randomised to placebo). The treated set (TS) included the randomised patients who took at least one dose of the randomised treatment. The efficacy results are based on the randomised set. The safety analyses are based on the treated set; thus, the safety parameters are evaluated based on data from the first date of drug intake to 28 days after the last drug intake.

EGFR mutation results from tissue testing are shown in Table 39:

Table 39. EGFR mutation results from tissue testing

	Number of Patients
Positive	96 (68% positivity rate[1])
Del 19	50
L858R	19
T790M[2]	8
Other	3
Type not specified	16
Negative	45
Unclear results	45
Total with an interpretable result	141
Total with archival tissue for testing	186

[1]Positivity rate determined by the number of positive patients (96) divided by the number of patients with an interpretable result (total 141: 96 positive + 45 negative).
[2]Includes T790M mutations together with Del 19 or with L858R mutations.

Post-hoc analyses identified a patient subgroup considered to be highly clinically enriched for EGFR mutations (i.e. patients with CR/PR to prior EGFR TKI therapy and/or a long duration [⩾48 weeks] of prior EGFR TKI treatment): this subgroup comprised 391 patients with an estimated overall EGFR mutation positivity rate of 83%. The complementary subgroup not meeting the criteria for 'highly clinically enriched for EGFR mutations' (194 patients) had an estimated EGFR mutation positivity rate of 26%.

Overall, 214 patients (36.6%) met the criteria of acquired resistance to erlotinib or gefitinib (PR/CR or at least 6 months of SD prior to PD and no systemic therapy between end of TKI therapy and enrolment and less than 4 weeks between end of TKI treatment and enrolment)according to Jackman et al (Jackman et al, J Clin Oncol 2010;28(2):357-360). These criteria were published in 2010, i.e. after initiation of the study.

Outcomes and estimations

Primary Endpoint: Overall survival

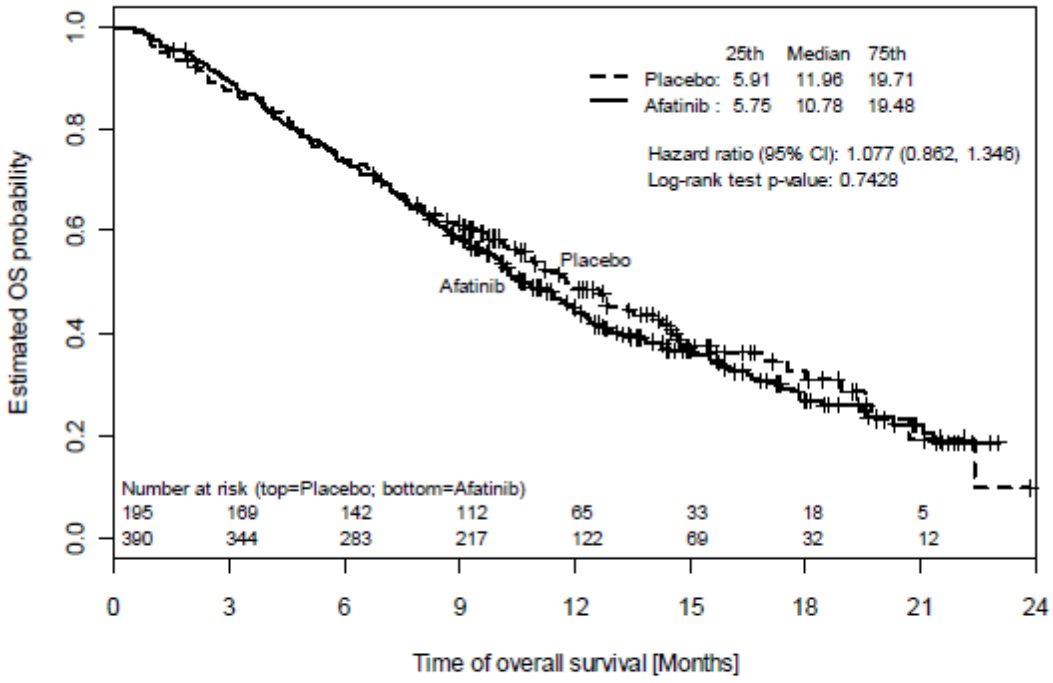
The primary analysis of the primary endpoint, OS, was conducted when a total of 358 patients were reported as dead, data cut-off 8 July 2010. Results are shown in Table 40 and Figure 10.

Table 40. Summary of overall survival – randomised set

	Placebo	Afatinib
Total randomised (N [%])	195 (100.00)	390 (100.00)
Patients died (N [%])	114 (58.46)	244 (62.56)
Survival time [months]		
25th percentile	5.91 (4.63, 7.06)	5.75 (4.90, 6.80)
Median	11.96 (10.15, 14.26)	10.78 (9.95, 11.99)
75th percentile	19.71 (17.51, NA)	19.48 (17.22, NA)
Afatinib vs. Placebo		
Hazard ratio[1]		1.077
(95% CI)		(0.862, 1.346)
P−value[2]		0.7428

[1]Hazard ratio is estimated from Cox regression model stratified by gender and baseline ECOG performance score (0,1 vs. 2).
[2]P-value is one-sided (afatinib vs. placebo) log-rank test stratified by the same factors.

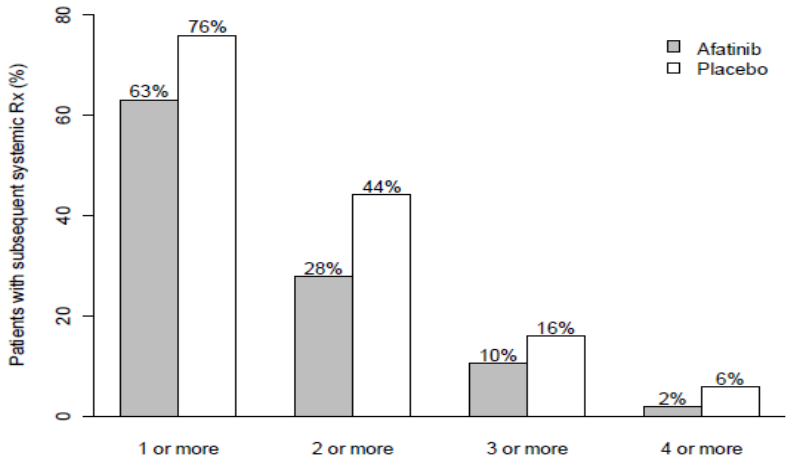
Figure 10. Kaplan-Meier estimates of overall survival.



OS data were updated February 2012 at an event rate of 86%. The HR was 1.01 (CI 95% 0.726-1.143, p=0.419) for the whole study population.

Data comparing the placebo and afatinib group for the number of anti-cancer therapies after discontinuation of study drugs is provided in Figure 11.

Figure 11. The number of subsequent systemic anti-cancer therapies after discontinuation of study medication



Secondary Endpoint: Progression free survival

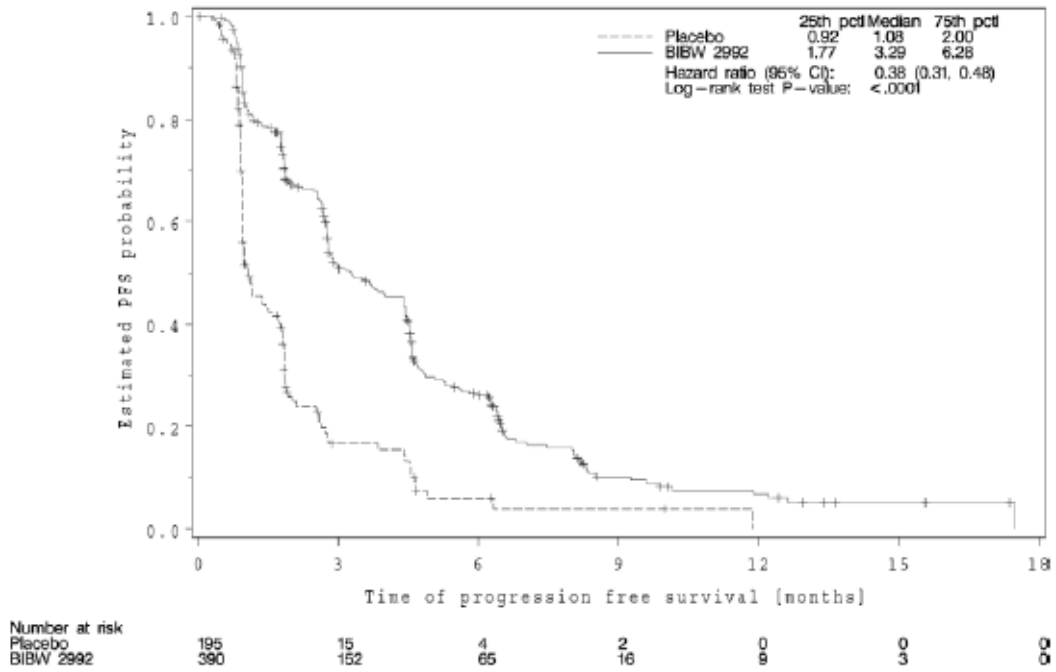
Details for the analyses of PFS by independent review are provided in Table 41 and Figure 12.

Table 41. summary of PFS based on independent review / RS

	Placebo	Afatinib
Total randomised (N [%])	195 (100.00)	390 (100.00)
Patients progressed or died (N [%])	133 (68.21)	275 (70.51)
PFS time (months)		
25th percentile	0.92 (0.89, 0.95)	1.77 (1.22, 1.84)
Median	1.08 (0.95, 1.68)	3.29 (2.79, 4.40)
75th percentile	2.00 (1.84, 2.79)	6.28 (4.86, 6.51)
Afatinib vs. Placebo:		
Hazard ratio[1]		0.381
(95% CI)		(0.306, 0.475)
P-value[2]		<0.0001

[1]Hazard ratio is estimated from Cox regression model stratified by gender and baseline ECOG performance score (0,1 vs. 2).
[2]P-value is one-sided (afatinib vs. placebo) log-rank test stratified by the same factors.
Source data: Table 15.2.2.1: 1

Figure 12. Kaplan-Meier curves of PFS based on independent review / RS



Ancillary analysis

A post-hoc analysis of efficacy based on enrichment for EGFR mutations in Trial 1200.23 is shown in Tables 42 and 43.

Table 42. Progression-free survival and overall survival results from the subgroup analysis of LUX-Lung 1 (afatinib vs. placebo)

	By likelihood of presence of EGFR mutation		By interval from the last dose of erlotinib/gefitinib*	
	Highly clinically enriched	Complementary subgroup	EGFR TKI-free < 4 weeks	EGFR TKI-free ≥ 4 weeks
Total N	391	194	230	352
PFS HR (95% CI) Median PFS	0.28 (0.21, 0.36) 4.4 vs. 1.0	0.67 (0.46, 0.98) 2.8 vs. 1.8	0.38 (0.27, 0.54) 4.4 vs. 1.1	0.40 (0.30, 0.53) 3.0 vs. 1.1
OS HR (95% CI) Median OS	**0.91 (0.73, 1.14) 12.0 vs. 11.2	****1.23** (0.89, 1.70) 8.7 vs. 14.4	**1.35** (0.94, 1.94) 11.4 vs. 14.1	0.91 (0.69, 1.21) 10.5 vs. 10.5

* For N=3 the EGFR TKI-free interval was not available
** Data from OS update in February 2012

Table 43. Outcomes for patients with low likelihood of EGFR mutations (complementary subgroup) and EGFR TKI-free interval < or ≥ 4 weeks in trial LUX Lung 1

	EGFR TKI-free **interval < 4 weeks** N=75		EGFR TKI-free **interval ≥4 weeks** N=118	
	afatinib	placebo	afatinib	placebo
Low likelihood of EGFR mutation (**complementary subgroup**) N (%)	51(100)	24 (100)	81 (100.0)	37 (100.0)
PFS events, N (%)	34 (66.7)	16 (66.7)	63 (77.8)	23 (62.2)
Median PFS , months	2.8	1.8	2.2	2.6
HR (95% CI) p-value	0.45 (0.24, 0.85) P=0.013		0.96 (0.59, 1.56) P=0.872	
OS events, N (%)	44 (86.3)	19 (79.2)	72 (88.9)	35 (94.6)
Median OS, months	9.4	18.0	8.7	10.3
HR (95% CI) p-value	1.69 (0.97, 2.93)		0.94 (0.62, 1.41)	

- **Study 1200.22 /Lux Lung 2**: A Phase II single-arm trial of afatinib in non-small cell lung cancer patients with EGFR activating mutations

The supportive trial 1200.22 was an exploratory open-label Phase II trial with a similar patient population as the pivotal trial 1200.32. Trial 1200.22 investigated afatinib as first- or second-line treatment (after chemotherapy) of EGFR TKI-naïve patients with EGFR mutations. The efficacy data from trial 1200.22 presented in this submission are based on an interim CTR (interim data cut-off 6 April 2011 and on an updated OS analysis (data cut-off 9 February 2012).

Patients with Stage IIIB or Stage IV adenocarcinoma of the lung whose tumor harbored exon 18 to exon 21 EGFR activating mutations and who had failed one line of cytotoxic chemotherapy or who had not received first-line cytotoxic chemotherapy (the latter only in Stage 2 of the trial per Amendment 1). All patients must have had biopsy samples available and the EGFR mutation status was determined in all patients prior to start of treatment with afatinib.

Afatinib was administered at an initial starting dose of 50 mg daily that followed a two-stage design. In the first stage only patients progressing or relapsing after one prior cytotoxic chemotherapy regimen (including neoadjuvant or adjuvant chemotherapy) were allowed to enter

into the trial (second-line patients). An early stopping rule was in place and an end of Stage 1 interim analysis was conducted after 40 second-line patients with NSCLC harboring activating EGFR mutations were treated and completed at least one 4-week course of treatment with afatinib. The trial passed from Stage 1 to Stage 2 after more than the required 16 second line patients achieved a complete or partial response (≥ 40% of patients with CR or PR). After the end of Stage 1 Interim Analysis on 3 March 2009 and amendments to the trial protocol, the trial was opened to first-line patients and subsequently the starting dose was lowered to 40 mg, resulting in four trial cohorts defined by line of treatment and afatinib starting dose (40 mg and 50 mg).

The primary efficacy endpoint was defined by the objective response rate (ORR) as determined by Response Criteria in Solid Tumors (RECIST 1.0). Secondary endpoints included Clinical benefit (CR, PR, stable disease) determined by RECIST, time to objective response, duration of objective response, progression-free survival (PFS) time, overall survival (OS) time safety and pharmacokinetics.

This is an interim report for an ongoing study with a cutoff date for data collection of 06 April 2011 for all safety and efficacy data.

An assessment of tumor response using RECIST was performed at the end of each course for the first three courses (i.e. every 4 weeks) and from thereon every other course (every 8 weeks). For the primary endpoint, adjudicated independent tumor assessment of the tumor response was performed by a central imaging unit.

Statistical methods were based on calculated ORR with exact 95% confidence interval; Kaplan-Meier estimation of PFS and OS; descriptive statistics for all other endpoints

The study enrolled a total of 129 patients including 61 first-line patients (23 who received a starting dose of 40 mg and 38 who received a starting dose of 50 mg) and 68 second-line patients (7 who received a starting dose of 40 mg and 61 who received a starting dose of 50 mg). The patients' mean age at study entry was 62 years, and most patients were Asian (86.8%), had never smoked (63.6%) and had an ECOG performance score of zero (64.3%). Nearly all patients had clinical Stage IV NSCLC (93.8%) with one (42.6%) or two (27.9%) metastatic sites, mostly located in the lung, bone and brain.

Results for the primary and secondary endpoints are summarised in Tables 44-46.

Table 44. Best overall response based on central independent review in trial 1200.22 / TS

	First-line Afatinib 40 mg		First-line Afatinib 50 mg		Second-line Afatinib 40 mg		Second-line Afatinib 50 mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients treated	23	(100.0)	38	(100.0)	7	(100.0)	61	(100.0)	129	(100.0)
Confirmed best overall response										
Disease control	18	(78.3)	35	(92.1)	5	(71.4)	48	(78.7)	106	(82.2)
Objective response	14	(60.9)	26	(68.4)	4	(57.1)	35	(57.4)	79	(61.2)
CR	0	(0.0)	2	(5.3)	0	(0.0)	0	(0.0)	2	(1.6)
PR	14	(60.9)	24	(63.2)	4	(57.1)	35	(57.4)	77	(59.7)
SD	4	(17.4)	8	(21.1)	1	(14.3)	13	(21.3)	26	(20.2)
No disease [1]	0	(0.0)	1	(2.6)	0	(0.0)	0	(0.0)	1	(0.8)
Progressive disease	4	(17.4)	2	(5.3)	2	(28.6)	10	(16.4)	18	(14.0)
Not evaluable	1	(4.3)	1	(2.6)	0	(0.0)	3	(4.9)	5	(3.9)
Best overall response regardless of confirmation										
Disease control	20	(87.0)	37	(97.4)	6	(85.7)	53	(86.9)	116	(89.9)
Objective response	15	(65.2)	28	(73.7)	4	(57.1)	37	(60.7)	84	(65.1)
CR	0	(0.0)	2	(5.3)	0	(0.0)	0	(0.0)	2	(1.6)
PR	15	(65.2)	26	(68.4)	4	(57.1)	37	(60.7)	82	(63.6)
SD	5	(21.7)	8	(21.1)	1	(14.3)	16	(26.2)	30	(23.3)
No disease [1]	0	(0.0)	1	(2.6)	1	(14.3)	0	(0.0)	2	(1.6)
Progressive disease	3	(13.0)	1	(2.6)	1	(14.3)	6	(9.8)	11	(8.5)
Not evaluable	0	(0.0)	0	(0.0)	0	(0.0)	2	(3.3)	2	(1.6)

[1] 'No disease' refers to patients for whom no target or non-target lesions were identified at baseline, and no new lesions appeared during the trial. One patient with 'no disease' for more than 8 months was considered having disease control.

Table 45. PFS in trial 1200.22 / TS

	First-line Afatinib 40 mg		First-line Afatinib 50 mg		Second-line Afatinib 40 mg		Second-line Afatinib 50 mg		Total	
Patients treated, n (%)	23	(100.0)	38	(100.0)	7	(100.0)	61	(100.0)	129	(100.0)
PFS based on central independent review										
Patients with PFS event, n (%)	15	(65.2)	22	(57.9)	6	(85.7)	48	(78.7)	91	(70.5)
PFS time [months]										
Median	11.9		13.8		4.5		8.3		10.1	
Probability to be alive and progression-free at 12 months [%]	40.5		53.8		28.6		42.4		44.6	
PFS based on investigator assessment										
Patients with PFS event, n (%)	16	(69.6)	26	(68.4)	5	(71.4)	49	(80.3)	96	(74.4)
PFS time [months]										
Median	15.6		15.8		8.2		11.8		13.7	
Probability to be alive and progression-free at 12 months [%]	60.5		64.4		34.3		47.6		54.3	

Source data: [U11-3644, Tables 15.2.3.1: 1, 15.2.3.1: 2, 15.2.3.2: 1, 15.2.3.2: 2, Appendix 16.1.9.2, Statdocs 6.2.2.1, 6.2.2.2]

Table 46. Overall survival in trial 1200.22 / TS

	First-line Afatinib 40 mg		First-line Afatinib 50 mg		Second-line Afatinib 40 mg		Second-line Afatinib 50 mg		Total	
Patients treated, N(%)	23	(100.0)	38	(100.0)	7	(100.0)	61	(100.0)	129	(100.0)
Deaths, n (%)	9	(39.1)	15	(39.5)	5	(71.4)	36	(59.0)	65	(50.4)
Survival time [months]										
Median	23.1		NE		14.6		24.0		24.8	
Probability to be alive										
At 12 months	73.9		89.5		71.4		74.6		78.7	
At 24 months	-		58.6		-		50.8		51.6	

NE = not estimable

Results differentiating first line (treatment-naïve) and second line (after previous chemotherapy) treatments are summarised in Tables 47 and 48.

Table 47. Efficacy comparison in first and second line settings.

	First line (treatment-naïve) N=61	Second line (after previous chemo) N=68
Dose of afatinib	40 mg or 50 mg	40 mg or 50 mg
ORR, % independent/investigator	65.6 / 60.7	57.4 / 60.3
Median PFS, months, independent/investigator	12.0 / 15.6	8.0 / 10.5
Median OS, months	31.7	23.3

Table 48. Efficacy comparison of 40 and 50 mg.

	1st line		2nd line	
Population	40 mg	50 mg	40 mg	50 mg
N	23	38	7	61
ORR %	60.9	68.4	57.1	57.4

Comparison of efficacy with other second line treatment options

The results included in Table 49 are based on the investigator assessment of response, disease control and PFS for afatinib for consistency with the data presented for chemotherapy agents and gefitinib.

Table 49: Efficacy results in 2nd line (chemotherapy pre-treated) population

	Afatinib LUX-Lung 2	Docetaxel [1]	Pemetrexed [1]	Gefitinib [2]	Gefitinib* [3]
No of patients	68	288	283	27	26
Disease control rate (%)	85.3	46.4	45.8	NA	NA
Objective response rate (%)	60.3	8.8	9.1	42.1	37.5
Median PFS (months)	10.5	2.9	2.9	7.0	10.8**
Median OS (months)	23.3	7.9	8.3	14.2	NA

Source: LUX-Lung 2
* includes 3rd line patients
* * time to treatment failure
[1] Hanna et al, J Clin Oncol 22 (9), 1589 - 1597 (2004).
[2] Kim et al, Lancet 372 (22), 1809 - 1818 (2008)
[3] Thatcher, Lancet 366, 1527 - 1537 (2005)

- **Study 1200.42 /LUX-Lung 5**

The supportive trial 1200.42 was a Phase III randomised trial of afatinib plus weekly paclitaxel vs. the investigators choice of chemotherapy following afatinib monotherapy in NSCLC patients failing previous erlotinib or gefitinib treatment.

The interim report includes only data from Part A of trial, in which all patients received afatinib monotherapy. The data from the ongoing Part B (in which patients with progressive disease who derived clinical benefit from afatinib over at least 12 weeks in Part A were randomised to receive either afatinib plus paclitaxel or the investigator's choice of chemotherapy) are not included in the interim report and are not relevant for this application. All descriptions in the following narrative refer to trial Part A.

Objective: To further explore the efficacy and safety of afatinib as second- or later-line therapy in patients with NSCLC and progressive disease after chemotherapy and at least 12 weeks of treatment with erlotinib or gefitinib.
The objective of the interim analysis was to reaffirm the safety and clinical benefit of afatinib monotherapy in a treatment-refractory population of patients who were likely to be EGFR mutation positive; in addition, the interim analysis was to support any regulatory submission for afatinib treatment for patients with NSCLC.

Methods: Trial Part A was a global, multi-centre, open-label, non-randomised Phase III trial in patients with NSCLC of stage IIIB (with pleural or pericardial effusion) or stage IV who had previously received treatment with at least 1 line of cytotoxic chemotherapy for advanced or metastatic disease and either gefitinib or erlotinib over at least 12 weeks, on which they had undergone disease progression. The original trial protocol stated that patients without prior chemotherapy were eligible if they had a known EGFR mutation after treatment with a reversible EGFR TKI or if they had derived clinical benefit for 6 months or longer from previous treatment with erlotinib or gefitinib; a global protocol amendment (Protocol Amendment 4, dated 12 January 2011) changed this to include only patients pretreated with at least 1 line of chemotherapy and at least 12 weeks of treatment with erlotinib or gefitinib. The results presented below are based on an interim data cut-off on 12 December 2011; the study is currently ongoing.

Patients were treated with a starting dose of 50 mg/day afatinib monotherapy, with the continuous dosing regimen to be continued until disease progression. An afatinib dose- reduction scheme from 50 mg to 40 mg and then to 30 mg was to be followed in the case of grade ≥3 drug-related AEs; grade ≥2 worsening of renal function; grade ≥2 diarrhoea for 2 or more consecutive days despite anti-diarrhoeal treatment/hydration; or grade ≥2 nausea/vomiting for 7 or more consecutive days despite antiemetic treatment/hydration.

The primary efficacy endpoint specified for the interim analysis of Part A of the trial was PFS based on investigator assessment (calculated as the time from treatment start to the occurrence of PD or death), which was to be assessed when all patients had been treated in Part A for at least 12 weeks. However, patients might have discontinued treatment early; therefore, not all patients included in the interim analysis received study treatment for 12 weeks. Assessment of tumour response was performed at 6-weekly intervals in Part A and evaluated according to RECIST version 1.1. The secondary endpoint was objective response (CR or PR, based on investigator assessment) to afatinib monotherapy in Part A; further endpoints comprised time to and duration of objective response, OS, tumour shrinkage, disease control, and duration of disease control. Safety was assessed in terms of the incidence and intensity of AEs, graded according to CTCAE version 3.0, AEs of special interest (including skin reactions and gastrointestinal events), laboratory evaluation, and cardiac left ventricular function. In addition

to the standard analysis of AEs by primary SOC and preferred term, safety analyses were performed using grouped terms (based on SMQs) for predefined events of special interest.

Results - Efficacy: A total of 1154 patients were entered into the study and received at least 1 dose of afatinib (with a starting dose of 50 mg/day). The mean age was 60.1 years; 56.7% of patients were female. The majority of patients were Eastern Asian (42.5%) or Caucasian (39.4%). The percentages of patients from Eastern Asian countries and from Europe and Australia were 43.0% and 52.5%, respectively. The ECOG performance score was 0 in 29.5% of patients, 1 in 59.9% of patients, and 2 in 10.6% of patients. The percentage of never-smokers was 53.6%; 11.0% of patients had smoked <15 pack years and stopped smoking >1 year before diagnosis, and 35.4% were other ex-smokers or current smokers. Almost all patients (98.6%) had NSCLC stage IV at screening; 1.3% of patients had stage IIIb disease. The predominant tumour histology was adenocarcinoma (85.4%). Patients with squamous cell carcinoma constituted 7.9% of the trial population. All but 17 patients had metastatic disease. The most frequent metastatic sites were the bones (38.6%), followed by pleural effusion (32.1%), liver (22.4%), and brain (22.1%).

The trial was designed to enrol a trial population that was clinically enriched for EGFR mutations by requiring that all patients had undergone at least 12 weeks of prior therapy with erlotinib or gefitinib. All patients had received at least 1 previous chemotherapy; 64.6% had received ≥3 previous chemotherapies. Overall, 37.3% of patients had received >48 weeks of treatment with an EGFR TKI, and the majority of patients (73.7%) had experienced clinical benefit from prior EGFR TKI treatment (best response of CR/PR in 32.1% of patients, best response of SD in 41.6% of patients). A total of 84 patients had evaluable central testing results for tumour tissue samples, including 49 patients carrying EGFR mutations (i.e. 58.3% of patients with evaluable samples) and 35 patients without EGFR mutations (41.7%). The subgroup of patients who were 'highly clinically enriched for EGFR mutations' (i.e. had a best response of CR or PR to prior EGFR TKI therapy and/or ≥48 weeks treatment with a prior EGFR TKI) comprised 598 patients with an estimated EGFR mutation positivity rate of 83%. In the complementary subgroup of patients who were not highly clinically enriched for EGFR mutations (n=556), the estimated EGFR mutation positivity rate was 33%.

The interim analysis included 872 patients (75.6%) with a PFS event, i.e. disease progression or death. Median PFS (based on investigator assessment) was 3.25 months (95% CI 2.85, 3.81). The probability to be alive and progression-free at 6 months was 24.5%. The percentage of patients with confirmed objective tumour response was 7.6% (95% CI 6.16, 9.31). The availability of OS data for the interim analysis was limited, because survival data of patients who did not enter Part B of the trial were only collected up to the date of study discontinuation of each patient. The number of patients with an OS event included in the interim analysis was 301 (26.1%). Median OS was 13.70 months (95% CI 12.61, 14.88).

Median PFS was longer in patients whose tumours harboured EGFR mutations (4.17 months) than in mutation negative patients (2.62 months). This was in line with the longer PFS (4.17 months) in patients 'highly clinically enriched for EGFR mutations'. In patients who were 'highly clinically enriched' as well as in patients who were EGFR mutation positive, the 6-month PFS rate was 29.9%. Results confirmed the findings of trial 1200.23 (see Table 50).

Table 50. PFS based on investigator assessment in trial 1200.42 /TS

	Overall trial population		Subgroup 'highly clinically enriched for EGFR mutations'	
	Afatinib 50 mg		Afatinib 50 mg	
Patients treated, n (%)	1154	(100.0)	598	(100.0)
Patients with PFS event, n (%)	872	(75.6)	426	(71.2)
PFS time [months]				
Median	3.25		4.17	
Probability to be alive and progression-free after 6 months [%]	24.5		29.9	

Source data: [U12-1167, Tables 15.2.1.1: 1 and 15.2.1.3: 4, Appendix 16.1.9.2, Statdoc 6.1.2.7]

- **Study 1200.34 /LUX-Lung 6**

The supportive study 1200.34 / LUX-Lung 6 was a randomised, open-label, phase III study of afatinib versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR-activating mutation in the Asian population.

Dates of Trial: From 27 April 2010 to 29 October 2012 (cut-off date for the primary analysis)

Objectives: To compare the efficacy and safety of afatinib monotherapy with gemcitabine / cisplatin chemotherapy as first-line treatment in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-naïve patients with Stage IIIB (with cytologically-proven pleural effusion or pericardial effusion) or Stage IV adenocarcinoma of the lung harbouring an EGFR mutation.

Methodology: Two-arm, randomised (2:1 ratio), open-label, active-controlled, parallel-group comparison of afatinib versus gemcitabine / cisplatin. The study was planned to enrol 360 patients, i.e. 240 in the afatinib arm and 120 in the gemcitabine /cisplatin chemotherapy arm

Diagnosis and main criteria for inclusion: Patients with Stage IIIB (with cytologically-proven pleural effusion or pericardial effusion) or Stage IV adenocarcinoma of the lung with an EGFR mutation, who had no prior systemic treatment for locally-advanced, recurrent or metastatic non-small cell lung cancer (NSCLC), who were EGFR TKI-naïve, and not eligible for standard curative-intent treatment with surgery or chemoradiotherapy.

Treatments:
Afatinib (film-coated tablets): 40 mg once daily (lq.d.) with possible dose escalation to 50 mg q.d. and dose reduction to 40 mg q.d. (if applicable), 30 mg q.d., or 20 mg q.d. (according to the protocol-defined dose escalation and dose reduction scheme), if required.

Gemcitabine (lyophilised powder) / cisplatin (solution for infusion): Gemcitabine 1000 mg/m² as an infusion over 30 minutes followed by cisplatin 75 mg/m² as an infusion on Day 1 of each 21-day treatment course; gemcitabine 1000 mg/m² as an infusion over 30 minutes on Day 8. Chemotherapy could be delayed or the dose could be reduced in accordance with the guidance in the current summary of product characteristics.

Each treatment course was planned to be 21 days. For afatinib, patients received continuous daily dosing as long as they did not develop disease progression. For gemcitabine / cisplatin, patients were to receive a maximum of 6 treatment courses unless they developed disease progression.

Criteria for evaluation Efficacy:
The primary endpoint was progression-free survival (PFS) as assessed by central independent review according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.

Key secondary endpoints included objective response (defined as complete response [CR], or partial response [PR]) according to RECIST version 1.1 (time to objective response, duration of objective response); disease control (defined as a patient with objective response or stable disease [SD]) according to RECIST version 1.1 (duration of disease control); overall survival (OS). Other secondary endpoints included tumour shrinkage; change from baseline in body weight; change from baseline in Eastern Cooperative Oncology Group (ECOG) performance status; Health- Related Quality of Life (HRQOL) as measured by standardised questionnaires (European Organisation for Research and Treatment of Cancer quality of life questionnaire C30 [QLQ-C30] and its lung cancer-specific module LC13 [QLQLC13]), with the main endpoints being cough (QLQ-LC13 question 1), dyspnoea (QLQ-LC13 questions 3-5; QLQ-C30 question 8), and pain (QLQ-C30 questions 9 and 19; QLQ-LC13 questions 10, 11, 12); afatinib pharmacokinetics.

Statistical methods: The aim of this trial was to determine whether afatinib was more effective than gemcitabine / cisplatin as a first-line treatment in patients with Stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR mutation. The primary analysis was the analysis of PFS based on central independent review. It was planned for after 217 patients developed progressive disease (based on central independent review) or died. An analysis of OS was also planned for this time point. A second OS analysis is scheduled for when the data are considered mature enough for meaningful analysis, this is expected to be when approximately 209 deaths have been observed.
The stratified log-rank test (stratification factor at randomisation by EGFR mutation category [L858R vs. Del 19 vs. Other]) was used to test PFS for the effect of afatinib at the 2-sided alpha-level of 0.05.

Efficacy results:
A total of 910 patients were screened in 36 centres in 3 Asian countries; 364 patients with a positive EGFR mutation test were randomised in a 2:1 ratio to treatment with afatinib or chemotherapy.
Randomisation was stratified by EGFR mutation category. Demographic characteristics were balanced between the treatment arms: patients had a median age of 58.0 years (range 27 to 79 years); the trial included substantial proportions of females (65.4%) and never smokers (76.9%); most patients (75.5%) had an ECOG performance score of 1 at baseline. The TheraScreen®: EGFR29 Mutation Kit (QIAGEN Manchester Ltd, Manchester, UK) was used to categorise each patient's EGFR mutation status. Most patients had a tumour sample with an EGFR mutation categorised as 'Common' (89.0%), comprising Del 19 alone (51.1%) or L858R (37.9%). All other patients (11.0%) had a tumour sample with various different EGFR mutations or mutation combinations, categorised as 'Other' EGFR mutations. Most patients (94.0%) were NSCLC Stage IV at screening, with 22 patients (6.0%) having Stage IIIB disease (disease staging according to the American Joint Committee on Cancer staging system, 6th edition). Overall 31.9% of patients had pleural effusion at baseline and bone was the most frequent site of distant metastatic disease (44.2% of patients).

The primary endpoint, PFS based on central independent review is shown in Table 51.

Table 51. Incidence and analysis of PFS (independent review) / RS

	Afatinib 40	Ge1000+Cis75
Total randomised [N(%)]	242 (100.0)	122 (100.0)
Patients progressed or died [N(%)]	157 (64.9)	64 (52.5)
PFS time [months]		
25th percentile (95% CI)	6.87 (5.55, 8.08)	4.04 (3.06, 4.53)
Median (95% CI)	11.01 (9.66, 13.73)	5.59 (5.06, 6.70)
75th percentile (95% CI)	19.25 (16.56, 22.11)	8.08 (6.77, 9.17)
Afatinib 40 vs. Ge1000+Cis75:		
Hazard ratio*	0.279	
(95% CI)	(0.201, 0.388)	
p-value#	<0.0001	

* Hazard ratio from Cox proportional hazard model stratified by EGFR mutation group
\# P-value from log-rank stratified by EFGR mutation group (two-sided)

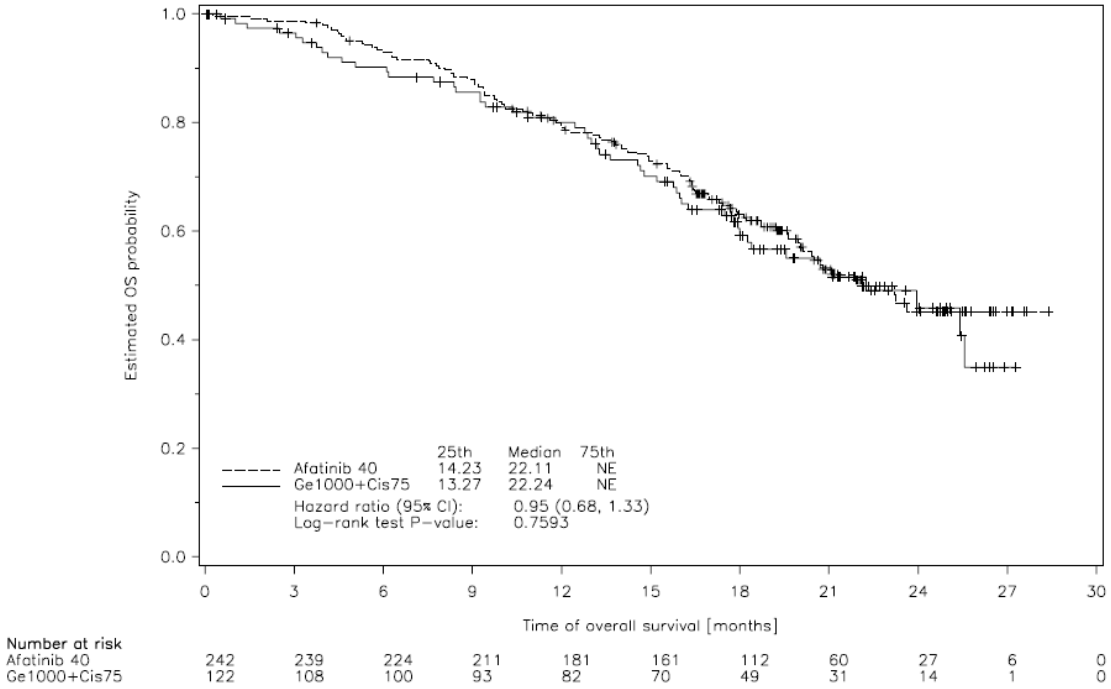
The secondary endpoint overall survival is shown in Table 52 and Figure 13.

Table 52. Incidence and analysis of overall survival / RS

	Afatinib 40	Ge1000+Cis75
Total randomised [N(%)]	242 (100.0)	122 (100.0)
Patients died [N(%)]	104 (43.0)	51 (41.8)
Survival time [months]		
25th percentile (95% CI)	14.23 (11.60, 16.30)	13.27 (9.43, 15.97)
Median (95% CI)	22.11 (20.01, NE)	22.24 (18.00, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (25.56, NE)
Afatinib 40 vs. Ge1000+Cis75:		
Hazard ratio*	0.949	
(95% CI)	(0.676, 1.330)	
p-value#	0.7593	

* Hazard ratio from Cox proportional hazard model stratified by EGFR mutation group
\# P-value from log-rank stratified by EFGR mutation group (two-sided)
NE = not estimable

Figure 13. Kaplan-Meier curves of overall survival / RS



The secondary endpoints, objective response rate and disease control, are shown in Table 53.

Table 53. Best overall tumour response from independent review (regardless of confirmation) / RS

	Afatinib 40	Ge1000+Cis75
Total randomised [N (%)]	242 (100.0)	122 (100.0)
Disease control [N (%)]	224 (92.6)	93 (76.2)
Objective response (OR)	162 (66.9)	28 (23.0)
Complete response	3 (1.2)	0 (0.0)
Partial response	159 (65.7)	28 (23.0)
Stable disease (SD)	52 (21.5)	65 (53.3)
Non-CR/non-PD$	10 (4.1)	0 (0.0)
Progressive disease [N (%)]	9 (3.7)	6 (4.9)
SD/NN for less than 35 days*	0 (0.0)	2 (1.6)
Not evaluable [N (%)]	9 (3.7)	23 (18.9)

Note: Stable disease (SD) and Non-CR/non-PD (NN) must have minimum duration of 35 days from randomisation
$ NN identifies stable non-target disease in the absence of baseline target disease
* SD/NN best response but less than 35 days from randomisation, followed by PD

- **Other studies**

The 4 trials discussed above are complemented by 2 additional trials (1200.33 and .72). Trial 1200.33 was an open-label, uncontrolled Phase I/II trial performed exclusively in Japan (N = 74). In the Phase II part of trial 1200.33, only patients pre-treated with 1 or 2 lines of chemotherapy and with erlotinib or gefitinib were included, thus constituting a similar patient population as those of trials 1200.23 and 1200.42. The results from trial 1200.33 presented in this submission are based on an interim CTR of the Phase II part of the trial (see Table 54). Efficacy was observed in the heavily pretreated population. The median number of courses

(range) was 2.5 (1 to 18). Six out of 12 patients had tumour size reductions with 3 patients achieving prolonged stable disease (SD). One patient with EGFR exon 19 deletion remained progression free for 310 days despite the presence of the T790M resistance mutation. Of the 12 patients, 6 patients were assessed to have SD: the EGFR mutation status was wild-type for 4 patients and EGFR exon 19 deletion and T790M for 2 patients.

Table 54. Key results of trial 1200.33

	Afatinib 50 mg
Patients treated and evaluated for efficacy, n (%)	61 (100)
Median PFS time [1] [months]	4.4
Probability to be alive and progression-free at 6 months [%]	24.7
Objective response [1]	5 (8.2%)
Disease control [1]	40 (65.6%)
Median OS time [months]	19.0
Probability to be alive at 12 months [%]	73.0

NA = not available from the Kaplan-Meier curve
[1] Based on independent review

The open-label, uncontrolled Phase II trial 1200.72 investigated afatinib in patients without EGFR mutations. The primary objective of this open-label, single-arm trial was to explore the efficacy of afatinib defined by the objective response rate (complete response [CR], partial response [PR]) and disease control (CR, PR, stable disease [SD]) as determined by the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria in patients with advanced (stage IIIB/IV) adenocarcinoma of the lung harbouring wild-type Epidermal Growth Factor Receptor (EGFR). Main inclusion/exclusion criteria included patients (n=47) with locally advanced or metastatic adenocarcinoma of the lung (stage IIIB, IV) following second line cytotoxic chemotherapy, whose tumours harbour wild-type EGFR. No patients in the FAS had a confirmed objective response. One patient had an unconfirmed PR. Nine patients (24%) in the FAS had a best overall confirmed response of SD. Median duration of disease control in these 9 patients was 19.29 weeks (range 11.6 to 28.0 weeks). Key results are included in Table 55.

Table 55. Key results of trial 1200.72

	Afatinib 40 mg
Patients treated, n	42
Patients evaluated for efficacy, n (%)	38 (100.0)
Median PFS time [1] [weeks]	4.07
Objective response [1]	0 (0%)
Disease control [1]	9 (24%)
Median OS time [weeks]	31.43

[1] Based on investigator assessment

- **Studies performed across trials**

Efficacy in patients harbouring common or uncommon *EGFR* mutations

Trials LUX-Lung 3 and LUX-Lung 6 used the EGFR29 mutation test. The test is able to detect 29 somatic mutations in the EGFR tyrosine kinase domain: 19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A, G719C (collectively referred to as G719X) and S768I.

Trial LUX-Lung 2 employed a direct DNA sequencing method to detect EGFR mutations and identified a few more additional rare mutations.

The treatment effect of afatinib on PFS in patients with common EGFR mutations (Del 19 and L858R) was studied across trials. The results are summarised in Table 56.

Table 56. Progression-free survival in patients with tumours harbouring Del19 and L858R mutations (by independent review)

	LUX-Lung 3		**LUX-Lung 2**	**LUX-Lung 6**	
Del19	Afatinib	Chemo	Afatinib	Afatinib	Chemo
Patients randomised/treated	113 (100.0)	57 (100.0)	52 (100.0)	124 (100.0)	62 (100.0)
Patients with a PFS event	67 (59.3)	35 (61.4)	33 (63.5)	78 (62.9)	30 (48.4)
Median PFS, months	13.70	5.55	13.7	13.73	5.55
HR, p-value	**0.28** <0.0001		n/a	**0.20** <0.0001	
L858R	Afatinib	Chemo	Afatinib	Afatinib	Chemo
Patients randomised/treated	91 (100.0)	47 (100.0)	54 (100.0)	92 (100.0)	46 (100.0)
Patients with a PFS event	63 (69.2)	26 (55.3)	38 (70.4)	62 (67.4)	27 (58.7)
Median PFS, months	10.84	8.11	13.7	9.56	5.55
HR, p-value	**0.73** 0.1871		n/a	**0.32** <0.0001	

Efficacy results in patients with tumours harbouring uncommon mutations in LUX-Lung 3 and LUX-Lung 6 (independent review) are summarised in Table 57.

Table 57. Efficacy results in patients with tumours harbouring uncommon mutations in LUX-Lung 3 and LUX-Lung 6 (independent review)

	LUX-Lung 3 (n=37)		LUX-Lung 6 (n=40)	
	Afatinib	Pem/Cis	Afatinib	Gem/Cis
Patients with uncommon mutations, N (%)	26 (100.0)	11 (100.0)	26 (100)	14 (100)
Progressed	22 (84.6)	8 (72.7)	17 (65.4)	7 (50.0)
Median PFS (months)	2.76	9.92	9.6	8.3
HR for PFS, p-value	**1.89 p= 0.1198**		**0.55 p=0.2149**	
ORR, N (%)	5 (19.2)	3 (27.3)	17 (65.4)	3 (21.4)
Odds ratio for response, p-value	**0.64 p=0.5886**		**6.93 p=0.0121**	

In addition, effects of individual mutations were investigated. The results are shown in Table 58.

Table 58. Best overall response, PFS and OS in afatinib-treated patients with uncommon mutations (trials LUX-Lung 2, -3, and -6 combined)

Exon	Types of mutations	N	Best overall response		Median PFS		Median OS
			Indep	Invest	Indep	Invest	
Single mutation							
18	**G719X alone**	8	1CR, 5PR, 1PD, 1NEV	6PR, 1PD, 1NEV	NE (0-19.4*)	12.4 (0-19.4*)	NE (0.7* - 23.2*)
19	K739_1744dup6	1	PR	PR	10.7	11.8	17.2
20	Insertions	23	2PR, 13SD, 7PD, 1NEV	4PR, 15SD, 2PD, 2NEV	2.7 (0.4-11.9)	3.5 (0.4-17.4)	9.4 (0.4-24.8)
	T790M alone	3	1 SD, 2 PD	2SD, 1PD	1.3 (1.3–2.8)	1.5 (1.3-2.8)	NE (1.5-14.9)
	S768I	1	PR	PR	19.2*	19.2*	19.2*
21	**L861Q**	12	7PR, 3SD, 1 PD, 1 NEV	7PR, 4SD, 1NEV	6.0 (1.1-22)	9.4 (1.1–24.9)	18.6 (1.1– 25.6*)
	L861P	1	PR	PR	3.7	5.4	5.4
	P848L	1	NEV	NEV	0*	0*	0*
Complex mutations							
18+ 20	G719X+ T790M	1	SD	SD	5.5	5.5	8.7
	G719X + S768I	5	5 PR	4PR, 1SD	14.7 (6.8-35.8*)	16.6 (2.6-35.8*)	NE (15.7–41.1*)
18+ 21	**G719X + L861Q**	3	2 PR, 1SD	3PR	NE (5.5*-9.7*)	9.7 (5.5-10.0)	16.9 (16.3*- 17.3)
	E709G or V+ L858R	2	1 PR, 1PD	2PR	1.8-4.5	8.2-10.1	13.8-18.5
20+ 19	T790M+ Del19	3	1SD, 2PD	1SD, 2PD	1.2 (0.3-3.0)	1.4 (1.2-3.0)	8.1 (7.5-21.7*)
20+ 21	T790M+ L858R	6	1PR, 4SD, 1PD	1PR, 4SD, 1PD	7.5 (0.8-11.0)	8.9 (0.8-13.7*)	24.9 (8.7-25.6*)
	S768I+ L858R	2	2PR	2PR	2.6-13.8*	2.6-13.8*	3.4-13.8*
	R776H+ L858R	1	PR	PR	11.9	13.7	20.3*
21+ 19	L861Q+ Del19	1	SD	PR	1.4*	1.3*	9.7
18+ 20+ 21	G719X + T790M+ L858R	1	PR	PR	13.8	16.6*	16.6*

* - censored observation; NE = Not Estimable

2.5.3. Discussion on clinical efficacy

The pivotal study for this application (LUX Lung 3) was a conventionally designed, well conducted, chemotherapy (pemetrexed/cisplatin) comparative study in treatment naïve patients with activating EGFR-TK mutations. The results (PFS HR 0.58) are considered of clinically benefit and statistically robust and in-line with what has been shown before for the reversible EGFR-TKIs erlotinib and gefitinib (see Table 59). As supportive evidence of efficacy, the results of study LUX Lung 6 have been submitted in response to the CHMP LoQ. This cisplatin/gemcitabine comparative study also showed superiority in terms of PFS (HR 0.28) in treatment naïve patients with activating EGFR-TK mutations.

As for the other EGFR-TKIs in studies conducted with similar designs, no survival benefit (HR 0.91) was shown in LUX Lung 3 (and 6), interpreted as being due to high cross-over rates to EGFR-TKI treatment. In this regards OS data has not shown any negative trends on survival and it is considered reassuring.

Table 59. Efficacy results for afatinib, erlotinib and gefitinib in the 1st line trials in the overall EGFR mutation positive population

		LUX-Lung 3 Afatinib	LUX-Lung 6 Afatinib	IPASS Gefitinib	EURTAC Erlotinib [a]
N in the experimental arm (%)		230	242	132	86
EGFR Mutations screened		29 activating mutations	29 activating mutations	29 activating mutations	Del19 and L858R only
PFS: Median (months), HR	Independent	11.1 HR=0.58	11.0 HR=0.28	---	10.4 [b] HR=0.47
	Investigator	11.1 **HR=0.49**	13.7 **HR=0.26**	9.5 **HR=0.48**	9.7 **HR=0.37**
12-months PFS rate , %	Independent	47	47	---	---
	Investigator	46	56	≈ 38 [c]	40
ORR, %	Independent	56	67	---	---
	Investigator	69	74	71	58
OS, median (months), HR		28.1 [d] **HR=0.91**	22.1 **HR=0.95**	21.6 **HR=1**	19.3 **HR=1.04**

[a] results from updated analysis from Jan 2011
[b] retrospective and incomplete central independent review of available scans at time of primary analysis (107 patients assessed, 30 in the erlotinib arm)
[c] estimated from Kaplan –Meier curve
[d] updated OS analysis, January 2013

The relative efficacy of afatinib, gefitinib and erlotinib is currently not known, as data with direct head to head comparison are not available. Further information on the efficacy of afatinib versus gefitinib will be available from a currently ongoing comparative head-to-head study.

Additional supportive evidence based on study LUX-Lung 2 have shown that that the activity of afatinib in patients with EGFR mutations is not limited by line of therapy; both first- and second-line patients evidenced response rates. Specifically, by independent review, first-line patients

treated with an afatinib starting dose of either 40 mg or 50 mg had a 66% confirmed ORR and a 12- month median PFS, and a median OS has not yet been reached; second-line patients treated with 50 mg of afatinib had a 57% confirmed ORR, a 8.3-month median PFS, and a 24-month median OS.

The treatment effect of afatinib in PFS was stronger in the subgroup of patients with common activating EGFR mutations (Del 19, L858R). In the complementary subgroup of uncommon mutations results are not consistent among trials, showing opposite trends in studies Lux-Lung 3 and 6 (HR 1.89 vs HR 0.55). In addition, non-clinical data has shown activity in vitro and/or in vivo models expressing EGFR mutants harbouring both common and uncommon mutations, and only limited activity was observed in NSCLC tumours with insertion mutations in exon 20. Taking into account all available clinical and non-clinical data the CHMP did not find strong evidence to exclude patients harbouring uncommon mutations.

LUX-Lung 1 was planned as a confirmatory study, but failed to meet its primary objective, i.e. to show a survival benefit over placebo in patients previously treated with one to two lines of chemotherapy and with secondary resistance to erlotinib/gefitinib. To undertake a confirmatory, global study third-fourth line study in patients with NSCLC with mandatory tumour biopsies prior to enrolment would have been unfeasible at the time when the study was initiated (April 2008). Study baseline mutation status is thus largely missing and, e.g. the proportion of the resistance mutation T790M in patients failing erlotinib/gefitinib can only be estimated based on circulating DNA and appears to be about 1/3.

In study LUX-Lung 1 secondary resistance was defined on clinical grounds in the protocol; stable disease for at least 3 months followed by PD. Data external to the study, however, showed that these criteria were too liberal to identify patients with tumours with EGFR TK activating mutations being a prerequisite for meaningful activity at least for gefitinib (estimated 68% of patients included harbour EGFR TK activating mutations). By restricting the clinical definition of secondary resistance to patients with at least PR or stable disease for 48 weeks followed by PD, sufficient enrichment was achieved (83% of patients included harbour EGFR TK activating mutations).

In the subgroup clinically enriched for secondary resistance to erlotinib/gefitinib therapy (the proposed indication) the PFS HR was 0.3, median benefit 3+ months. No statistically significant OS benefit was shown (HR 0.9). It is likely that next-line therapies administered to a larger extent in the placebo arm contributed to lack of an observed effect in OS.

An unexpected finding was that OS was worse in the complementary subgroup to the highly clinically enriched for secondary resistance (HR 1.5, update 1.2) despite a statistically significant PFS HR benefit of 0.67. Further analyses showed that these findings were driven by patients in the complementary set with a short TKI-free interval prior to study enrolment (<4 weeks). No explanation to this finding was identified. Of note the median survival was exceptionally long in the placebo group. As these analyses were not protected by stratification, a reasonable explanation would be that favourable prognostic factors were enriched in the placebo group, even though it is hard to understand why median PFS would be only less than 2months in this group resulting in a favourable PFS HR of 0.45, p=0.013.

Attempts were also made to investigate whether there were signs indicating that afatinib induces resistance to next-line chemotherapy. Data are not conclusive, but there are no signs of major effects on the activity of next line chemotherapy in LUX-Lung 1 or 3.

Whilst the attempt to retrospectively identify patients with secondary resistance to treatment with gefitinib/erlotinib was considered justified, unexpected findings, whether mechanistically related or compatible with imbalances in prognostic factors, cast serious doubt on the validity of the results in the enriched population in patients resistant to EGFR-TKIs.

Additional expert consultation

The oncology Scientific Advisory group (SAG-O) was convened on 11 July 2013 to discuss the benefits of afatinib from a clinical perspective in particular in the second and third line settings i.e. after chemotherapy and EGFR TKI respectively.

The SAG-O provided advice on the following questions raised by the CHMP:

1. *Has the efficacy been adequately demonstrated in patients resistant to EGFR-TKIs? The inconsistent trends in the population enriched for EGFR mutations and the complementary subgroup as well as the differences in post-progression outcomes in study Lux Lung 1 study should be taken into account in the discussion.*

The SAG agreed that efficacy has not been adequately demonstrated in patients resistant to EGFR-TKIs. The SAG endorsed the position of the Rapporteurs as stated in their assessment reports.

The Phase III study LUX-Lung 1 comparing afatinib versus placebo in NSCLC patients failing erlotinib/gefitinib did not meet its primary endpoint of Overall Survival (OS) (HR=1.08, CI 95% 0.862-1.346, p=0.7428). Although activity in progression free survival (PFS) was observed as a secondary endpoint (HR=0.38, CI 95% 0.31, 0.48), p<0.0001), it did not translate into a survival benefit to the patients.

Post-hoc analysis performed by the company further enriched the population of EGFR mutation patients to 83% (originally estimated 68%). Although OS in the enriched population improved (HR=0.91, CI 95% 0.73, 1.14), there are too many uncertainties related to the post-hoc nature of the analysis which preclude to provide enough evidence to demonstrate a benefit in this patient population. In addition, it was worrisome that the complementary set had a negative trend in survival (HR=1.23, CI 95% 0.89, 1.70) and that patients in the afatinib arm in this complementary set experienced an increased number of on-treatment deaths compared to placebo.

Moreover, further subgroup analysis have shown that patients in the complementary for whom the EGFR TKI-free interval was less than 4 weeks (not affected by subsequent therapies), had an even poorer survival outcome (HR=1.69, CI 0.97, 2.93).

2. *The experts are invited to discuss whether efficacy in patients previously treated with chemotherapy can be reasonably foreseen in the light of the available knowledge and whether it makes sense to split the indication between 1st and 2nd line given that it is expectable that any patient with mutational positive status is going to be treated with*

TKIs instead of chemotherapy. Or, by contrary, does the SAG-O think that additional evidence is deemed necessary, and can be reasonably obtained, in patients previously treated with chemotherapy.

The SAG agreed that efficacy can be reasonably expected in patients with advanced non-small cell lung cancer (NSCLC) with activating sensitizing EGFR mutations previously treated with chemotherapy, although it was acknowledged that there is no definitive evidence that 1st and 2nd line treatments (where 2nd line indicates after 1st line chemotherapy) have the same benefit-risk balance based on the results of the pivotal Phase III study LUX-Lung 3. The SAG was of the opinion that there are no mechanistic arguments that would justify a detrimental effect of chemotherapy on the efficacy of TKIs in 2nd line. Moreover, prognostic factors are not expected to change significantly due to previous treatment with chemotherapy.

In addition, anti-tumour activity in patients previously treated with chemotherapy has been shown based on the Phase II study LUX-Lung 2 in terms of response rates (ORR=57.1) and there is convincing evidence from several meta-analyses available in the literature where other TKIs have shown equal activity in 1st and 2nd line.

Nevertheless, the SAG members highlighted the need to better understand the safety profile of afatinib in comparison with other TKIs. It was acknowledged that comparative data in the 2nd line setting is not currently available, and therefore the SAG would like to see further safety data comparing afatinib with other TKIs in order to help the clinical decision making.

2.5.4. Conclusions on the clinical efficacy

Efficacy of afatinib vs. chemotherapy as first-line treatment in patients with NSCLC with EGFR mutations has been shown based on the pivotal trial Phase III trial 1200.32/Lux-Lung 3 in terms of improved PFS (HR=0.577, CI 95% 0.425,0.789, p=0.0004). Results from this study are considered clinically meaningful. Patients treated with afatinib in first line of NSCLC (adenocarcinoma) have a higher probability of remain stable without tumour progression than those treated with the traditional chemotherapy (gain of 4.2 months). This positive effect on the PFS was supported by sensitivity analyses. In addition, the subgroups analyses on PFS both the IRC as the investigators give robustness to the main analysis. Secondary variables point out in the same direction, though data on OS are still immature so as to observe a clear trend.

The benefit of afatinib therapy in patients with secondary resistance to EGFR-TKIs has not been convincingly demonstrated. The post hoc analyses aiming at identifying the target population was not protected by stratification and imbalances in the complementary set favouring the placebo arm cast serious doubt on the outcome in the enriched population.

2.6. Clinical safety

The examination of safety included all available data on the use of afatinib in patients and in healthy volunteers; patients and subjects were included if they had taken at least 1 dose of afatinib. Included in the safety evaluation are a total of 48 clinical trials in overall 3868 patients with different tumour types and 7 trials in a total of 181 healthy volunteers or non-cancer patients. In addition, safety data from 1151 NSCLC patients treated under named-patient use (NPU) and from 44 patients treated in investigator-initiated studies (IIS) were provided.

The applicant has summarised available safety data in safety analysis sets (SAFs) (see Table 60). Pivotal in this safety assessment report are data derived from SAF-1 and SAF-3.

Table 60. Overview of safety analysis sets (SAFs)

	SAF description	Trials included	Groups displayed	N
EGFR TKI-naïve patients with NSCLC with EGFR mutations (afatinib 40 mg starting dose)				
SAF-1	Pivotal trial 1200.32	1200.32	Afatinib vs. Control [1]	340
SAF-2	Pooled Phase II/III NSCLC trials with afatinib 40 mg starting dose	1200.22 [2], .32, .34, .123	Afatinib	497
EGFR TKI pre-treated patients with NSCLC (afatinib 50 mg starting dose)				
SAF-3	Trial 1200.23	1200.23	Afatinib vs. Placebo	585
SAF-4	Pooled phase II/III NSCLC trials with afatinib 50 mg starting dose	1200.23, .33, .41 [3], .42	Afatinib	1638
All patients with cancer or healthy volunteers				
SAF-5	All patients with cancer	All trials except those included in SAFs 6, 7, 8.1, 8.2	Afatinib	3865
SAF-6	1200.131 (blinded data)	1200.131	Afatinib	3
SAF-7	Healthy volunteers and non-cancer patient trials	1200.25, .35, .79, .80, .86, .151, .152	Afatinib	181
SAF-8.1	Named Patient Use (NPU)	All patients treated under NPU	Afatinib	1151
SAF-8.2	Investigator-initiated studies (IIS)	All IIS	Afatinib	44

[1] Trial 1200.32 was an active-controlled trial with an afatinib arm (40 mg starting dose) and a pemetrexed/cisplatin arm.
[2] Trial 1200.22 comprises 4 cohorts. Included in SAF-2 are both cohorts (first- and second-line) of EGFR TKI-naïve patients treated at a 40 mg starting dose.
[3] Trial 1200.41 comprises 3 cohorts. Included in SAF-4 is only cohort 1, i.e. patients with progressive disease after treatment with a reversible EGFR TKI following diagnosis of an EGFR mutation.

Patient exposure

An overview of duration of treatment with afatinib and comparator, according to the different SAFs, is summarised in Table 61.

Table 61. Overview of duration of treatment with afatinib and comparator, according to analysis set and treatment group in EGFR-TKI naïve (SAF-1, SAF-2) and EGFR TKI pre-treated patients (SAF-3, SAF-4)

	EGFR TKI-naïve patients			EGFR TKI pre-treated patients		
	SAF-1		SAF-2	SAF-3		SAF-4
	Afatinib 40 mg	Chemo-therapy	Afatinib 40 mg	Afatinib 50 mg	Placebo	Afatinib 50 mg
Patients, N (%)	229 (100.0)	111 (100.0)	497 (100.0)	389 (100.0)	195 (100.0)	1637 (100.0)
Total treatment time						
Mean (StD) [months]	11.0 (6.9)	2.8 (1.4)	10.2 (6.4)	4.3 (4.3)	1.9 (2.3)	4.2 (3.9)
Patient years	210	26	421	139	30	572
≤1 month, N (%)	11 (4.8)	20 (18.0)	20 (4.0)	70 (18.0)	107 (54.9)	250 (15.3)
>1 to ≤2 months, N (%)	12 (5.2)	9 (8.1)	30 (6.0)	75 (19.3)	42 (21.5)	365 (22.3)
>2 to ≤4 months, N (%)	26 (11.4)	65 (58.6)	48 (9.7)	81 (20.8)	25 (12.8)	363 (22.2)
>4 to ≤6 months, N (%)	18 (7.9)	17 (15.3)	56 (11.3)	71 (18.3)	12 (6.2)	299 (18.3)
>6 to ≤9 months, N (%)	29 (12.7)	0	63 (12.7)	55 (14.1)	6 (3.1)	172 (10.5)
>9 to ≤12 months, N (%)	32 (14.0)	0	95 (19.1)	19 (4.9)	1 (0.5)	113 (6.9)
>12 to ≤15 months, N (%)	35 (15.3)	0	80 (16.1)	8 (2.1)	0	43 (2.6)
>15 to ≤18 months, N (%)	23 (10.0)	0	50 (10.1)	1 (0.3)	1 (0.5)	11 (0.7)
>18 months, N (%)	43 (18.8)	0	55 (11.1)	9 (2.3)	1 (0.5)	21 (1.3)

Generally, for all trials, the afatinib starting dose was to be reduced according to a pre-defined dose reduction scheme if intolerable adverse events occurred (see Tables 62 and 63).

Table 62. Analysis of Afatinib patients requiring dose reduction, according to analysis set and treatment group (SAF−1 and SAF−2)

	SAF-1 40 mg [N(%)]	SAF-2 40 mg [N(%)]
Total treated	229 (100.0)	497 (100.0)
Discontinued due to AE while on 40 mg	14 (6.1)	35 (7.0)
Patients with dosage reduction from 40 mg to 30 mg	120 (52.4)	182 (36.6)
Discontinued due to AE while on 30 mg	9 (3.9)	17 (3.4)
Patients with dosage reduction from 30 mg to 20 mg	40 (17.5)	45 (9.1)
Discontinued due to AE while on 20 mg	9 (3.9)	9 (1.8)
Time to first dosage reduction within interval number of patients with initial reduction within the interval (cumulative incidence at interval end)		
<=14 days	2 (0.9)	6 (1.2)
>14 to <=28 days	34 (15.7)	47 (10.7)
>28 to <=56 days	27 (27.5)	41 (18.9)
>56 to <=84 days	19 (35.8)	27 (24.3)
>84 to <=168 days	22 (45.4)	37 (31.8)
>168 to <=252 days	7 (48.5)	13 (34.4)
>252 to <=420 days	9 (52.4)	11 (36.6)
>420 to <=820 days	2 (53.3)	2 (37.0)
>820 to <=920 days		1 (37.2)
Time to first dose reduction (days)		
Median	52.0	53.0
Min	14.0	7.0
Max	443.0	869.0

Table 63. Analysis of Afatinib patients requiring dose reduction, according to analysis set and treatment group (SAF−3 and SAF−4)

	SAF-3 50 mg [N(%)]	SAF-4 50 mg [N(%)]
Total treated	389 (100.0)	1637 (100.0)
Discontinued due to AE while on 50 mg	38 (9.8)	226 (13.8)
Patients with dosage reduction from 50 mg to 40 mg	151 (38.8)	684 (41.8)
Discontinued due to AE while on 40 mg	21 (5.4)	112 (6.8)
Patients with dosage reduction from 40 mg to 30 mg	42 (10.8)	212 (13.0)
Discontinued due to AE while on 30 mg	10 (2.6)	65 (4.0)
Patients with dosage reduction from 30 mg to 20 mg		
Discontinued due to AE while on 20 mg		
Time to first dosage reduction within interval number of patients with initial reduction within the interval (cumulative incidence at interval end)		
<=14 days	2 (0.5)	19 (1.2)
>14 to <=28 days	42 (11.3)	197 (13.2)
>28 to <=56 days	53 (24.9)	241 (27.9)
>56 to <=84 days	22 (30.6)	100 (34.0)
>84 to <=168 days	24 (36.8)	98 (40.0)
>168 to <=252 days	3 (37.5)	16 (41.0)
>252 to <=420 days	5 (38.8)	12 (41.7)
>420 to <=588 days		1 (41.8)
>588 to <=700 days		
Time to first dose reduction (days)		
Median	42.0	36.0
Min	10.0	8.0
Max	375.0	557.0

The proportion of EGFR TKI-naïve patients who increased their daily afatinib dose from 40 mg to 50 mg was small (SAF-1: 16 patients = 7.0%; SAF-2: 30 patients = 6.0%). In the pooled analysis of patients on 40 mg as starting dose (SAF-2), about 40 % reduced to 30 mg and about 10% to 20 mg. Dose escalation was possible based on rather strict criteria. The pattern was similar in those who started with 50 mg, i.e. about 40% reduced to 40 mg and 10% to 30mg. The pattern over time is illustrated by data from SAF-3 in Table 64.

Table 64. Afatinib dose over time / SAF-3 patients treated with afatinib 50 mg.

Days from the start of treatment	Number of patients treated n (%)	Afatinib 50 mg n (%)	Afatinib 40 mg n (%)	Afatinib 30 mg n (%)
Day 1	389 (100.0)[1]	389 (100.0)	0 (0.0)	0 (0.0)
Day 28	353 (100.0)	314 (89.0)	38 (10.8)	1 (0.3)
Day 56	277 (100.0)	203 (73.3)	65 (23.5)	9 (3.2)
Day 84	215 (100.0)	140 (65.1)	61 (28.4)	14 (6.5)
Day 168	101 (100.0)	49 (48.5)	38 (37.6)	14 (13.9)
Day 336	23 (100.0)	9 (39.1)	10 (43.5)	4 (17.4)
Day 672	2 (100.0)	0 (0.0)	1 (50.0)	1 (50.0)
Day 924	2 (100.0)	0 (0.0)	1 (50.0)	1 (50.0)

Off-treatment pauses were ignored and assigned to the dose level before the pause.
[1]Patient 31102 switched treatment during the trial by error and was, therefore, excluded.

Adverse events

A summary of adverse events for SAF 1 and 3 are shown in Tables 65-69.

Table 65. Summary of adverse events for the key safety groupings, according to analysis set and treatment / SAF-1 (chemotherapy/afatinib 40 mg), SAF-2 (afatinib 40 mg), SAF-3 (placebo/afatinib 50 mg), and SAF-4 (afatinib 50 mg).

		SAF-1		SAF-2	SAF-3		SAF-4
		Chemotherapy (3.7 months[1]) n (%)	Afatinib 40 mg (11.7 months[1]) n (%)	Afatinib 40 mg (10.7 months[1]) n (%)	Placebo (2.8 months[1]) n (%)	Afatinib 50 mg (5.1 months[1]) n (%)	Afatinib 50 mg (4.9 months[1]) n (%)
All patients treated		111 (100.0)	229 (100.0)	497 (100.0)	195 (100.0)	390 (100.0)	1638 (100.0)
Patients with any AE		109 (98.2)	229 (100.0)	491 (98.8)	169 (86.7)	384 (98.5)	1620 (98.9)
Patients with any drug-related AE		106 (95.5)	228 (99.6)	489 (98.4)	74 (37.9)	372 (95.4)	1552 (94.7)
Patients with any AE leading to dose reduction		18 (16.2)	131 (57.2)	199 (40.0)	2 (1.0)	150 (38.5)	694 (42.4)
Patients with any AE leading to discontinuation		17 (15.3)	32 (14.0)	61 (12.3)	12 (6.2)	70 (17.9)	375 (22.9)
Patients with any drug-related AE leading to discontinuation		13 (11.7)	18 (7.9)	35 (7.0)	1 (0.5)	30 (7.7)	192 (11.7)
Patients with any SAE		25 (22.5)	66 (28.8)	101 (20.3)	37 (19.0)	135 (34.6)	620 (37.9)
Fatal		3 (2.7)	13 (5.7)	28 (5.6)	15 (7.7)	44 (11.3)	234 (14.3)
Immediately life-threatening		4 (3.6)	1 (0.4)	3 (0.6)	3 (1.5)	11 (2.8)	36 (2.2)
Disability/incapacity		0 (0.0)	0 (0.0)	1 (0.2)	1 (0.5)	4 (1.0)	7 (0.4)
Required hospitalisation		20 (18.0)	62 (27.1)	90 (18.1)	32 (16.4)	118 (30.3)	548 (33.5)
Prolonged hospitalisation		6 (5.4)	4 (1.7)	11 (2.2)	2 (1.0)	18 (4.6)	96 (5.9)
Other		1 (0.9)	2 (0.9)	4 (0.8)	0 (0.0)	4 (1.0)	9 (0.5)
Highest CTCAE grade	Grade 1	14 (12.6)	12 (5.2)	74 (14.9)	61 (31.3)	28 (7.2)	138 (8.4)
	Grade 2	32 (28.8)	78 (34.1)	171 (34.4)	58 (29.7)	133 (34.1)	482 (29.4)
	Grade 3	49 (44.1)	117 (51.1)	201 (40.4)	33 (16.9)	160 (41.0)	687 (41.9)
	Grade 4	11 (9.9)	9 (3.9)	17 (3.4)	2 (1.0)	19 (4.9)	79 (4.8)
	Grade 5	3 (2.7)	13 (5.7)	28 (5.6)	15 (7.7)	44 (11.3)	234 (14.3)

Adverse events were assessed using MedDRA version 14.1.
[1]Mean time at risk.

Table 66. Adverse events occurring in more than 10% of patients in either treatment group at any event grade, according to study treatment, CTCAE grade, and by preferred or grouped term / SAF-1 (chemotherapy/afatinib 40 mg)

MedDRA preferred term or grouped term	Chemotherapy (3.7 patient months[1])				Afatinib 40 mg (11.7 patient months[1])			
	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
All patients treated	111 (100.0)	111 (100.0)	111 (100.0)	111 (100.0)	229 (100.0)	229 (100.0)	229 (100.0)	229 (100.0)
Patients with any AE	109 (98.2)	49 (44.1)	11 (9.9)	3 (2.7)	229 (100.0)	117 (51.1)	9 (3.9)	13 (5.7)
Diarrhoea	25 (22.5)	2 (1.8)	0 (0.0)	0 (0.0)	220 (96.1)	34 (14.8)	0 (0.0)	0 (0.0)
Rash/acne[+]	12 (10.8)	0 (0.0)	0 (0.0)	0 (0.0)	206 (90.0)	37 (16.2)	0 (0.0)	0 (0.0)
Rash[2]	12 (10.8)	0 (0.0)	0 (0.0)	0 (0.0)	163 (71.2)	32 (14.0)	0 (0.0)	0 (0.0)
Dermatitis acneiform[2]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	80 (34.9)	6 (2.6)	0 (0.0)	0 (0.0)
Stomatitis[+]	19 (17.1)	1 (0.9)	0 (0.0)	0 (0.0)	168 (73.4)	19 (8.3)	1 (0.4)	0 (0.0)
Nail effects[+]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	141 (61.6)	27 (11.8)	0 (0.0)	0 (0.0)
Dry skin	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	69 (30.1)	1 (0.4)	0 (0.0)	0 (0.0)
Decreased appetite	61 (55.0)	4 (3.6)	0 (0.0)	0 (0.0)	66 (28.8)	10 (4.4)	0 (0.0)	0 (0.0)
Fatigue[+]	55 (49.5)	14 (12.6)	0 (0.0)	0 (0.0)	62 (27.1)	7 (3.1)	0 (0.0)	0 (0.0)
Nausea	75 (67.6)	4 (3.6)	0 (0.0)	0 (0.0)	58 (25.3)	3 (1.3)	0 (0.0)	0 (0.0)
Ocular effects[+]	8 (7.2)	0 (0.0)	0 (0.0)	0 (0.0)	52 (22.7)	1 (0.4)	0 (0.0)	0 (0.0)
Vomiting	52 (46.8)	3 (2.7)	0 (0.0)	0 (0.0)	52 (22.7)	10 (4.4)	0 (0.0)	0 (0.0)
Pruritus	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	46 (20.1)	1 (0.4)	0 (0.0)	0 (0.0)
Epistaxis	2 (1.8)	1 (0.9)	0 (0.0)	0 (0.0)	39 (17.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight decreased	16 (14.4)	1 (0.9)	0 (0.0)	0 (0.0)	39 (17.0)	2 (0.9)	0 (0.0)	0 (0.0)
Cough	21 (18.9)	1 (0.9)	0 (0.0)	0 (0.0)	35 (15.3)	0 (0.0)	0 (0.0)	0 (0.0)
Lip effects[+]	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	35 (15.3)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	10 (9.0)	0 (0.0)	0 (0.0)	0 (0.0)	34 (14.8)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	19 (17.1)	0 (0.0)	0 (0.0)	0 (0.0)	33 (14.4)	1 (0.4)	0 (0.0)	0 (0.0)
Back pain	13 (11.7)	2 (1.8)	0 (0.0)	0 (0.0)	32 (14.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngitis	9 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)	32 (14.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	39 (35.1)	0 (0.0)	0 (0.0)	0 (0.0)	30 (13.1)	0 (0.0)	0 (0.0)	0 (0.0)
Alopecia	20 (18.0)	0 (0.0)	0 (0.0)	0 (0.0)	29 (12.7)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	7 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	28 (12.2)	0 (0.0)	0 (0.0)	0 (0.0)
ALT increased	4 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	25 (10.9)	4 (1.7)	0 (0.0)	0 (0.0)
Dizziness	12 (10.8)	0 (0.0)	0 (0.0)	0 (0.0)	25 (10.9)	1 (0.4)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	4 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	25 (10.9)	1 (0.4)	0 (0.0)	0 (0.0)
Dyspnoea	13 (11.7)	0 (0.0)	0 (0.0)	1 (0.9)	17 (7.4)	2 (0.9)	0 (0.0)	1 (0.4)
Anaemia	31 (27.9)	5 (4.5)	2 (1.8)	0 (0.0)	14 (6.1)	4 (1.7)	0 (0.0)	0 (0.0)
Chest pain	14 (12.6)	1 (0.9)	0 (0.0)	0 (0.0)	13 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	14 (12.6)	1 (0.9)	0 (0.0)	0 (0.0)	11 (4.8)	2 (0.9)	0 (0.0)	0 (0.0)
Oedema	13 (11.7)	0 (0.0)	0 (0.0)	0 (0.0)	8 (3.5)	1 (0.4)	0 (0.0)	0 (0.0)
Leukopenia	21 (18.9)	9 (8.1)	0 (0.0)	0 (0.0)	6 (2.6)	1 (0.4)	0 (0.0)	0 (0.0)
Haemoglobin decreased	13 (11.7)	2 (1.8)	1 (0.9)	0 (0.0)	3 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	35 (31.5)	18 (16.2)	3 (2.7)	0 (0.0)	3 (1.3)	2 (0.9)	0 (0.0)	0 (0.0)

Adverse events were assessed using MedDRA version 14.1.
[1]Mean time at risk.

Table 67. Frequency of patients with drug-related adverse events by highest CTCAE grada, using grouped catergories and MedRA preferred terms – SAF 1/Trial 1200.32

System organ class/ Preferred term	SAF-1 Control All Grades N (%)	SAF-1 Control Grade 3 N (%)	SAF-1 Control Grade 4 N (%)	SAF-1 Control Grade 5 N (%)	SAF-1 40 mg All Grades N (%)	SAF-1 40 mg Grade 3 N (%)	SAF-1 40 mg Grade 4 N (%)	SAF-1 40 mg Grade 5 N (%)
Total treated	111 (100.0)	111 (100.0)	111 (100.0)	111 (100.0)	229 (100.0)	229 (100.0)	229 (100.0)	229 (100.0)
Total with drug-related adverse events	106 (95.5)	45 (40.5)	8 (7.2)		228 (99.6)	104 (45.4)	4 (1.7)	4 (1.7)
Diarrhoea	17 (15.3)				218 (95.2)	33 (14.4)		
Rash/Acne+ Rash++ Acne/Dermatitis acneiform++	7 (6.3) 7 (6.3)				204 (89.1) 161 (70.3) 80 (34.9)	37 (16.2) 32 (14.0) 6 (2.6)		
Stomatitis+	17 (15.3)	1 (0.9)			165 (72.1)	19 (8.3)	1 (0.4)	
Nail effect+					140 (61.1)	27 (11.8)		
Dry skin	2 (1.8)				67 (29.3)	1 (0.4)		
Decreased appetite	59 (53.2)	3 (2.7)			47 (20.5)	7 (3.1)		
Pruritus	1 (0.9)				43 (18.8)	1 (0.4)		
Nausea	73 (65.8)	4 (3.6)			41 (17.9)	2 (0.9)		
Ocular effect+	2 (1.8)				41 (17.9)	1 (0.4)		
Fatigue+	52 (46.8)	14 (12.6)			40 (17.5)	3 (1.3)		
Vomiting	47 (42.3)	3 (2.7)			39 (17.0)	7 (3.1)		
Lip effect+	2 (1.8)				33 (14.4)			
Epistaxis	1 (0.9)	1 (0.9)			30 (13.1)			
Weight decreased	10 (9.0)				24 (10.5)			
Alopecia	19 (17.1)				23 (10.0)			

Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 14.1

+ or ++: Individual preferred terms for these grouped categories are displayed in section 1.2.8.
Cut-off date: 09FEB2012

Table 68. Adverse events occurring in more than 10% of patients in either group at any event grade, according to study treatment, CTCAE grade, and by preferred or grouped term / SAF-3 (placebo/afatinib 50 mg)

MedDRA preferred term or grouped term	Placebo (2.8 patient months[1]) Any grade n (%)	Placebo (2.8 patient months[1]) Grade 3 n (%)	Placebo (2.8 patient months[1]) Grade 4 n (%)	Placebo (2.8 patient months[1]) Grade 5 n (%)	Afatinib 50 mg (5.1 patient months[1]) Any grade n (%)	Afatinib 50 mg (5.1 patient months[1]) Grade 3 n (%)	Afatinib 50 mg (5.1 patient months[1]) Grade 4 n (%)	Afatinib 50 mg (5.1 patient months[1]) Grade 5 n (%)
All patients treated	195 (100.0)	195 (100.0)	195 (100.0)	195 (100.0)	390 (100.0)	390 (100.0)	390 (100.0)	390 (100.0)
Patients with any AE	169 (86.7)	33 (16.9)	2 (1.0)	15 (7.7)	384 (98.5)	160 (41.0)	19 (4.9)	44 (11.3)
Diarrhoea	18 (9.2)	0 (0.0)	0 (0.0)	0 (0.0)	339 (86.9)	67 (17.2)	0 (0.0)	0 (0.0)
Rash/acne[+]	31 (15.9)	0 (0.0)	0 (0.0)	0 (0.0)	305 (78.2)	56 (14.4)	0 (0.0)	0 (0.0)
Rash[2]	30 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	290 (74.4)	52 (13.3)	0 (0.0)	0 (0.0)
Dermatitis acneiform[2]	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	53 (13.6)	5 (1.3)	0 (0.0)	0 (0.0)
Stomatitis[+]	5 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	237 (60.8)	11 (2.8)	0 (0.0)	0 (0.0)
Nail effects[+]	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	153 (39.2)	20 (5.1)	0 (0.0)	0 (0.0)
Decreased appetite	22 (11.3)	1 (0.5)	0 (0.0)	0 (0.0)	120 (30.8)	14 (3.6)	0 (0.0)	0 (0.0)
Fatigue[+]	43 (22.1)	3 (1.5)	0 (0.0)	0 (0.0)	116 (29.7)	23 (5.9)	0 (0.0)	0 (0.0)
Nausea	39 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	93 (23.8)	8 (2.1)	0 (0.0)	0 (0.0)
Vomiting	26 (13.3)	1 (0.5)	0 (0.0)	0 (0.0)	79 (20.3)	9 (2.3)	0 (0.0)	0 (0.0)
Epistaxis	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	73 (18.7)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	11 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	72 (18.5)	1 (0.3)	0 (0.0)	0 (0.0)
Dry skin	14 (7.2)	0 (0.0)	0 (0.0)	0 (0.0)	61 (15.6)	1 (0.3)	0 (0.0)	0 (0.0)
Dyspnoea	26 (13.3)	9 (4.6)	0 (0.0)	1 (0.5)	60 (15.4)	15 (3.8)	2 (0.5)	1 (0.3)
Cough	38 (19.5)	6 (3.1)	0 (0.0)	0 (0.0)	54 (13.8)	3 (0.8)	0 (0.0)	0 (0.0)
Ocular effects[+]	5 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	52 (13.3)	2 (0.5)	0 (0.0)	0 (0.0)
Constipation	24 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)	43 (11.0)	1 (0.3)	0 (0.0)	0 (0.0)

Adverse events were assessed using MedDRA version 14.1.
[+]Grouped terms are specified in Section 2.
[1]Mean time at risk.

Table 69. Drug-related adverse events occurring in more than 5% of patients in either group at any event grade, according to study treatment, CTCAE grade, and by preferred or grouped term / SAF-3

MedDRA preferred term or grouped term	Placebo (2.8 patient months[1])				Afatinib 50 mg (5.1 patient months[1])			
	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
All patients treated	195 (100.0)	195 (100.0)	195 (100.0)	195 (100.0)	390 (100.0)	390 (100.0)	390 (100.0)	390 (100.0)
Patients with any drug-related AE	74 (37.9)	3 (1.5)	0 (0.0)	0 (0.0)	372 (95.4)	151 (38.7)	4 (1.0)	2 (0.5)
Diarrhoea	12 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)	330 (84.6)	64 (16.4)	0 (0.0)	0 (0.0)
Rash/acne[+]	26 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)	299 (76.7)	56 (14.4)	0 (0.0)	0 (0.0)
Rash[2]	25 (12.8)	0 (0.0)	0 (0.0)	0 (0.0)	282 (72.3)	52 (13.3)	0 (0.0)	0 (0.0)
Dermatitis acneiform[2]	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	53 (13.6)	5 (1.3)	0 (0.0)	0 (0.0)
Stomatitis[+]	5 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	227 (58.2)	11 (2.8)	0 (0.0)	0 (0.0)
Nail effects[+]	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	150 (38.5)	19 (4.9)	0 (0.0)	0 (0.0)
Decreased appetite	6 (3.1)	1 (0.5)	0 (0.0)	0 (0.0)	81 (20.8)	11 (2.8)	0 (0.0)	0 (0.0)
Nausea	21 (10.8)	0 (0.0)	0 (0.0)	0 (0.0)	73 (18.7)	5 (1.3)	0 (0.0)	0 (0.0)
Pruritus	8 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	69 (17.7)	1 (0.3)	0 (0.0)	0 (0.0)
Epistaxis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	57 (14.6)	0 (0.0)	0 (0.0)	0 (0.0)
Dry skin	12 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)	56 (14.4)	1 (0.3)	0 (0.0)	0 (0.0)
Fatigue[+]	13 (6.7)	2 (1.0)	0 (0.0)	0 (0.0)	56 (14.4)	12 (3.1)	0 (0.0)	0 (0.0)
Vomiting	12 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)	52 (13.3)	6 (1.5)	0 (0.0)	0 (0.0)
Ocular effects[+]	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	36 (9.2)	2 (0.5)	0 (0.0)	0 (0.0)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	30 (7.7)	5 (1.3)	0 (0.0)	0 (0.0)

Adverse events were assessed using MedDRA version 14.1.

Serious adverse event / deaths / other significant events

Serious adverse events in EGFR TKI-naïve patients (SAF-1 and SAF-2) and in EGFR TKI pre-treated patients (SAF-3 and SAF-4) are shown in Tables 70 and 71.

Table 70. Serious adverse events occurring in more than 1 patient in either treatment group at any event grade, according to study treatment, CTCAE grade, and by preferred or grouped term / SAF-1 (chemotherapy/afatinib 40 mg)

MedDRA preferred term or grouped term	Chemotherapy (3.7 patient months[1])				Afatinib 40 mg (11.7 patient months[1])			
	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
All patients treated	111 (100.0)	111 (100.0)	111 (100.0)	111 (100.0)	229 (100.0)	229 (100.0)	229 (100.0)	229 (100.0)
Patients with any SAE	25 (22.5)	14 (12.6)	4 (3.6)	3 (2.7)	66 (28.8)	33 (14.4)	6 (2.6)	13 (5.7)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (6.6)	13 (5.7)	0 (0.0)	0 (0.0)
Vomiting	3 (2.7)	1 (0.9)	0 (0.0)	0 (0.0)	11 (4.8)	8 (3.5)	0 (0.0)	0 (0.0)
Dyspnoea	2 (1.8)	0 (0.0)	0 (0.0)	1 (0.9)	4 (1.7)	2 (0.9)	0 (0.0)	1 (0.4)
Fatigue[+]	3 (2.7)	2 (1.8)	0 (0.0)	0 (0.0)	4 (1.7)	2 (0.9)	0 (0.0)	0 (0.0)
Hypokalaemia	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	4 (1.7)	0 (0.0)	3 (1.3)	0 (0.0)
Dehydration	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)	3 (1.3)	2 (0.9)	0 (0.0)	0 (0.0)
Metastases to CNS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.3)	2 (0.9)	0 (0.0)	1 (0.4)
Pneumonia	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	3 (1.3)	0 (0.0)	1 (0.4)	1 (0.4)
Stomatitis[+]	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	3 (1.3)	3 (1.3)	0 (0.0)	0 (0.0)
Acute respiratory distress syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	2 (0.9)
Cholecystitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.4)	0 (0.0)	0 (0.0)
Confusional state	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.9)	0 (0.0)	0 (0.0)
Convulsion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.4)	0 (0.0)	0 (0.0)
Death	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)	2 (0.9)	0 (0.0)	0 (0.0)	2 (0.9)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.9)	0 (0.0)	0 (0.0)
Deep vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.9)	0 (0.0)	0 (0.0)
Disease progression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	2 (0.9)

Table 71. Serious adverse events occurring in more than 0.5% of patients at any event grade, according to CTCAE grade and by preferred or grouped term / SAF-2 (afatinib 40 mg)

MedDRA preferred term or grouped term	Afatinib 40 mg			
	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
All patients treated	497 (100.0)	497 (100.0)	497 (100.0)	497 (100.0)
Patients with any SAE	101 (20.3)	46 (9.3)	10 (2.0)	28 (5.6)
Diarrhoea	16 (3.2)	14 (2.8)	0 (0.0)	0 (0.0)
Vomiting	13 (2.6)	9 (1.8)	0 (0.0)	0 (0.0)
Dyspnoea	8 (1.6)	3 (0.6)	1 (0.2)	1 (0.2)
Metastases to CNS	7 (1.4)	2 (0.4)	0 (0.0)	5 (1.0)
Fatigue[+]	5 (1.0)	3 (0.6)	0 (0.0)	0 (0.0)
Pneumonia	5 (1.0)	0 (0.0)	1 (0.2)	3 (0.6)
Respiratory failure	5 (1.0)	0 (0.0)	1 (0.2)	4 (0.8)
Decreased appetite	4 (0.8)	2 (0.4)	0 (0.0)	0 (0.0)
Dehydration	4 (0.8)	3 (0.6)	0 (0.0)	0 (0.0)
Hypokalaemia	4 (0.8)	0 (0.0)	3 (0.6)	0 (0.0)
Neoplasm malignant	4 (0.8)	1 (0.2)	0 (0.0)	1 (0.2)
Pneumothorax	4 (0.8)	1 (0.2)	1 (0.2)	0 (0.0)
Pyrexia	4 (0.8)	1 (0.2)	0 (0.0)	0 (0.0)
Convulsion	3 (0.6)	2 (0.4)	0 (0.0)	0 (0.0)
Pleural effusion	3 (0.6)	2 (0.4)	0 (0.0)	0 (0.0)
Rash/acne[+]	3 (0.6)	3 (0.6)	0 (0.0)	0 (0.0)
Rash[1]	3 (0.6)	3 (0.6)	0 (0.0)	0 (0.0)
Stomatitis[+]	3 (0.6)	3 (0.6)	0 (0.0)	0 (0.0)
Urinary tract infection	3 (0.6)	3 (0.6)	0 (0.0)	0 (0.0)

Adverse events were assessed using MedDRA version 14.1.
[+]Grouped terms are specified in Section 2.
[1]Adverse events classified under the subgrouping of rash are specified in [U12-3312, Table 2.8.4.1].

Serious adverse events in EGFR TKI pre-treated patients (SAF-3 and SAF-4) are shown in Tables 72 and 73.

Table 72. Serious adverse events occurring in more than 0.5% of patients at any event grade, according to CTCAE grade and by preferred or grouped term / SAF-3 (afatinib 50 mg)

MedDRA preferred term or grouped term	Placebo (2.8 patient months[1])				Afatinib 50 mg (5.1 patient months[1])			
	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
All patients treated	195 (100.0)	195 (100.0)	195 (100.0)	195 (100.0)	390 (100.0)	390 (100.0)	390 (100.0)	390 (100.0)
Patients with any SAE	37 (19.0)	13 (6.7)	1 (0.5)	15 (7.7)	135 (34.6)	48 (12.3)	14 (3.6)	44 (11.3)
Diarrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	18 (4.6)	10 (2.6)	0 (0.0)	0 (0.0)
Neoplasm malignant	7 (3.6)	0 (0.0)	0 (0.0)	7 (3.6)	16 (4.1)	1 (0.3)	0 (0.0)	14 (3.6)
Pleural effusion	7 (3.6)	4 (2.1)	0 (0.0)	0 (0.0)	14 (3.6)	9 (2.3)	1 (0.3)	0 (0.0)
Metastases to CNS	3 (1.5)	0 (0.0)	0 (0.0)	2 (1.0)	11 (2.8)	2 (0.5)	2 (0.5)	2 (0.5)
Pneumonia	4 (2.1)	1 (0.5)	0 (0.0)	0 (0.0)	10 (2.6)	1 (0.3)	3 (0.8)	2 (0.5)
Respiratory failure	2 (1.0)	0 (0.0)	0 (0.0)	2 (1.0)	9 (2.3)	2 (0.5)	1 (0.3)	6 (1.5)
Dehydration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.1)	6 (1.5)	0 (0.0)	0 (0.0)
Dyspnoea	4 (2.1)	2 (1.0)	0 (0.0)	1 (0.5)	8 (2.1)	5 (1.3)	1 (0.3)	1 (0.3)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Renal failure acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.8)	5 (1.3)	0 (0.0)	1 (0.3)
Deep vein thrombosis	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.3)	4 (1.0)	1 (0.3)	0 (0.0)
Fatigue[+]	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.3)	5 (1.3)	0 (0.0)	0 (0.0)
Hypokalaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.3)	2 (0.5)	1 (0.3)	0 (0.0)
Pulmonary embolism	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	5 (1.3)	1 (0.3)	3 (0.8)	1 (0.3)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.3)	2 (0.5)	0 (0.0)	3 (0.8)
Vomiting	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	5 (1.3)	2 (0.5)	0 (0.0)	0 (0.0)
Blood creatinine increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.0)	1 (0.3)	0 (0.0)	0 (0.0)
Lung infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.0)	1 (0.3)	2 (0.5)	1 (0.3)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.0)	2 (0.5)	0 (0.0)	0 (0.0)
Pancreatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.0)	1 (0.3)	0 (0.0)	0 (0.0)
Death	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	3 (0.8)	0 (0.0)	0 (0.0)	3 (0.8)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	3 (0.8)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	2 (0.5)	0 (0.0)	0 (0.0)
Muscular weakness	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	1 (0.3)	0 (0.0)	0 (0.0)
Stomatitis[+]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	1 (0.3)	0 (0.0)	0 (0.0)
Cough	3 (1.5)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysphagia	3 (1.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	2 (1.0)	2 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Chest pain	2 (1.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Adverse events were assessed using MedDRA version 14.1.
[+]Grouped terms are specified in Section 2.
[1]Mean time at risk.

Table 73. Serious adverse events occurring in more than 0.5% of patients at any event grade, according to CTCAE grade and by preferred or grouped term / SAF-4 (afatinib 50 mg)

MedDRA preferred term or grouped term	Afatinib 50 mg			
	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
All patients treated	1638 (100.0)	1638 (100.0)	1638 (100.0)	1638 (100.0)
Patients with any SAE	620 (37.9)	215 (13.1)	58 (3.5)	234 (14.3)
Diarrhoea	85 (5.2)	55 (3.4)	4 (0.2)	0 (0.0)
Dyspnoea	72 (4.4)	29 (1.8)	9 (0.5)	23 (1.4)
Neoplasm malignant	70 (4.3)	4 (0.2)	2 (0.1)	62 (3.8)
Pleural effusion	65 (4.0)	38 (2.3)	3 (0.2)	4 (0.2)
General physical health deterioration	51 (3.1)	12 (0.7)	8 (0.5)	27 (1.6)
Pneumonia	49 (3.0)	16 (1.0)	7 (0.4)	18 (1.1)
Dehydration	28 (1.7)	17 (1.0)	0 (0.0)	1 (0.1)
Vomiting	23 (1.4)	9 (0.5)	0 (0.0)	0 (0.0)
Pulmonary embolism	22 (1.3)	4 (0.2)	9 (0.5)	5 (0.3)
Respiratory failure	20 (1.2)	3 (0.2)	3 (0.2)	14 (0.9)
Fatigue+	18 (1.1)	9 (0.5)	0 (0.0)	1 (0.1)
Metastases to CNS	18 (1.1)	5 (0.3)	2 (0.1)	4 (0.2)
Pyrexia	17 (1.0)	2 (0.1)	0 (0.0)	0 (0.0)
Renal failure acute	16 (1.0)	10 (0.6)	1 (0.1)	1 (0.1)
Decreased appetite	15 (0.9)	12 (0.7)	0 (0.0)	0 (0.0)
Lung infection	14 (0.9)	7 (0.4)	3 (0.2)	2 (0.1)
Nausea	13 (0.8)	5 (0.3)	0 (0.0)	0 (0.0)
Deep vein thrombosis	11 (0.7)	8 (0.5)	2 (0.1)	0 (0.0)
Back pain	10 (0.6)	7 (0.4)	1 (0.1)	0 (0.0)

Adverse events were assessed using MedDRA version 14.1.
+Grouped terms are specified in Section 2.

Adverse events leading to death

Adverse events with fatal outcome are summarised in for SAF 1 and 3 in Tables 74 and 75. Death due to progression of the underlying disease was a frequent event. As a result death was recorded as an outcome event rather than an adverse event, unless it was the consequence of an SAE in which case the fatal SAE was reported.

Table 74. Adverse events with a fatal outcome, according to study treatment by preferred term / SAF-1 (chemotherapy/afatinib 40 mg).

MedDRA preferred term	Chemotherapy (3.7 patient months[1]) n (%)	Afatinib 40 mg (11.7 patient months[1]) n (%)
All patients treated	111 (100.0)	229 (100.0)
Patients with any AE with a fatal outcome	3 (2.7)	13 (5.7)
Disease progression	0 (0.0)	2 (0.9)
Acute respiratory distress syndrome	0 (0.0)	2 (0.9)
Death	1 (0.9)	2 (0.9)
Metastases to CNS	0 (0.0)	1 (0.4)
Metastases to meninges	0 (0.0)	1 (0.4)
Neoplasm malignant	1 (0.9)	1 (0.4)
Neoplasm progression	0 (0.0)	1 (0.4)
Dyspnoea	1 (0.9)	1 (0.4)
Pneumonia	0 (0.0)	1 (0.4)
Sepsis	0 (0.0)	1 (0.4)

[1]Mean time at risk

When considering the frequency of those fatal events not attributed to disease progression by the investigator in SAF-1, the frequencies (not corrected for differences in time at risk) were similar in the two treatment groups (2.6% in the afatinib arm compared to 1.8% in the control arm).

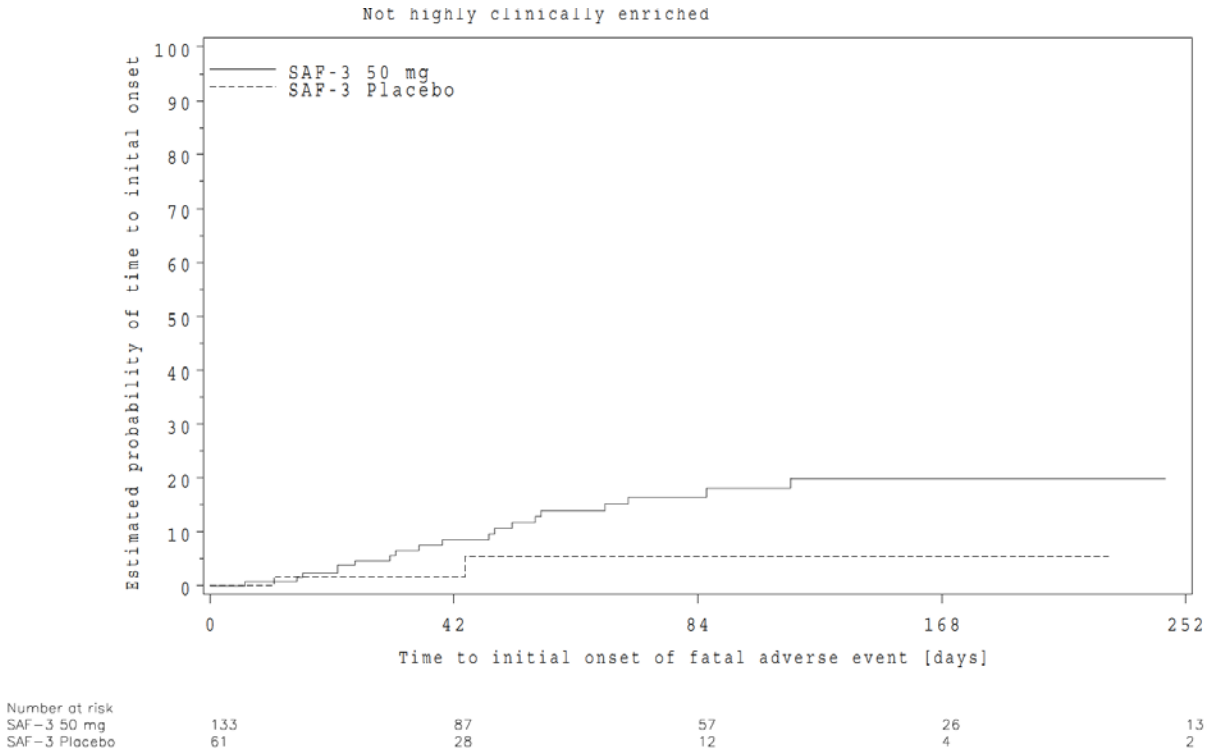
Table 75. Adverse events with a fatal outcome according to study treatment and by preferred term / SAF-3 (placebo/afatinib 50 mg).

MedDRA preferred term	Placebo (2.8 patient months[1]) n (%)	Afatinib 50 mg (5.1 patient months[1]) n (%)
All patients treated	195 (100.0)	390 (100.0)
Patients with any AE with a fatal outcome	15 (7.7)	44 (11.3)
Neoplasm malignant	7 (3.6)	14 (3.6)
Respiratory failure	2 (1.0)	6 (1.5)
Septic shock	0 (0.0)	3 (0.8)
Death	1 (0.5)	3 (0.8)
Pneumonia	0 (0.0)	2 (0.5)
Metastases to CNS	2 (1.0)	2 (0.5)
Pneumonitis	0 (0.0)	2 (0.5)
Lung infection	0 (0.0)	1 (0.3)
Cerebrovascular accident	0 (0.0)	1 (0.3)
Acute left ventricular failure	0 (0.0)	1 (0.3)
Cardiac failure	1 (0.5)	1 (0.3)
Cardiac tamponade	0 (0.0)	1 (0.3)
Cardio-respiratory arrest	0 (0.0)	1 (0.3)
Pericardial effusion	0 (0.0)	1 (0.3)
Sick sinus syndrome	0 (0.0)	1 (0.3)
Dyspnoea	1 (0.5)	1 (0.3)
Haemoptysis	0 (0.0)	1 (0.3)
Pulmonary embolism	0 (0.0)	1 (0.3)
Acute hepatic failure	0 (0.0)	1 (0.3)
Renal failure acute	0 (0.0)	1 (0.3)
General physical health deterioration	0 (0.0)	1 (0.3)
Multi-organ failure	0 (0.0)	1 (0.3)
Sudden cardiac death	0 (0.0)	1 (0.3)
Sudden death	0 (0.0)	1 (0.3)
Lymphangiosis carcinomatosa	1 (0.5)	0 (0.0)
NSCLC	1 (0.5)	0 (0.0)

[1]Mean time at risk.

Post hoc the study population was dichotomised in patients showing secondary resistance to erlotinib/gefitinib and the complementary subgroup. Despite longer time at risk in the enriched population, AEs with a fatal outcome were as frequently reported in the afatinib arm as in the placebo arm (10%). In the complementary group and despite more similar durations of time on study drug, however, the event rate was clearly higher in the afatinib arm, (14.2 % vs. 3.3). The Kaplan-Meier analysis is presented in Figure 14.

Figure 14. Kaplan–Meier (KM) analysis of fatal Adverse Events in the complementary subgroup of trial LUX-Lung 1



Adverse events of special interest

Diarrhoea

Diarrhoea was very frequent (>86%) with afatinib treatment regardless of whether the patient was EGFR TKI treatment-naïve (40 mg starting dose) or had been pre-treated with EGFR TKIs (50 mg starting dose) (see Table 76). In most patients, the first episode of diarrhoea occurred within the first 14 days of treatment with afatinib. Dehydration and renal impairment can be the more serious sequelae of diarrhoea, occurring subsequently to gastrointestinal fluid loss. In SAF-1, the incidence of dehydration was higher in the afatinib group (3.1%) than in the chemotherapy group (1.8%). Also in SAF-3, dehydration was more frequently reported for afatinib (4.6%) than for placebo (0.0%). In the afatinib trials, the incidence of renal impairment occurred with an overall incidence of 5.6% (SAF-5). In SAF-1, renal impairment was less frequent with afatinib 40 mg (6.1%) than with chemotherapy (16.2%), as was the incidence of drug-related renal impairment (3.5% vs. 14.4%). In SAF-3, renal impairment was reported for 5.4% of patients receiving afatinib 50 mg and for 1.5% of patients receiving placebo. The incidence of drug-related renal impairment in the afatinib group was 3.6%, whereas none of the renal events in the placebo group was considered drug-related. In both SAF-1 and SAF-3, few patients (<1%) discontinued treatment permanently due to renal impairment

Table 76. Frequency of patients with diarrhoea, outcome, and clinical consequences for SAFs 1 to 4 / TS

	EGFR TKI naïve patients (40 mg)			EGFR TKI pre-treated patients (50 mg)		
	SAF-1 Afatinib N (%)	Chemo N (%)	SAF-2 Afatinib N (%)	SAF-3 Afatinib N (%)	Placebo N (%)	SAF-4 Afatinib N (%)
Patients	229 (100.0)	111 (100.0)	497 (100.0)	390 (100.0)	195 (100.0)	1638 (100.0)
Patients with diarrhoea	220 (96.1)	25 (22.5)	453 (91.1)	339 (86.9)	18 (9.2)	1414 (86.3)
Patients with drug-related diarrhoea	218 (95.2)	17 (15.3)	449 (90.3)	330 (84.6)	12 (6.2)	1385 (84.6)
Patients with SAE	15 (6.6)	0	16 (3.2)	18 (4.6)	0	85 (5.2)
Highest CTCAE grade						
Grade 1	99 (43.2)	20 (18.0)	252 (50.7)	147 (37.7)	18 (9.2)	607 (37.1)
Grade 2	86 (37.6)	3 (2.7)	149 (30.0	125 (32.1)	0	508 (31.0)
Grade 3	34 (14.8)	2 (1.8)	51 (10.3)	67 (17.2)	0	295 (18.0)
Grade 4	0	0	0	0	0	4 (0.2)
Grade 5	0	0	0	0	0	0
Missing	1 (0.4)	0	1 (0.2)	0	0	0
Outcome of diarrhoea [1]						
Recovered	170 (74.2)	24 (21.6)	352 (70.8)	287 (73.6)	17 (8.7)	1127 (68.8)
Not yet recovered	46 (20.1)	1 (0.9)	94 (18.9)	41 (10.5)	1 (0.5)	206 (12.6)
Sequelae	0	0	3 (0.6)	1 (0.3)	0	2 (0.1)
Fatal	0	0	0	0	0	0
Unknown	4 (1.7)	0	4 (0.8)	10 (2.6)	0	79 (4.8)
Clinical consequences						
Dose reduced	45 (19.7)	1 (0.9)	64 (12.9)	80 (20.5)	0	372 (22.7)
Discontinued	3 (1.3)	0	4 (0.8)	14 (3.6)	0	73 (4.5)
Therapy required	204 (89.1)	10 (9.0)	381 (76.7)	289 (74.1)	6 (3.1)	1231 (75.2)

[1] Status at the time of the data cut-off for the submission

Rash / acne

Rash/acne was a very common event in patients treated with afatinib regardless of whether patients were EGFR TKI-naïve or pre-treated (see Table 77). In almost all patients in the afatinib groups was the occurrence of rash/acne+ considered as being related to study drug. For the majority of patients, the event started within the first 28 days of treatment (SAF-1: 79.7%, SAF-3: 65.1%). Substantial proportions of patients had recovered from rash/acne+ by the time of the data cut-off for the submission. In almost all cases, the occurrence of rash/acne+ could be managed by dose reduction or the instigation of additional therapy; less than 2% of patients in the afatinib groups permanently discontinued due to rash/acne.

Table 77. Frequency of patients with rash/acne+, outcome, and clinical consequences for SAFs 1 to 4 / TS

	EGFR TKI-naïve patients (40 mg)			EGFR TKI pre-treated patients (50 mg)		
	SAF-1 Afatinib N (%)	Chemo N (%)	SAF-2 Afatinib N (%)	SAF-3 Afatinib N (%)	Placebo N (%)	SAF-4 Afatinib N (%)
Patients	229 (100.0)	111 (100.0)	497 (100.0)	390 (100.0)	195 (100.0)	1638 (100.0)
Patients with rash/acne+	206 (90.0)	12 (10.8)	401 (80.7)	305 (78.2)	31 (15.9)	1193 (72.8)
Patients with drug-related rash/acne+	204 (89.1)	7 (6.3)	398 (80.1)	299 (76.7)	26 (13.3)	1168 (71.3)
Patients with SAE	1 (0.4)	0	3 (0.6)	2 (0.5)	0	6 (0.4)
Highest CTC grade						
Grade 1	69 (30.1)	8 (7.2)	163 (32.8)	117 (30.0)	25 (12.8)	526 (32.1)
Grade 2	100 (43.7)	4 (3.6)	166 (33.4)	132 (33.8)	6 (3.1)	470 (28.7)
Grade 3	37 (16.2)	0	71 (14.3)	56 (14.4)	0	196 (12.0)
Grade 4	0	0	1 (0.2)	0	0	1 (0.1)
Grade 5	0	0	0	0	0	0
Outcome of rash/acne+ [1]						
Recovered	111 (48.5)	10 (9.0)	194 (39.0)	211 (54.1)	23 (11.8)	776 (47.4)
Not yet recovered	89 (38.9)	2 (1.8)	194 (39.0)	71 (18.2)	6 (3.1)	312 (19.0)
Sequelae	1 (0.4)	0	1 (0.2)	0	0	1 (0.1)
Fatal	0	0	0	0	0	0

Unknown	5 (2.2)	0	12 (2.4)	23 (5.9)	2 (1.0)	104 (6.3)
Clinical consequences						
Dose reduced	44 (19.2)	0	69 (13.9)	58 (14.9)	0	205 (12.5)
Discontinued	0	0	6 (1.2)	7 (1.8)	0	31 (1.9)
Therapy required	188 (82.1)	10 (9.0)	293 (59.0)	201 (51.5)	10 (5.1)	809 (49.4)

[1] Status at the time of the data cut-off for the submission

Stomatitis

Stomatitis was a very frequent adverse event in the afatinib groups with slightly higher incidences in EGFR TKI-naïve patients than in EGFR TKI pre-treated patients (see Table 78). Almost all cases of stomatitis+ were considered drug-related, both in the afatinib groups and in the comparator groups. Stomatitis+ on treatment with afatinib tended to develop within the first 14 days of treatment (SAF-1: 57.2%, SAF-3: 42.9%).

Table 78. Frequency of patients with stomatitis, outcome, and clinical consequences for SAFs1 to 4 / TS

	EGFR TKI naïve patients (40 mg)			EGFR TKI pre-treated patients (50 mg)		
	SAF-1 Afatinib N (%)	Chemo N (%)	SAF-2 Afatinib N (%)	SAF-3 Afatinib N (%)	Placebo N (%)	SAF-4 Afatinib N (%)
Patients	229 (100.0)	111 (100.0)	497 (100.0)	390 (100.0)	195 (100.0)	1638 (100.0)
Patients with stomatitis+	168 (73.4)	19 (17.1)	297 (59.8)	237 (60.8)	5 (2.6)	890 (54.3)
Patients with drug-related stomatitis+	165 (72.1)	17 (15.3)	291 (58.6)	227 (58.2)	5 (2.6)	846 (51.6)
Patients with SAE	3 (1.3)	1 (0.9)	3 (0.6)	3 (0.8)	0	9 (0.5)
Highest CTC grade						
Grade 1	96 (41.9)	16 (14.4)	180 (36.2)	147 (37.7)	5 (2.6)	551 (33.6)
Grade 2	52 (22.7)	2 (1.8)	84 (16.9)	79 (20.3)	0	264 (16.1)
Grade 3	19 (8.3)	1 (0.9)	32 (6.4)	11 (2.8)	0	75 (4.6)
Grade 4	1 (0.4)	0	1 (0.2)	0	0	0
Grade 5	0	0	0	0	0	0
Outcome of stomatitis+ [1]						
Recovered	126 (55.0)	17 (15.3)	210 (42.3)	198 (50.8)	3 (1.5)	709 (43.3)
Not yet recovered	32 (14.0)	2 (1.8)	77 (15.5)	23 (5.9)	2 (1.0)	116 (7.1)
Sequelae	0	0	0	0	0	0
Fatal	0	0	0	0	0	0
Unknown	10 (4.4)	0	10 (2.0)	16 (4.1)	0	65 (4.0)
Clinical consequences						
Dose reduced	23 (10.0)	1 (0.9)	34 (6.8)	16 (4.1)	0	83 (5.1)
Discontinued	0	0	1 (0.2)	1 (0.3)	0	14 (0.9)
Therapy required	143 (62.4)	11 (9.9)	210 (42.3)	142 (36.4)	2 (1.0)	582 (35.5)

[1] Status at the time of the data cut-off for the submission

Ocular effects

The most frequent adverse events reported were conjunctivitis, dry eyes, and blepharitis as. As such, ocular effects generally manifested as superficial corneal irritation and inflammation. In study 1200.32 (SAF-1), 22.7% of patients in the afatinib 40 mg starting dose group experienced superficial ocular effects+. In most cases in the afatinib group (22.2%) the severity of ocular effects+ was CTCAE grade 1 or 2 and no events were classified as SAEs. One patient was reported to have keratitis (grade 3) that was classified as non-serious and resolved.

Hepatic impairment

In study 1200.32 (SAF-1), according to the Applicant comparable proportions of patients in the afatinib 40 mg starting dose and chemotherapy groups experienced adverse events of hepatic impairment+ (17.5% of patients in the afatinib group and 11.7% in the chemotherapy group; hazard ratio 0.83, p=0.5858) (see Table 79). The most frequent comprised adverse events were hepatic enzyme elevations for both treatment groups (16.6% of patients in the afatinib group and 10.8% of patients in the chemotherapy group). In afatinib-treated patients adverse events of hepatic enzyme elevations were mostly of grade 1 or 2; no event led to treatment discontinuation. All grade 3 events were transient and did not result in afatinib discontinuation. In study 1200.23 (SAF-3), slightly higher proportions of patients in the afatinib 50 mg starting dose group experienced adverse events of hepatic impairment+ (8.2% of patients in the afatinib group vs. 3.6% in the placebo group; hazard ratio 1.55, p=0.2992). The most frequent events reported comprised adverse events of hepatic enzyme elevations for both treatment groups. In patients treated with afatinib these events were mostly of grade 1 or 2, and did not lead to discontinuation. Three patients in the afatinib group experienced grade 3 adverse events of hepatic enzyme elevation, which were transient and did not result in discontinuation of the study medication. In the larger SAF-5 set, 10.1% of patients (95% CI 9.1%, 11.1%) experienced adverse events indicative of hepatic impairment.

Table 79. Incidende of hepatic impairment adverse events identified using modified SMQs, according to analysis set and treatment group/SAF-1 (chemotherapy/afatinib 40 mg) and SAF-3 (placebo/afatinib).

	SAF-1		SAF-3	
	Chemotherapy	Afatinib 40 mg	Placebo	Afatinib 50 mg
All patients treated n (%)	111 (100.0)	229 (100.0)	195 (100.0)	390 (100.0)
Mean (STD) time at risk [days][1]	103.2 (48.7)	316.0 (210.9)	82.9 (70.8)	146.1 (124.0)
Patients with hepatic impairment+ n (%)	13 (11.7)	40 (17.5)	7 (3.6)	32 (8.2)
95% CI	6.4, 19.2	12.8, 23.0	1.5, 7.3	5.7, 11.4
Hazard ratio, significance level	0.83, p=0.5858		1.55, p=0.2992	
Patients with AEs of hepatic enzyme elevations n (%)	12 (10.8)	38 (16.6)	5 (2.6)	22 (5.6)
ALT increased	4 (3.6)	25 (10.9)	3 (1.5)	15 (3.8)
AST increased	2 (1.8)	19 (8.3)	1 (0.5)	11 (2.8)
Blood alkaline phosphatase increased	2 (1.8)	8 (3.5)	2 (1.0)	3 (0.8)
Hepatic function abnormal	1 (0.9)	5 (2.2)	1 (0.5)	0 (0.0)
Liver function test abnormal	2 (1.8)	3 (1.3)	0 (0.0)	0 (0.0)
Blood bilirubin increased	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.3)
Gamma-glutamyltransferase increased	4 (3.6)	1 (0.4)	0 (0.0)	1 (0.3)
Hyperbilirubinaemia	0 (0.0)	1 (0.4)	0 (0.0)	4 (1.0)
Transaminases increased	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Patients with other hepatic AEs n (%)	1 (0.9)	3 (1.3)	2 (1.0)	11 (2.8)
Hepatitis	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Hypoalbuminaemia	1 (0.9)	1 (0.4)	2 (1.0)	6 (1.5)
Jaundice	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Acute hepatic failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Anorectal varices	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Cytolytic hepatitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hepatic pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hepatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

Adverse events were assessed using MedDRA version 14.1.
+Search terms are specified in Table 2: 2.
[1]Mean time at risk is assessed to the time of the first event for each patient.

Overall 7 patients in SAF-5, experienced fatal hepatic impairment+: of these 3 patients experienced fatal hepatic adverse events that were considered drug-related (as previously described): 1 patient in trial 1200.23 had fatal events of acute renal failure and acute hepatic failure that began approximately 10 days after starting afatinib treatment, and occurred in a patient with hepatitis B infection; 1 patient in trial 1200.42 with cytolitic hepatitis and disease progression; and 1 patient in trial 1200.42 with congestive heart failure and hepatic failure. The 4 remaining fatal hepatic impairment+ adverse events were considered not related to the study medication but were associated with progressive disease and/or sepsis.

The frequency of liver enzyme elevations is summarised in Table 80.

Table 80. Incidence of liver enzyme elevations, according to analysis set and treatment group/SAF-1 (chemotherapy/afatinib 40 mg), SAF-3 (placebo/afatinib 50 mg), and SAF-5 (any afatinib dose).

	SAF-1		SAF-3		SAF-5[1]
	Chemotherapy	Afatinib 40 mg	Placebo	Afatinib 50 mg	Any Afatinib dose
All patients treated n (%)	111 (100.0)	229 (100.0)	195 (100.0)	390 (100.0)	3865 (100.0)
Mean (STD) time at risk [days][2]	113 (43)	355 (203)	84 (70)	156 (130)	175 (166)
Maximum ALT level n (%)					
>5x ULN	2 (1.8)	8 (3.5)	0 (0.0)	5 (1.3)	93 (2.4)
Hazard ratio, significance level	1.11, p=0.9004		p=0.2189		-
>3x and ≤5x ULN	3 (2.7)	15 (6.6)	3 (1.5)	6 (1.5)	141 (3.6)
>5x and ≤10x ULN	1 (0.9)	6 (2.6)	0 (0.0)	4 (1.0)	68 (1.8)
>10x ULN and ≤20x ULN	1 (0.9)	2 (0.9)	0 (0.0)	1 (0.3)	20 (0.5)
>20xULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)
Maximum AST level n (%)					
>5x ULN	1 (0.9)	6 (2.6)	0 (0.0)	2 (0.5)	77 (2.0)
Hazard ratio, significance level	1.60, p=0.6683		p=0.4326		-
>3x and ≤5x ULN	0 (0.0)	10 (4.4)	3 (1.5)	6 (1.5)	118 (3.1)
>5x and ≤10x ULN	0 (0.0)	5 (2.2)	0 (0.0)	2 (0.5)	61 (1.6)
>10x ULN and ≤20x ULN	1 (0.9)	1 (0.4)	0 (0.0)	0 (0.0)	15 (0.4)
>20x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Maximum alkaline phosphatase n (%)					
>5x ULN	1 (0.9)	10 (4.4)	2 (1.0)	4 (1.0)	131 (3.4)
Hazard ratio, significance level	4.36, p=0.1263		0.62, p=0.5940		-
>3x and ≤5x ULN	1 (0.9)	12 (5.2)	4 (2.1)	11 (2.8)	162 (4.2)
>5x and ≤10x ULN	0 (0.0)	9 (3.9)	2 (1.0)	4 (1.0)	108 (2.8)
>10x ULN and ≤20x ULN	1 (0.9)	1 (0.4)	0 (0.0)	0 (0.0)	21 (0.5)
>20x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)

Based on normalised values.

Cardiac safety

The Phase II trial 1200.24 in patients with advanced solid tumours was specifically designed to assess a potential impact of afatinib on the QT-interval Table 81.

Table 81. Summary of QTcF changes from baseline to Day 14 in terms of 24-hour, time-matched mean / trial 1200.24

	N (%)	Mean QTcF (STD) in ms	Mean (SE) change from baseline in ms	2-sided 90% CI
All patients treated	60 (100.0)			
Baseline	60 (100.0)	393.8 (17.7)	-	-
Day 14	49 (81.7)	391.9 (17.0)	-0.3 (1.5[1])	-2.8, 2.3

SE = standard error
[1]Calculated using the t-distribution

Further information on the possible effect of afatinib on the QT-interval was provided by the retrospective, integrated analysis of ECG data from 4 Phase I studies with afatinib monotherapy in patients with advanced solid tumours. In addition, 12-lead resting ECGs were recorded at screening, during treatment (in approximately 12-weekly intervals), and at the end of treatment in the controlled studies 1200.32 (EGFR TKI-naïve patients) and 1200.23 (EGFR TKI pre-treated patients) and were analysed regarding a possible effect of afatinib on the QT-interval. Furthermore, afatinib studies included regular assessments of the left ventricular ejection fraction (LVEF) by Multiple Gated Acquisition scan (MUGA) or echocardiography. All analyses of ECG parameters and of LVEF were descriptive in nature.

The integrated analysis of ECG data from 4 Phase I studies with afatinib monotherapy in cancer patients did not suggest any clinically meaningful effect of afatinib on heart rate, atrioventricular node conduction (PR interval), or cardiac depolarisation (QRS interval). In trial 1200.24, afatinib 50 mg (given as a single dose or as a daily dose for 14 days) did not prolong the QT interval.

Findings based on QTcF were supported by those for the heart rate and the uncorrected QT interval. Afatinib did not alter the repolarisation morphology nor increased or changed other cardiac abnormalities as assessed by standard ECG monitoring. No clinically meaningful relationship was observed between afatinib exposure and changes in the QT-interval. Likewise, no clinically relevant changes in QTcF were observed in the controlled Phase III-studies with afatinib starting doses of 40 mg (trial 1200.32) or 50 mg (trial 1200.23).

The assessment of LVEF based on MUGA or echocardiography showed that treatment with afatinib did not result in a LVEF reduction relative to chemotherapy (SAF-1) or placebo (SAF-3) (see Table 82). The incidence of heart failure events or decreases in LVEF (reported as AEs) was low; in the large SAF-5, 1.4% of patients were reported with these events (heart failure events: 0.8%; decrease in LVEF: 0.5%).

Table 82. Incidence of adverse events identified using the modified SMQ for cardiac failure and/or decreased LVEF / SAF-1,2 and 5.

	SAF-1		SAF-3		SAF-5
	Chemotherapy	Afatinib 40 mg	Placebo	Afatinib 50 mg	Any Afatinib dose
All patients treated n (%)	111 (100.0)	229 (100.0)	195 (100.0)	390 (100.0)	3865 (100.0)
Mean (STD) time at risk [days][1]	112.6 (43.3)	349.2 (202.9)	83.9 (70.3)	156.1 (129.8)	174.0 (165.4)
Patients with any heart failure AE+ or LVEF decrease[2] n (%)	1 (0.9)	5 (2.2)	1 (0.5)	4 (1.0)	53 (1.4)
95% CI	0.0, 4.9	0.7, 5.0	0.0, 2.8	0.3, 2.6	1.0, 1.8
Hazard ratio, significance level	1.18, p=0.8870		1.32, p=0.8086		-
LVEF decrease[2]	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	21 (0.5)
Cardiac failure	1 (0.9)	0 (0.0)	1 (0.5)	2 (0.5)	7 (0.2)
Pulmonary oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.1)
Acute left ventricular failure	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	3 (0.1)
Acute pulmonary oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Cardiopulmonary failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Diastolic dysfunction	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	3 (0.1)
Left ventricular dysfunction	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	3 (0.1)
Cardiac failure congestive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Dilatation ventricular	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.0)
Cardiomegaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Hepatic congestion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Pulmonary congestion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Ventricular failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

Adverse events were assessed using MedDRA version 14.1.
+Search terms are specified in Table 2: 3.
[1]Mean time at risk is assessed to the time of the first event for each patient.
[2]Assessed by echocardiography or MUGA and reported as an AE.

Interstitial lung disease

The occurrence of ILD-like events was evaluated based on the largest safety set SAF-5. Using the broad SMQ search, 59 patients (1.5%) in SAF-5 were identified with ILD-like events, and 38 patients (1.0%) with ILD-like events of grade 3 or higher; 15 events (0.4%) were fatal. It should be considered that the broad SMQ used for identifying ILD-like events included events such as acute respiratory distress syndrome, pneumonitis, and radiation pneumonitis. Therefore, the ILD-like events considered as drug-related by the investigator are regarded as more informative. A total of 28 patients (0.7%) in SAF-5 were reported with drug-related ILD-like events, including 5 patients who died due to these events. Drug-related ILD was reported for 20 patients; of those, 2 patients died.

Laboratory findings

When considering trial 1200.32 (SAF-1) and taking into account the difference in study drug exposure between treatment groups, a higher proportion of patients in the chemotherapy group experienced a possibly clinically significant haemoglobin abnormality (46.3% of patients vs. 8.9% in the afatinib 40 mg starting dose group); however higher proportions of patients treated with afatinib experienced a possibly clinically significant laboratory abnormalities in potassium

(8.4% of patients vs. 1.9% in the chemotherapy group), AST (8.4% vs. 0.9%), and ALT (10.2% vs. 4.6%) levels (see Table 83).

Table 83. Patients with a possibly clinically significant laboratory abnormality, according to treatment group / SAF-1 (chemotherapy/afatinib 40 mg)

Parameter	Chemotherapy (3.7 months[1])		Afatinib 40 mg (11.7 months[1])	
	All patients	Number with PCSA n (%)	All patients	Number with PCSA n (%)
Haematology				
Haemoglobin	108	50 (46.3)	225	20 (8.9)
Biochemistry				
Potassium	107	2 (1.9)	225	19 (8.4)
Sodium	108	3 (2.8)	225	13 (5.8)
AST	107	1 (0.9)	225	19 (8.4)
ALT	108	5 (4.6)	225	23 (10.2)
Total bilirubin	107	0 (0.0)	225	11 (4.9)
Creatinine	107	5 (4.7)	225	7 (3.1)

PCSA = possibly clinically significant abnormality, which was defined as an increase of at least one CTC grade from baseline to CTC grade 2 or higher.
Based on standardised values.
[1]Mean time at risk.

When considering trial 1200.23 (SAF-3) and taking into account the difference in study drug exposure between treatment groups, a higher proportion of patients in the afatinib 50 mg starting dose group experienced possibly clinically significant abnormalities in haemoglobin (14.5% of patients vs. 4.2% in the placebo group) and potassium (6.2% vs. 0.0%) (see Table 84).

Table 84. Patients with a possibly clinically significant laboratory abnormality, according to treatment group / SAF-3 (placebo/afatinib 50 mg)

Parameter	Placebo (2.8 months[1])		Afatinib 50 mg (5.1 months[1])	
	All patients	Number with PCSA n (%)	All patients	Number with PCSA n (%)
Haematology				
Haemoglobin	190	8 (4.2)	385	56 (14.5)
Biochemistry				
Potassium	190	0 (0.0)	385	24 (6.2)
Sodium	190	5 (2.6)	385	17 (4.4)
AST	188	5 (2.7)	384	8 (2.1)
ALT	188	2 (1.1)	384	14 (3.6)
Total bilirubin	188	1 (0.5)	384	6 (1.6)
Creatinine	189	0 (0.0)	385	11 (2.9)

PCSA = Possibly clinically significant abnormality, which was defined as an increase of at least one CTC grade from baseline to CTC grade 2 or higher.
Based on standardised values.
[1]Mean time at risk.

Afatinib was associated with small to moderate changes in haematology parameters which remained, however, notably below the changes observed with chemotherapy in study 1200.32 (SAF-1). The proportion of patients with a worst on-treatment haemoglobin value of grade 3 or above observed with afatinib (SAF-1: 2.7%, SAF-3: 1.8%). There was no indication of an increased risk to experience bleeding events in patients receiving afatinib.

For lymphocytes, a worst grade of 3 or above was seen in slightly more patients receiving afatinib (SAF-1: 8.4%, SAF-3: 6.8%) than receiving placebo (4.7%); still, percentages were lower than those with chemotherapy (10.2%) (see Table 85). No relevant changes were observed with afatinib for platelets, white blood cells, or neutrophils.

Table 85. Patients with leukopenia+, clinical consequences, outcome, and time of onset, by treatment / TS

	Afatinib	Chemotherapy
Patients [N (%)]	229 (100.0)	111 (100.0)
Mean total time at risk[1] [days]	354.8	112.8
Patients with leukopenia+ [N (%)]	11 (4.8)	48 (43.2)
Hazard ratio vs. chemotherapy (95% CI)[2]	0.050 (0.023, 0.109)	
p-value (2-sided)	<0.0001	
Considered as drug-related	8 (3.5)	48 (43.2)
Reported as SAE	0 (0.0)	0 (0.0)
Outcome of leukopenia+ [N (%)]		
Recovered	9 (3.9)	47 (42.3)
Not recovered	2 (0.9)	1 (0.9)
Sequelae	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)
Clinical consequences of leukopenia+ [N (%)]		
Dose reduction	3 (1.3)	3 (2.7)
Permanent discontinuation	0 (0.0)	1 (0.9)
Therapy required	1 (0.4)	10 (9.0)
Patients with leukopenia+ by worst CTCAE Grade [N (%)]		
Grade 1	4 (1.7)	8 (7.2)
Grade 2	3 (1.3)	11 (9.9)
Grade 3	4 (1.7)	26 (23.4)
Grade 4	0 (0.0)	3 (2.7)
Grade 5	0 (0.0)	0 (0.0)
Time to first onset by category[3] [N (%)]		
Day 1 to 14	0 (0.0)	8 (7.2)
Day 15 to 28	1 (0.4)	13 (18.9)
Day 29 to 84	4 (2.2)	20 (39.4)
>Day 84	6 (6.3)	7 (49.5)

[1] Time at risk = (EOT date - start of treatment date) + 1 day + 28 day post-treatment period.
[2] Hazard ratio of first leukopenia+ from Cox proportional hazards model with treatment fitted as only factor; p-value derived from log-rank test.
[3] Number of patients with initial onset of leukopenia+ within the time interval (cumulative Kaplan-Meier estimate of AE onset by interval end).

Safety in special populations

No specific studies have been submitted. Safety in special populations was analysed using standard subgroups, to determine the influence of demographic characteristics (gender, age, race, body weight), disease characteristics (Eastern Cooperative Oncology Group [ECOG] performance score at baseline, renal function at baseline, hepatic function at baseline), and and extrinsic factors (geographic region, smoking status) on the afatinib safety profile.

Higher incidences of adverse events were observed for elderly patients than for younger patients (≥65 years vs. <65 years); this was seen for both starting doses. Similar observations were made for Caucasians (compared with Asians); however, this might also be explained by the fact that the adverse event incidences reported by Asian patients are generally lower than those reported by Caucasian patients.

A summary of the frequency of ADRs by age group is shown in Table 86.

Table 86. Summary of the frequency of ADRs by age group.

MedDRA Terms	Age <65 number (percentage) [2]	Age 65-74 number (percentage) [2]	Age 75-84 number (percentage) [2]	Age 85+ number (percentage [2]
Total ADRs	2486 (94.7)	927 (95.8)	247 (95.7)	11 (84.6)
Serious ADRs – Total	329 (12.5)	156 (16.1)	39 (15.1)	0
- Fatal	18 (0.7)	10 (1.0)	2 (0.8)	0
- Hospitalization/prolong existing hospitalization	291 (11.1)	141 (14.6)	35 (13.6)	0
- Life-threatening	12 (0.5)	4 (0.4)	1 (0.4)	0
- Disability/incapacity	5 (0.2)	1 (0.1)	1 (0.4)	0
- Other (medically significant)	19 (0.7)	5 (0.5)	5 (1.9)	0
AE leading to drop-out	295 (11.2)	176 (18.2)	**57 (22.1)**	3 (23.1)
Psychiatric disorders (SOC)	51 (1.9)	14 (1.4)	6 (2.3)	0
Nervous system disorders (SOC)	365 (13.9)	159 (16.4)	43 (16.7)	0
Accidents and injuries (SMQ)	26 (1.0)	8 (0.8)	6 (2.3)	0
Cardiac disorders (SOC)	18 (0.7)	9 (0.9)	4 (1.6)	1 (7.7)
Vascular disorders (SOC)	67 (2.6)	24 (2.5)	13 (5.0)	0
Cerebrovascular disorders (SMQ)	4 (0.2)	2 (0.2)	2 (0.8)	0
Infections and infestations (SOC)	923 (35.1)	349 (36.1)	84 (32.6)	3 (23.1)
Quality of life decreased (PT)	2 (0.1)	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	52 (2.0)	29 (3.0)	3 (1.2)	0

[2] Cumulative number over all indications in the clinical trial programme and percentage over the age group

Discontinuation due to adverse events

Discontinuation due to adverse events is shown in Tables 87 and 88.

Table 87. Adverse events leading to discontinuation in at least 1% of patients in any treatment group for SAF-1 and SAF-2, all grades and CTCAE grade 3 and MedDRA preferred terms /TS

	SAF-1				SAF-2	
	Afatinib 40 mg		Chemotherapy		Afatinib 40 mg	
	All Grades N (%)	Grade 3 N (%)	All Grades N (%)	Grade 3 N (%)	All Grades N (%)	Grade 3 N (%)
Patients	229 (100.0)	229 (100.0)	111 (100.0)	111 (100.0)	497 (100.0)	497 (100.0)
Patients with AEs	229 (100.0)	117 (51.1)	109 (98.2)	49 (44.1)	491 (98.8)	201 (40.4)
Patients with AEs leading to discontinuation	32 (14.0)	14 (6.1)	17 (15.3)	5 (4.5)	61 (12.3)	27 (5.4)
Diarrhoea	3 (1.3)	2 (0.9)	0	0	4 (0.8)	3 (0.6)
Fatigue+	0	0	4 (3.6)	2 (1.8)	0	0
Rash/acne+	0	0	0	0	6 (1.2)	6 (1.2)
ILD	2 (0.9)	1 (0.4)	0	0	5 (1.0)	2 (0.4)
Patients with related AEs leading to discontinuation	18 (7.9)	8 (3.5)	13 (11.7)	4 (3.6)	35 (7.0)	18 (3.6)
Diarrhoea	3 (1.3)	2 (0.9)	0	0	3 (0.6)	2 (0.4)
Fatigue+	0	0	3 (2.7)	1 (0.9)	0	0
Rash/acne+	0	0	0	0	6 (1.2)	6 (1.2)
ILD	2 (0.9)	1 (0.4)	0	0	5 (1.0)	2 (0.4)

ILD=Interstitial lung disease

Table 88. Adverse events leading to discontinuation in at least 1% of patients in any treatment group for SAF-3 and SAF-4, all grades and CTCAE grade 3 and MedDRA preferred terms /TS

	SAF-3				SAF-4	
	Afatinib 50 mg		Placebo		Afatinib 50 mg	
	All Grades N (%)	Grade 3 N (%)	All Grades N (%)	Grade 3 N (%)	All Grades N (%)	Grade 3 N (%)
Patients	390 (100.0)	390 (100.0)	195 (100.0)	195 (100.0)	1638 (100.0)	1638 (100.0)
Patients with AEs	384 (98.5)	160 (41.0)	169 (86.7)	33 (16.9)	1620 (98.9)	687 (41.9)
Patients with AEs leading to discontinuation	70 (17.9)	29 (7.4)	12 (6.2)	3 (1.5)	375 (22.9)	194 (11.8)
Diarrhoea	14 (3.6)	8 (2.1)	0	0	73 (4.5)	43 (2.6)
Neoplasm malignant	7 (1.8)	1 (0.3)	3 (1.5)	0	13 (0.8)	1 (0.1)
Rash/acne+	7 (1.8)	5 (1.3)	0	0	31 (1.9)	21 (1.3)
Nausea	5 (1.3)	2 (0.5)	0	0	10 (0.6)	4 (0.2)
Respiratory failure	5 (1.3)	0	1 (0.5)	0	8 (0.5)	0
Vomiting	5 (1.3)	2 (0.5)	0	0	16 (1.0)	9 (0.5)
Decreased appetite	4 (1.0)	2 (0.5)	0	0	20 (1.2)	9 (0.5)
Lung infection	4 (1.0)	1 (0.3)	0	0	7 (0.4)	4 (0.2)
Fatigue+	3 (0.8)	3 (0.8)	0	0	22 (1.3)	15 (0.9)
Dyspnoea	2 (0.5)	2 (0.5)	0	0	32 (2.0)	15 (0.9)
General physical health deterioration	2 (0.5)	1 (0.3)	0	0	23 (1.4)	14 (0.9)
Patients with related AEs leading to discontinuation	30 (7.7)	15 (3.8)	1 (0.5)	1 (0.5)	192 (11.7)	112 (6.8)
Diarrhoea	14 (3.6)	8 (2.1)	0	0	73 (4.5)	43 (2.6)
Rash/acne+	7 (1.8)	5 (1.3)	0	0	31 (1.9)	21 (1.3)
Vomiting	4 (1.0)	1 (0.3)	0	0	13 (0.8)	7 (0.4)
Decreased appetite	3 (0.8)	2 (0.5)	0	0	18 (1.1)	9 (0.5)

Post marketing experience

No studies have been submitted.

2.6.1. Discussion on clinical safety

The safety evaluation of afatinib is based on the data from more than 3,800 patients, including more than 1,638 NSCLC patients treated with 50 mg monotherapy and more than 497 NSCLC patients treated with 40 mg monotherapy. The safety data provided by the applicant are considered comprehensive.

All subjects (100%) who received afatinib have presented any AEs and 60.7% were ≥ grade CTCAE 3. The most common AEs observed in afatinib group were diarrhoea (96.1%), rash/acne (90.0%), stomatitis (73.4%), and nail effects (61.6%). Ocular effects were seen in 22.7%, nauseas (25%), vomits (22%), epistaxis (17%), hepatic enzyme elevation (16.6%), cough (15%), headache (14%), back pain (14%), nasopharyngitis (14%), constipation (13%), pyrexia (12.2%), upper respiratory tract infection (10.9%) and dizziness (10.9%).

In patients treated with once daily afatinib 40 mg, dose reductions due to ADRs occurred in 57% of the patients. Discontinuation due to ADRs diarrhoea and rash/acne was 1.3% and 0%, respectively. Overall, dose reduction led to a lower frequency of common adverse reactions.

In LUX Lung 1, in the complementary set of patients to those with tumours showing secondary resistance to reversible TKIs there were more AEs leading to death in the afatinib arm 19/133 vs. 2/61. According to standard practice patients were followed for AEs on study therapy plus 28 days and AEs related to tumour progression were reported as AEs, including AEs with fatal outcome. The event pattern is not unexpected and in most cases was likely related to tumour progression.

The main identified risks include diarrhoea (including dehydration and renal impairment secondary to diarrhoea), rash/acne, ILD and keratitis. In addition, important potential risks include decreased LVEF/heart failure, hepatic failure and pancreatitis. Sections 4.4 and 4.8 of the SmPC contain adequate information addressing these risks:

Diarrhoea

Diarrhoea, including severe diarrhoea, has been reported during treatment with GIOTRIF. Diarrhoea may result in dehydration with or without renal impairment, which in rare cases has resulted in fatal outcomes. Diarrhoea usually occurred within the first 2 weeks of treatment. Grade 3 diarrhoea most frequently occurred within the first 6 weeks of treatment.

Proactive management of diarrhoea including adequate hydration combined with anti-diarrhoeal medicinal products especially within the first 6 weeks of the treatment is important and should start at first signs of diarrhoea. Antidiarrhoeal medicinal products (e.g. loperamide) should be used and if necessary their dose should be escalated to the highest recommended approved dose. Anti-diarrhoeal medicinal products should be readily available to the patients so that treatment can be initiated at first signs of diarrhoea and continued until loose bowel movements cease for 12 hours. Patients with severe diarrhoea may require interruption and dose reduction or discontinuation of therapy with afatinib. Patients who become dehydrated may require administration of intravenous electrolytes and fluids.

Skin related adverse events

Rash/acne has been reported in patients treated with afatinib. In general, rash manifests as a mild or moderate erythematous and acneiform rash, which may occur or worsen in areas exposed to sun. For patients who are exposed to sun, protective clothing, and use of sun screen is advisable. Early intervention (such as emollients, antibiotics) of dermatologic reactions can facilitate continuous GIOTRIF treatment. Patients with severe skin reactions may also require temporary interruption of therapy, dose reduction (see section 4.2), additional therapeutic intervention, and referral to a specialist with expertise in managing these dermatologic effects.

Bullous, blistering and exfoliative skin conditions have been reported including rare cases suggestive of Stevens-Johnson syndrome. Treatment with this medicinal product should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

Interstitial Lung Disease (ILD)

There have been reports of ILD or ILD-like adverse reactions (such as lung infiltration, pneumonitis, acute respiratory distress syndrome, allergic alveolitis), including fatalities, in patients receiving afatinib for treatment of NSCLC. ILD-like adverse reactions were reported in 0.7%. CTCAE Grade ≥ 3 ILD-like adverse reactions were reported in 0.5% of patients. A warning addressing this risk has been included in section 4.4 of the SmPC.

Keratitis

Symptoms such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. This medicinal product should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration. A warning addressing this risk has been included in section 4.4 of the SmPC.

Severe hepatic impairment

Hepatic failure, including fatalities, has been reported during treatment with afatinib in less than 1% of patients. In these patients, confounding factors have included pre-existing liver disease and/or comorbidities associated with progression of underlying malignancy. Periodic liver function testing is recommended in patients with pre-existing liver disease. In addition, liver function test abnormalities (including elevated ALT and AST) were observed in patients receiving afatinib 40 mg. These elevations were mainly transient and did not lead to discontinuation. Grade 2 (> 2.5 to 5.0 times upper limit of normal (ULN) ALT elevations occurred in < 8% of patients treated with this medicinal product. Grade 3 (> 5.0 to 20.0 times ULN) elevations occurred in <4% of patients treated with afatinib. This risk has been adequately highlighted in sections 4.4 and 4.8 of the SmPC.

Left ventricular function

Left ventricular dysfunction has been associated with HER2 inhibition. Based on the available clinical trial data, there is no suggestion that afatinib causes an adverse reaction on cardiac contractility. However, this medicinal product has not been studied in patients with abnormal left ventricular ejection fraction (LVEF) or those with significant cardiac history. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during afatinib treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered. In addition patients with an ejection fraction below the institution's lower limit of normal, cardiac consultation as well as treatment interruption or discontinuation should be considered. A warning addressing this risk has been included in section 4.4 of the SmPC.

The highest dose of afatinib studied in a limited number of patients in Phase I clinical trials was 160 mg once daily for 3 days and 100 mg once daily for 2 weeks. The adverse reactions observed at these doses were primarily dermatological (rash/acne) and gastrointestinal events (especially diarrhoea). Overdose in 2 healthy adolescents involving the ingestion of 360 mg each of afatinib (as part of a mixed drug ingestion) was associated with adverse events of nausea,

vomiting, asthenia, dizziness, headache, abdominal pain and elevated amylase (< 1.5 times ULN). Both individuals recovered from these adverse events.

Despite a large safety data base, adverse reactions related to the pan-HER character of afatinib and the covalent binding properties have not been identified. Formation of covalent protein adducts might result in hypersensitivity reactions. There were, however, no non-clinical data indicative of this. The putative consequences of adducts constituting a "deep compartment" from a PK perspective will be further addressed post-marketing in patients who have been treated long-term with afatinib and where PK data are sampled after stopping afatinib therapy.

The types of adverse reactions (ADRs) were generally associated with the EGFR inhibitory mode of action of afatinib. In addition, based on indirect comparisons, the toxicity profile of afatinib appears very similar to what has been reported for other available EGFR-TKIs (see cross-trial comparison of safety and tolerability of afatinib, erlotinib and gefitinib in Tables 89-91).

Table 89. Patients included into safety analyses in the experimental arm of 1st line NSCLC trials and median treatment duration.

	LUX-Lung 3 Afatinib	**LUX-Lung 6 Afatinib**	**IPASS Gefitinib**	**EURTAC Erlotinib**
Mutation status	EGFR mutation positive	EGFR mutation positive	Unselected	EGFR mutation positive
N (%)	229 (100)	239 (100)	607 (100)	86 (100)
Median treatment duration (months), range	11.0 (0.2-27.2)	13.1 (0.1 – 28.6)	5.6 (0.1 - 22.8)	8.2 (0.3 – 32.9)

Table 90. Categories of AEs in 1st line trials of EGFR mutation positive NSCLC.

	LUX-Lung 3 Afatinib	**LUX-Lung 6 Afatinib**	**IPASS Gefitinib**	**EURTAC Erlotinib**
N (%)	229 (100)	239 (100)	607 (100)	86 (100)
Treatment-related AEs (%)	100.0	98.7		92.0
Any AE ≥Grade 3 (%)	**60.7**	**46.9**	**28.7**	**54.6**
Related AEs ≥ Grade 3 (%)	48.9	36.0		
AEs leading to dose reduction and or modification (%)	**57.0**	**32.2**	**16.1**	**26.7**
AE leading to treatment discontinuation (%)	14.0 [a]	9.6 [a]	6.9	13.3
Related AEs leading to treatment discontinuation (%)	7.9	5.9		6.7
SAE (%)	**28.8**	**15.1**	**16.3**	**32.0**
Fatal SAE (%)	**5.7**	**5.9**	**3.8**	**9.3**
Related fatal SAE (%)	1.7	0.4		1.0

[a] includes AE associated with progressive disease

Table 91. Most frequently reported Grade 3/4 *AEs in 1st line trials of EGFR mutation positive NSCLC trials (>20% for at least one agent).

	LUX-Lung 3 Afatinib	LUX-Lung 6 Afatinib	IPASS Gefitinib	EURTAC Erlotinib
N (%)	229 (100)	239 (100)	607 (100)	86 (100)
Diarrhoea	14.8	5.9	3.8	5.0
Rash/acne	16.2+	14.6+	3.1	13.0
Stomatitis/mucositis	8.7+	5.4+	0.2	NR
Paronychia	11.4	0	0.3	NR
Dry skin	0.4	0	0	NR
Decreased appetite	4.4	2.5	1.5	0
Pruritus	0.4+	0.4+	0.7	NR
Nausea	1.3	0.4	0.3	NR
Fatigue	3.1+	2.1+	0.3	6.0
Vomiting	4.4	1.3	0.2	NR
Dyspnoea	0.9	1.7	NR	NR
Cough	0	0	NR	NR

* IPASS data include the Grade 5 events as per the published data

\+ grouped term

Altogether there might be quantitative differences in the safety profiles comparing afatinib with gefitinib and erlotinib, but these differences are not of a magnitude constituting a blocking issue from a regulatory perspective.

The CHMP was of the opinion that due to the limited number of patients in study Lux-Lung 2, further characterisation of the safety and efficacy of afatinib 40 mg qd in patients pre-treated with chemotherapy was needed. This concern has been addressed in the RMP, where it has been included as missing information. The applicant will perform a post-authorisation safety study (PASS) to collect additional safety and efficacy data in this subgroup of patients, as reflected in the PhV plan of the RMP as a category 3 (required) study.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety profile of afatinib in treatment of EGFR TKI-naïve adult patients with locally advanced or metastatic NSCLC with activating EGFR mutation(s) has been adequately characterised based on a comprehensive safety database in overall 3868 patients, including 497 NSCLC patients treated with 40 mg monotherapy. The most frequent ADRs were diarrhoea and skin related adverse events as well as stomatitis and paronychia. The main identified risks include diarrhoea (including dehydration and renal impairment secondary to diarrhoea), rash/acne, ILD and keratitis.

Patients resistant to EGFR-TKIs in the complementary set experienced an increased number of on-treatment deaths compared to placebo.

Based on indirect comparisons, the toxicity profile of afatinib appears similar to what has been reported for other available EGFR-TKIs.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1.2, the PRAC considers by consensus that the risk management system for afatinib (Giotrif) in the treatment:

- of Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).

is agreeable.

The PRAC however noted that some updates to the RMP might be warranted following further discussions at the CHMP with regards to the final indication of Giotrif and the possible need for a PK study in the post-authorisation phase.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The Applicant identified the identified the following safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	- Diarrhoea (incl. dehydration and renal impairment secondary to diarrhoea) - Severe skin reactions - Interstitial Lung Disease - Keratitis -Hepatic impairment
Important potential risks	- Decreased Left ventricular ejection fraction (LVEF)/heart failure - Pancreatitis -Developmental toxicity -Gastrointestinal perforation -Hypersensitivity reactions
Missing information	- Paediatric patients (<18 years) - Patients with severe renal impairment - Patients with severe hepatic impairment - Patients with cardiac impairment

The PRAC agreed.

- **Pharmacovigilance plans**

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures

- **Risk minimisation measures**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Diarrhoea (incl. dehydration and renal impairment secondary to diarrhoea)	*Diarrhoea has been added to sections 4.4 (special warnings and precautions for use) and 4.8 (undesirable effects) of the SmPC.*	*None*
Severe skin reactions	*Rash/acne has been added to sections 4.4 (special warnings and precautions for use) and 4.8 (undesirable effects) of the SmPC.*	*None*
ILD	*ILD has been added to sections 4.4 (special warnings and precautions for use) and 4.8 (undesirable effects) of the SmPC.*	*None*
Keratitis	*Keratitis has been added to sections 4.4 (special warnings and precautions for use) and 4.8 (undesirable effects) of the SmPC.*	*None*
Hepatic impairment	*Hepatic failure has been added to section 4.4 (special warnings and precautions for use) of the SmPC.*	*None*
Decreased LVEF/heart failure	*Decreased LVEF/heart failure as been added to section 4.4 (special warnings and precautions for use) of the SmPC.*	*None*
Pancreatitis	*Not applicable*	*None*
Developmental toxicity	*Warnings on the potential of EGFR targeting medicinal products to cause foetal harm have been included in section 4.6 (Fertility, pregnancy and*	*None*

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	lactation)	
Gastrointestinal perforation	*Not applicable*	*None*
Hypersensitivity reactions	*Giotrif is contraindicated in patients with hypersensitivity to afatinib or any of the excipients contained in the product.*	*None*
Paediatric patients (<18 years)	*Information on paediatric patients has been added to section 4.2 (posology and method of administration) of the SmPC.*	*None*
Patients with severe renal impairment	*Information on patients with renal impairment has been added to section 4.2 (posology and method of administration) of the SmPC.*	*None*
Patients with severe hepatic impairment	*Information on patients with hepatic impairment has been added to section 4. 2 (posology and method of administration) of the SmPC.*	*None*
Patients with cardiac impairment	*Information on left ventricular function has been added to section 4.4 (special warnings and precautions for use) of the SmPC.*	*None*

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes. In addition, the CHMP considered that due to the limited number of patients treated with afatinib after having received prior chemotherapy treatment, the Applicant should conduct a post-authorisation safety study to further characterise of the safety and efficacy of afatinib in this sub-population of patients.

Finally the CHMP also requested a post-authorisation PK study to further characterise the potential developmental toxicity of afatinib.

Following these recommendations the Applicant submitted an updated RMP to address these issues.

In the latest RMP, the following safety concerns have been included:

Table of safety concerns:

Summary of safety concerns	
Important identified risks	- Diarrhoea (incl. dehydration and renal impairment secondary to diarrhoea) - Severe skin reactions - Interstitial Lung Disease - Keratitis -Hepatic impairment
Important potential risks	- Decreased Left ventricular ejection fraction (LVEF)/heart failure - Pancreatitis -Developmental toxicity -Gastrointestinal perforation -Hypersensitivity reactions
Missing information	- Paediatric patients (<18 years) - Patients with severe renal impairment - Patients with severe hepatic impairment - Patients with cardiac impairment -Chemotherapy pre-treated patients with EGFR M +NSCLC

The Applicant also provided an updated Pharmacovigilance Plan to include the two safety studies requested by the CHMP:

Ongoing and planned additional PV studies/activities in the pharmacovigilance plan

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Pharmacokinetics of afatinib for the determination of washout following multiple and prolonged dosing (cat 3)	Time for complete wash out of afatinib	Developmental toxicity	Planned	Q4 2015 (planned)
Additional safety and efficacy data of afatinib 40mg qd in chemotherapy pre-treated patients with EGFR M +NSCLC (cat 3)	Further characterise safety and efficacy of afatinib 40 mg qd in patients pre-treated with chemotherapy	Chemotherapy pre-treated patients with EGFR M +NSCLC (additional characterisation)	Planned	Q4 2017 (planned)

Further changes were implemented to the RMP to reflect the CHMP approved indication for afatinib.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

First line: The pivotal study for this application (LUX Lung 3) was a conventionally designed, well conducted, afatinib versus chemotherapy (pemetrexed/cisplatin) comparative study in the treatment of naïve NSCLC patients with activating EGFR-TK mutations. The results in terms of progression free survival (HR 0.58, CI 95% 0.425, 0.784, p=0.0004) were statistically significant in favour of afatinib and of clinically benefit for NSCLC patient with activating EGFR-TK mutations.

As supportive evidence of efficacy, the results of the afatinib versus cisplatin/gemcitabine comparative study LUX Lung 6 also showed superiority in terms of PFS (HR 0.28, CI 95% 0.201, 0.388, p<0.0001) in the treatment of naïve NSCLC patients with activating EGFR-TK mutations.

In addition improved symptom control has been shown.

Evidence provided robustly demonstrates patient benefit. These results are in-line with available data for other approved EGFR-TKIs erlotinib and gefitinib.

Chemotherapy pre-treated patients:

Supportive evidence based on the Phase II study LUX-Lung 2 has shown that that the activity of afatinib in patients with EGFR mutations is not limited by line of therapy; both first- and second-line patients evidenced response rates. First-line patients treated with an afatinib starting dose of either 40 mg or 50 mg had a 66% confirmed ORR and a 12- month median PFS, and a median OS has not yet been reached; second-line patients treated with 50 mg of afatinib had a 57% confirmed ORR, a 8.3-month median PFS, and a 24-month median OS.

In addition there are no mechanistic arguments that would justify a detrimental effect of chemotherapy on the efficacy of TKIs in 2nd line. Moreover, prognostic factors are not expected to change significantly due to previous treatment with chemotherapy.

Patients with secondary resistance to erlotinib/gefitinib: The supportive Phase III study LUX-Lung 1 comparing afatinib versus placebo in NSCLC patients failing erlotinib/gefitinib did not meet its primary endpoint of Overall Survival (OS) (HR=1.08, CI 95% 0.862-1.346, p=0.7428). Although activity in progression free survival (PFS) was observed as a secondary endpoint (HR=0.38, CI 95% 0.31, 0.48), p<0.0001), it did not translate into a survival benefit to the patients.

Post-hoc analysis performed by the company further enriched the population of EGFR mutation patients to 83% (originally estimated 68%). OS in the enriched population improved (HR=0.91, CI 95% 0.73, 1.14). In this subgroup clinically enriched for activating mutations prior to erlotinib/gefitinib therapy, the secondary endpoint showed a benefit in terms of PFS (HR=0.279, CI 95 % 0.21-0.36), with a median PFS increase of 3.4 months.

Uncertainty in the knowledge about the beneficial effects

Patients with secondary resistance to erlotinib/gefitinib: Whilst the criteria selecting for secondary resistance are well justified, the results are based on a post-hoc analysis, not protected by stratification, where there are too many uncertainties to demonstrate a benefit in this patient population.

Risks

Unfavourable effects

All subjects (100%) who received afatinib in study LUX Lung 3 have presented any AEs and 60.7% were ≥ grade CTCAE 3. The most common AEs observed in afatinib group were diarrhoea (96.1%), rash/acne (90.0%), stomatitis (73.4%), and nail effects (61.6%). Ocular effects were seen in 22.7%, nauseas (25%), vomits (22%), epistaxis (17%), hepatic enzyme elevation (16.6%), cough (15%), headache (14%), back pain (14%), nasopharyngitis (14%), constipation (13%), pyrexia (12.2%), upper respiratory tract infection (10.9%) and dizziness (10.9%).

Digestive symptoms (diarrhoea, nauseas and vomits), skin toxicity (rash/acne) and respiratory disorders were the adverse reactions more commonly resulting in treatment discontinuation. Adverse events leading to treatment discontinuation were reported in 14% (LUX Lung 3) and 10% in LUX Lung 6. 27% patients required hospitalization due to SAEs. AEs leading to death (grade 5 CTCAE) were observed more frequently in afatinib groups than in chemotherapy groups (5.7% vs. 2.7% respectively). According to standard practice patients were followed for AEs on study therapy plus 28 days and AEs related to tumour progression were reported as AEs, including AEs with fatal outcome. The event pattern is not unexpected and in most cases was likely related to tumour progression.

In study LUX Lung 1, patients with tumours showing secondary resistance to reversible TKIs in the complementary set experienced significantly more AEs leading to death in the afatinib arm (14.2 % vs. 3.3). Therefore this imbalance constitutes a serious concern in this patient population.

In addition, it was worrisome that the complementary set had a negative trend in survival (HR=1.23, CI 95% 0.89, 1.70) and that further subgroup analyses have shown that patients in the complementary for whom the EGFR TKI-free interval was less than 4 weeks (not affected by subsequent therapies), had an even poorer survival outcome (HR=1.69, CI 0.97, 2.93). This might indicate that putative negative effects are more pronounced in patients with a more aggressive disease.

Uncertainty in the knowledge about the unfavourable effects

Despite a large safety data base, adverse reactions related to the pan-HER character of afatinib and the covalent binding properties have not been identified.

Formation of covalent protein adducts might result in hypersensitivity reactions. There were, however, no non-clinical data indicative of this. The putative consequences of adducts constituting a “deep compartment” from a PK perspective will be further addressed post-marketing in patients who have been treated long-term with afatinib and where PK data are sampled after stopping afatinib therapy.

Benefit-risk balance

Importance of favourable and unfavourable effects

The magnitude of the benefit in terms of PFS demonstrated for afatinib over chemotherapy in treatment naïve patients is statistically significant and clinically meaningful. In addition benefit was also shown in terms of symptom control. These data are considered robust.

Although a PFS benefit in patients with retrospectively defined secondary resistance to prior treatment with erlotinib/gefitinib has been shown, there are too many uncertainties related to the post-hoc nature of the analyses, the outcome in the complementary set pointing in the direction of imbalances in prognostic factors and also too sparse evidence as regards activity in relation to mutation T790M.

The main toxicity associated with afatinib included diarrhoea (including dehydration and renal impairment secondary to diarrhoea), rash/acne, ILD and keratitis. In addition, important potential risks include decreased LVEF/heart failure, hepatic failure and pancreatitis. Based on indirect comparisons, the toxicity was similar to other TKI inhibitors in similar settings.

Benefit-risk balance

The magnitude of the PFS benefit over chemotherapy demonstrated in the first-line setting is considered to be sufficiently large to outweigh the risks. Therefore the benefit-risk balance is positive in this patient population, both for treatment naïve and chemotherapy pre-treated patients.

In patients with secondary resistance to gefitinib/erlotinib, the efficacy has not been established and it is not possible to conclude that the benefit/risk balance is positive.

Discussion on the benefit-risk balance

The benefits with afatinib in the treatment of EGFR TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer with activating EGFR mutation have been shown in terms of an increased progression free survival in patients receiving afatinib compared to chemotherapy. The results are considered of clinical benefit and in-line with what has been shown before for EGFR-TKIs erlotinib and gefitinib. As for other EGFR-TKIs no survival was shown, interpreted as being due to high cross-over rates to EGFR-TKI treatment. In this regards OS data has not shown any negative trends on survival and it is considered reassuring.

The relative efficacy of afatinib, gefitinib and erlotinib is currently not known, as data with direct head to head comparison are not available. Further information on the efficacy of afatinib versus gefitinib will be available from a currently ongoing comparative head-to-head study.

In terms of safety the most common side effects are diarrhoea, stomatitis, rash, dermatitis acneiform, pruritus, dry skin, paronychia, decreased appetite and epistaxis. Based on indirect comparisons, the toxicity was similar to other TKI inhibitors in similar settings.

Supportive evidence has shown that that the activity of afatinib in patients with EGFR mutations is not limited by line of therapy; both treatment naïve and chemotherapy pre-treated evidenced response rates. In addition there are no mechanistic arguments that would justify a detrimental effect of chemotherapy on the efficacy of TKIs. Moreover, prognostic factors are not expected to change significantly due to previous treatment with chemotherapy.

Nevertheless the CHMP considered that further data is needed to better understand the efficacy and safety profile of afatinib in chemotherapy pre-treated patients. Therefore the applicant will conduct a post-authorisation safety study to further characterise of the safety and efficacy of afatinib in this sub-population of patients.

The CHMP also requested a post-authorisation PK study to further characterise the potential developmental toxicity of afatinib. Mechanistically, all EGFR targeting medicinal products have the potential to cause foetal harm, however animal studies with afatinib did not indicate direct or indirect harmful effects with respect to reproductive toxicity.

On the other hand, treatment of afatinib in patients with secondary resistance to erlotinib/gefitinib did not translate into a survival benefit. The results in terms of an increased progression free survival are based on a post-hoc analysis, not protected by stratification, where there are too many uncertainties to demonstrate a benefit in this patient population. Therefore the final indication agreed by the CHMP does not include this patient population as initially proposed by the applicant. The final indication is shown below (deletions in ~~strikethrough~~, additions underlined):

"GIOTRIF as monotherapy is indicated for the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating ~~Epidermal Growth Factor~~ Receptor ~~(~~EGFR~~)~~ mutation(s) (see section 5.1).

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Giotrif in the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naïve adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products on "restricted" medical prescription, reserved for use in certain specialised areas (see Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that afatinib is qualified as a new active substance.