22 October 2015
EMA/CHMP/465053/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

XALKORI

International non-proprietary name: CRIZOTINIB

Procedure No. EMEA/H/C/002489/II/0024

Note

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

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALK	Anaplastic lymphoma kinase
AUC	Area under the curve
BID	Twice daily
CR	Complete response
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical study report
DCR	Disease control rate
DMC	Data monitoring committee
DR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group performance status
EC-TTP	Extracranial time to progression
EGFR	Epidermal Growth Factor Receptor
EML4	Echinoderm microtubule-associated protein-like 4
EORTC	European Organization for the Research and Treatment of Cancer
EQ-5D	EurQol-5D
ER	Exposure-response
EU	European Union
FA	Full analysis (population)
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
HCRU	Health care resource utilization
HGFR	Hepatocyte growth factor receptor
HR	Hazard ratio
IC-TTP	Intracranial time to progression
IDE	Investigational device exemption
IM	Intramuscular

IRR	Independent radiology review
IUO	Investigational-use only
IV	Intravenous
KM	Kaplan-Meier
MAH	Marketing Authorization Holder
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
POPPK	Population pharmacokinetics
PR	Partial response
PRO	Patient-reported outcome
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire-Supplement Module for Lung Cancer (LC13)
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
RON	Recepteur d'Origine Nantais
ROS1	C-Ros Oncogene 1
RP2D	Recommended Phase 2 dose
RPSFTM	Rank-Preserving Structural Failure Time Model
RTK	Receptor tyrosine kinase
SA	Safety analysis (population)
SAP	Statistical Analysis Plan
SD	Stable disease
TKI	Tyrosine kinase inhibitor
TTD	Time to deterioration
TTP	Time to progression
TTR	Time to tumor response
US	United States

VAS	Visual Analogue Scale
VSAQ-ALK	Visual Symptom Assessment Questionnaire-ALK

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Limited submitted to the European Medicines Agency on 20 November 2014 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to add first-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) based on the results of the pivotal Study A8081014; a multinational, multicenter, randomized, open-label, Phase 3 study comparing the efficacy and safety of crizotinib to first-line chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) in patients with previously untreated ALK-positive advanced non-squamous NSCLC, as well as updated safety results from Studies A8081001, A8081005 and A8081007. As a result sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC were proposed to be updated and the Package Leaflet was proposed to be updated accordingly. In addition, the MAH took the opportunity to implement minor editorial and QRD-template related changes in the SmPC, Annex II and Package Leaflet. A revised RMP version 6.0 was provided as part of the application.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

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.

Scientific advice

The applicant received Scientific Advice from the CHMP on 20 May 2010. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Pierre Demolis Co-Rapporteur: Daniela Melchiorri

Timetable	Actual dates
CHMP Rapporteur's preliminary assessment report circulated on:	18 February 2015
CHMP Co-Rapporteur's preliminary assessment report circulated on:	21 February 2015
Joint CHMP Rapporteurs' updated assessment report circulated on:	20 March 2015
Request for supplementary information and extension of timetable adopted by the CHMP on:	26 March 2015
MAH's responses submitted to the CHMP on:	22 May 2015
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	29 June 2015
Joint CHMP Rapporteurs' updated assessment report on the MAH's responses circulated on:	17 July 2015
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	23 July 2015
MAH's responses submitted to the CHMP on:	25 August 2015
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	17 September 2015
Joint CHMP Rapporteurs' updated assessment report on the MAH's responses circulated on:	21 October 2015
CHMP opinion:	22 October 2015

2. Scientific discussion

2.1. Introduction

About the disease

Lung cancer is the leading cause of cancer-related mortality worldwide, and it is estimated that more patients will die of lung cancer than of breast, colon, and prostate cancer combined. In 2012, the annual incidence of lung cancer worldwide was 23.1 per 100,000 persons, and the incidence was higher in men (34.2 per 100,000) than women (13.6 per 100,000) according to estimates from the World Health Organization and International Agency for Research on Cancer (IARC) GLOBOCAN project. In Europe, lung cancer had an incidence of 46.6 per 100,000 men and 15.1 per 100,000 women (Ferlay et al, 2013). In the US, the incidence of lung or bronchial cancer was 76.4 per 100,000 men and 52.7 per 100,000 women (Howlander et al, 2012). Most lung cancers (85%) are NSCLC (Tyczynski et al, 2003) that present as inoperable locally advanced (Stage IIIB) or metastatic (Stage IV) disease with no curative treatment available. United States (US) Surveillance, Epidemiology, and

End Results (SEER) data indicated that the 5-year survival rate between 2002 and 2008 among all patients with NSCLC was 17.5% (Howlander et al, 2012). However, 5-year survival rates have been shown to be 5% and <1% for Stage IIIB and Stage IV NSCLC, respectively (Reck, 2012).

NSCLC is frequently further subdivided into non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other cell types) and squamous cell (epidermoid) carcinoma. Adenocarcinoma (40% of lung cancers) is the most common type of lung cancer, and is also the most frequently occurring in non-smokers as reported in United States (US) data (American Cancer Society 2013).

Standard first-line treatment of patients with advanced NSCLC of any histological subtype consisting normally of platinum-based chemotherapy has modest impact on efficacy outcomes, as objective response rates (ORRs) in the range of 15% to 32% have been reported with a median progression-free survival (PFS) of 3 to 6 months and a median overall survival (OS) of 8 to 12 months (1-year OS survival probabilities ranging from 34% to 44%) (Sandleret al, 2006; Scagliotti et al, 2008; Schiller et al, 2002; Herbst et al, 2004; Herbst et al, 2005; Kelly et al, 2001).

Evolution from the use of platinum doublets for all patients regardless of histology began to change with (1) the addition of bevacizumab, an antibody directed against the vascular endothelial growth factor (VEGF), to carboplatin/paclitaxel in the first-line treatment of advanced non-squamous NSCLC, which prolonged survival compared to the chemotherapy doublet alone resulting in a median OS of 12.3 months in the randomized Phase 3 study (Sandler et al, 2006); and (2) the addition of pemetrexed into first-line platinum-containing doublets, which showed that pemetrexed/cisplatin was generally better tolerated than gemcitabine/cisplatin. The efficacy of this regimen, based on OS, was superior to gemcitabine/cisplatin in patients with NSCLC of non-squamous cell histology whereas the opposite was observed in patients with NSCLC of squamous cell histology (Scagliotti et al, 2008). Retrospective analyses of the second-line studies with single-agent pemetrexed indicated selective benefit of this agent in patients with non-squamous NSCLC. Consequently, in all lines of therapy, the approved product label restricts pemetrexed usage to non-squamous histology only (Alimta EU SmPC).

With the evolving understanding of the molecular basis of the disease, agents that target specific molecular signalling pathways, particularly in genetically defined subsets of patients, have become the goal of cancer drug development. Examples include the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), gefitinib (Iressa), afatinib (Giotrif) and erlotinib (Tarceva), which have been shown to be effective in patients with specific activating EGFR mutations (Lynch et al, 2004; Pao et al, 2004). In the international, randomized, Phase 3, IRESSA Pan-Asia Study (IPASS) study, gefitinib was shown to significantly improve PFS compared to carboplatin/paclitaxel chemotherapy in the first-line advanced disease treatment setting in those patients whose tumours were positive for EGFR-activating mutations (Mok et al, 2009); however no OS benefit was demonstrated, as 95% of patients assigned to the control arm received second-line gefitinib (Iressa EPAR). Studies have also shown statistically significant benefit for the irreversible EGFR TKI, afatinib, when compared with chemotherapy in the first-line treatment for advanced and metastatic EGFR mutation-positive NSCLC. There was a statistically significant improvement in PFS with the use of afatinib versus cisplatin/pemetrexed in LUX-Lung 3 (median 11.1 months vs. 6.7 months; HR 0.49; 95% CI: 0.37, 0.65; p-value=0.001) (Giotrif EPAR) and versus cisplatin/gemcitabine in LUX-Lung 6 (11.0 vs. 5.6 months; HR 0.28; 95% CI: 0.20, 0.39; p-value< 0.001) (Wu et al, 2014). The EURTAC study has also shown statistically significant improved PFS of Tarceva used as monotherapy versus platinum based doublet chemotherapy (median 10.4 months vs. 5.1 months; HR 0.34; 95% CI: 0.23, 0.49; p-value <0.0001) in the first-line treatment for locally advanced and metastatic EGFR mutation-positive NSCLC (Tarceva EPAR).

One of the newer molecular targets identified in NSCLC is the echinoderm microtubule associated protein-like 4 (EML4)-ALK fusion oncogene. To date, at least 27 different ALK fusion variants have been reported in the literature, of which EML4-ALK is the predominant isoform (Ou et al, 2012). ALK-positive NSCLC constitutes a molecularly defined subgroup with an estimated prevalence of 3% to 5% of NSCLC (Garber, 2010; Choi et al, 2010). Currently, crizotinib (Xalkori) and ceritinib (Zykadia) are approved in this targeted population of ALK positive patients.

About the product

Xalkori (crizotinib) is a selective small-molecule inhibitor of the ALK receptor tyrosine kinase (RTK) and its oncogenic variants (i.e., ALK fusion events and selected ALK mutations). Crizotinib is also an inhibitor of the hepatocyte growth factor receptor (HGFR, c-Met), c-ros oncogene 1 (ROS1), and Recepteur d'Origine Nantais (RON) RTKs. Xalkori received a conditional approval in the EU on 23 October 2012, for the treatment of adults with previously treated ALK-positive advanced NSCLC.

This application is to extend the indication of Xalkori to the first-line treatment ALK-positive advanced NSCLC on the basis of results from Study A8081014 (also referred to as study 1014), a multinational, multicenter, randomized, open-label, Phase 3 study comparing the efficacy and safety of crizotinib to first-line chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) in patients with previously untreated ALK-positive advanced non-squamous NSCLC and updated safety results from Studies A8081001, A8081005 and A8081007 (also referred to as study 1001, 1005 and 1007). In addition to the clinical study report for study A8081014, the efficacy and safety analyses of patients with ALK-positive NSCLC of non-adenocarcinoma histology from studies A8081001, A8081005, A8081007 and A8081014 have been included as part of this application.

In addition, the MAH requested the conversion of the marketing authorisation from conditional to full based on the fact that two randomised phase 3 studies showing benefit of crizotinib versus standard-of-care chemotherapy in patients with advanced ALK-positive NSCLC would constitute comprehensive clinical data.

The proposed and recommended indication is as follows: XALKORI is indicated for the first-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

2.2. Non-clinical aspects

2.2.1. Ecotoxicity / environmental risk assessment

The MAH submitted a justification for not performing the ERA.

2.2.2. Discussion and conclusion on non-clinical aspects

A justification has been provided for not performing an updated Environmental Risk Assessment. The already submitted ERA for the initial Marketing Authorisation covers the treatment of ALK-positive advanced NSCLC irrespective of line of treatment therapy. Also considering that no changes of the maximum therapeutic dose were recommended, the MAH justification (in accordance with the EMA guideline EMEA/CHMP/SWP/4447/00) is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

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

Protocol No. (Country) *Status*	Study Design and Objective	Treatment Groups	No. of Patients Treated[a]	Demographics (No. of Patients)	Median Treatment Duration (min/max)
STUDY REPORTS OF CLINICAL STUDIES PERTINENT TO CLINICAL EFFICACY AND SAFETY					
Pivotal Study					
A8081014 (Austria[b], Australia, Belgium, Brazil, Canada, Chile[b], China, Finland, France, Germany, Hong Kong, India[b], Ireland, Italy, Japan, Republic of Korea, Luxembourg, Mexico, Netherlands, Norway, Peru[b], Portugal, Russia, Singapore, South Africa, Spain, Switzerland, Taiwan, Ukraine, United Kingdom, United States) *Ongoing*	Open-label, randomized, multicenter, multinational, Phase 3 study of the efficacy and safety of PF-02341066 versus pemetrexed/cisplatin or pemetrexed/ carboplatin in previously untreated patients in patients with advanced ALK-positive NSCLC	Crizotinib Route: Oral; Dose Regimen: 250 mg BID in 21-day cycles Pemetrexed/ Cisplatin Dose Regimen: 500 mg/m^2/75 mg/m^2 Day 1 of 21-day cycle or Pemetrexed/ Carboplatin Dose regimen: 500 mg/m^2/AUC of 5 or 6 mg.min/mL Day 1 of 21-day cycle	171 169[c]	Sex: 67M/104F Median Age (min/max): 52 years (22-76) Race: 90W/77A/4O Sex: 63M/106F Median Age (min/max): 54 years (19-78) Race: 85W/3B/80A/1O	47.4 weeks (1.9-148.9) 18 weeks (3.0-26.9)
Supportive Studies					
A8081001 (Australia, Republic of Korea, United States) *Ongoing*	Open-label, multi-center, Phase 1, multinational, dose-escalation, safety, PK, PD, and efficacy study of crizotinib in patients with advanced cancer	**RP2D Cohorts:** Crizotinib Route: Oral; Dose Regimen: 250 mg BID in 28-day cycles[d]	ALK-positive NSCLC cohort: 154 Other RP2D cohort: 204	Sex: 74M/80F Median Age (min/max): 52 years (22-86) Race: 98W/5B/43A/8O NA	56.9 weeks (0.7-267.3) NA
A8081005 (Australia, Brazil, Bulgaria, Canada,China, France, Germany, Greece, Hong Kong, Hungary, Ireland, Italy, Japan, Netherlands, Republic of Korea, Poland, Russian Federation, Spain, Sweden, Taiwan, United Kingdom, United States) *Ongoing*	Open-label, single-arm, multicenter, multinational, Phase 2 study of efficacy and safety of crizotinib in patients with advanced ALK-positive NSCLC	Crizotinib Route: Oral; Dose Regimen: 250-mg BID in 21-day cycles	ALK-positive NSCLC (all) Treated: 1063 ALK-positive NSCLC (by IUO) Treated: 905	Sex: 463M/600F Median Age (min/max): 52 years (19-84) Race: 530W/20B/493A/ 20O Sex: 391M/514F Median Age (min/max): 52 years (19-84) Race: 432W/16B/440A/ 17O	44.9 weeks (0.1-191.7) 47 weeks (0.1-191.7)

A8081007 (Australia, Brazil, Bulgaria[b], Canada, China, France, Germany, Greece, Hong Kong, Hungary, Ireland, Italy, Japan, Republic of Korea, Netherlands , Poland, Romania[b], Russian Federation, Spain, Sweden, Switzerland[b], Taiwan, United Kingdom, United States) *Ongoing (Comparative phase completed)*	Open-label, randomized, multicenter, multinational, 2-arm, Phase 3 study to evaluate the efficacy and safety of crizotinib versus standard of care chemotherapy (pemetrexed or docetaxel) in patients with advanced ALK-positive NSCLC	Crizotinib Route: Oral; Dose Regimen: 250-mg BID in 21-day cycles	172	Sex: 75M/98F Median Age (min/max): 51 years (22-81) Race: 90W/2B/79A/2O	48 weeks (1.3 – 189.9)
Protocol No. (Country) *Status*	**Study Design and Objective**	**Treatment Groups**	**No. of Patients Treated[a]**	**Demographics (No. of Patients)**	**Median Treatment Duration (min/max)**
A8081007 (cont.)		Chemotherapy: Pemetrexed Route: IV Infusion; Dose Regimen: 500 mg/m^2 on Day 1 of 21-day cycle or Docetaxel Route: IV Infusion; Dose Regimen: 75 mg/m^2 on Day 1 of 21-day cycle	171	Sex: 78M/96F Median Age (min/max): 49 years (24-85) Race: 91W/3B/78A/2O	13 weeks (3-144.7)
A8081013 (Italy , Japan, Republic of Korea, Russia, United States. China, Taiwan, Canada[b]) *Ongoing*	Open-label, multicenter, single arm, Phase 1B study to evaluate the safety and clinical activity of crizotinib in tumors with genetic events involving the ALK gene locus	Crizotinib Route: Oral; Dose Regimen: 250 mg BID in 21-day cycles	44	Sex: 25M/19F Median Age (min/max): 32 years (15-73) Race: 23W/21A	NA
Study 1029 (China, Hong Kong, Malaysia, Taiwan,Thailand) *Ongoing*	Phase 3, open-label, randomized study of efficacy and safety of crizotinib vs. first-line chemotherapy	Crizotinib Route: oral; Dose regimen: 250 mg BID Chemotherapy IV Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 Or Pemetrexed 500 mg/m^2 plus carboplatin	160 Treated includes 81 patients in the crizotinib arm and 15 patients who crossed over from chemotherapy to crizotinib	NA	NA
PHARMACOKINETIC STUDIES IN PATIENTS WITH ADVANCED CANCERS					
A8081012 (United States) *Ongoing*	Multicenter, open-label, non-randomized, Phase 1 study of pharmacokinetics, safety and antitumor activity	Crizotinib Route: Oral; Dose Regimen: 200 mg BID, 250 mg BID, or 250 mg QD	31	Sex: 22M/9F Median Age (min/max): 60 years (31-78) Race: 19W/2B/3A	NA

Note: Information is presented for the current submission only. Please see Section 5.2 of the Original Regulatory Submission and Section 5.2 of the Study 1007 Regulatory Submission for additional information.
Abbreviations: A=Asian, AE=adverse event, ALK=anaplastic lymphoma kinase, AUC=area under the curve, B =Black, BID=Twice daily, CSR=Clinical Study Report, F=Female, IUO=investigational use only (Vysis ALK-Break Apart fluorescence in situ hybridization [FISH] test developed by Abbott Molecular, Inc.); IV =Intravenous, M=Male, min=minimum, max=maximum, NA =Not available, O=Other, OS=Overall Survival, NO.=number; NSCLC=non-small cell lung cancer, PD=pharmacodynamics, PK=pharmacokinetics, QD=once daily, RP2D=recommended phase 2 dose, SAE=serious adverse event, SCE=Summary of Clinical Efficacy, SCS=Summary of Clinical Safety, W=White.
a. Number who received at least 1 dose of study medication.
b. No patients were randomized at sites in this country.
c. 109 patients crossed over from chemotherapy to receive crizotinib.
d. 21-Day cycles for ALK-negative cohort.

2.3.2. Clinical pharmacology

In the pivotal study A8081014, the PK of crizotinib, including its active moieties, based on population PK (POPPK) methods, was evaluated as secondary objective. In addition, the correlations between PK and response were also explored.

At the time of the initial MA, the MAH was requested to provide further PK analyses on dose proportionality, due to the non-linear pharmacokinetics of crizotinib in humans. Furthermore, the CHMP recommended conducting a definitive Exposure-Response (ER) analysis on final data from Study A8081014.

To fulfil these requests, steady-state trough plasma concentration values following 250 mg BID during repeated treatment cycles and ER analysis of selected efficacy endpoints (e.g. ORR, PFS, OS) have been submitted by the MAH.

2.3.2.1. Pharmacokinetics

Plasma samples were analysed for crizotinib and PF-06260182 (lactam metabolite; the most abundant metabolite of crizotinib in plasma) concentrations using high-performance liquid chromatography tandem mass spectrometric (HPLC-MS/MS) method. Blood samples for analysis of crizotinib and active moieties concentrations processed in local laboratories at all sites were unit-standardized. When comparison of laboratory test results was performed, laboratory tests expressed as continuous (quantitative) variables were normalized by a linear transformation.

A total of 169 patients who were treated with crizotinib and had at least 1 measured plasma concentration of crizotinib or its metabolite, PF-06260182 were included in PK concentration population. A total of 66 (39.1%) patients were male and 103 (60.9%) were female. A total of 89 (52.7%) patients were White, 76 (45.0%) were Asian, none were Black, and 4 (2.4%) were of other races.

Crizotinib capsules, 250 mg twice daily (BID), were to be administered orally at approximately the same time each day on a continuous daily dosing schedule. Cycles were defined in 21-day periods.

In the crizotinib arm only, plasma samples for PK assessment were to be obtained prior to (predose) and around the time to maximum plasma concentration (Tmax) following morning dosing on Day 1 of Cycles 1, 2, 3, and 5. No predose sample was to be collected on Day 1 of Cycle 1.

Absorption

One hundred and sixty-two (162) patients provided at least 1 predose (0 hours) plasma concentration of crizotinib or PF-06260182. The geometric mean predose concentrations (C_{trough}) of crizotinib and of PF-06260182 both following 250 mg BID dosing of crizotinib are reported in the table below.

Table 1: Predose concentrations (Ctrough) of crizotinib and its metabolite, PF-06260182, and PF-06260182 to crizotinib ratios following 250 mg BID oral dosing of crizotinib.

	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 5 Day 1
N/n	91/100	85/94	82/86
Crizotinib C_{trough}, ng/mL[a]	324.2 (39)	320.9 (40)	308.2 (39)
PF-06260182 C_{trough}, ng/mL[a]	98.4 (46)	99.0 (49)	92.9 (55)
PF-06260182 to Crizotinib ratio	0.302 (25)	0.300 (25)	0.290 (25)

Source: Section 14.4, Tables 14.4.3.1.1a, 14.4.3.1.2a, and 14.4.3.1.3a.
Abbreviations: BID=twice daily; C_{trough}=trough concentration; CV=coefficient of variation; n=number of observations for PF-06260182; N=number of observations for crizotinib and PF-06260182 to crizotinib ratio.
[a] Geometric mean (%CV).

Crizotinib and its active moieties PF-06260182 reach the steady-state plasma concentrations within the first cycle after repeated oral administration of crizotinib 250 mg BID.

A total of 126 patients provided at least 1 $C_{trough,ss,mean}$ for crizotinib or PF-06260182. As was done in other crizotinib patient studies, an exploratory comparison of the $C_{trough,\ ss,\ mean}$ from Asian versus non-Asian patients was performed (Table 2).

Table 2: Steady-State Mean Predose Concentration ($C_{trough,\ ss,\ mean}$) of Crizotinib and its Metabolite, PF-06260182, and PF-06260182-to-Crizotinib Ratios in Asian and Non-Asian Patients Following 250 mg BID Oral Dosing of Crizotinib

	Asian	Non-Asian	All Patients
N/n	49/52	71/74	120/126
Crizotinib $C_{trough,\ ss,\ mean}$, ng/mL[a]	330.4 (34)	307.1 (40)	316.4 (38)
PF-06260182 $C_{trough,\ ss,\ mean}$, ng/mL[a]	105.2 (36)	93.6 (52)	98.2 (45)
PF-06260182-to-crizotinib ratio[a]	0.307 (18)	0.292 (27)	0.298 (23)

Abbreviations: BID=twice a day; $C_{trough,\ ss,\ mean}$=mean steady-state trough concentration; CV=coefficient of variation; n=number of observations for PF-06260182; N=number of observations for crizotinib and PF-06260182 to crizotinib ratio.
a Geometric mean (%CV).

2.3.3. Pharmacodynamics

Correlation of ALK gene fusion variants to outcome measures was a secondary endpoint of study A8081014.

A mandatory tumour sample (archived or fresh) was required at screening for detecting ALK gene fusion events (inclusion criterion 2). The Vysis ALK Break Apart FISH test was used as primary assay and all samples were to be analysed by the central laboratory.

A summary of descriptive statistics for percentage of ALK-positive cells by the central laboratory investigational-use only (IUO) diagnostic test (Abbott Molecular) is provided in the table below.

Table 3: Descriptive statistics for percentage of cells that are ALK-positive by central laboratory test – full analysis population

	Crizotinib (N=172)	Chemotherapy (N=171)
Percentage of cells that are ALK-positive		
n	171[a]	171
Mean (SD)	55.4 (22.6)	57.2 (23.3)
Median	56.0	58.0
Range	15-100	15-100

Abbreviations: ALK=anaplastic lymphoma kinase; n/N=number of patients; SD=standard deviation.
a One patient was ALK negative based on central laboratory testing and was randomized by mistake.

The ALK variant evaluable population consisted of 148 patients. Overall, 88 samples (59.5%) were negative for the ALK gene variants tested (variants V1, V2, V3a, V3b, V4, V5a, V6, and V7).

The percentages of patients with each EML4-ALK gene fusion variant are reported in the table below.

Table 4: Best overall response based on independent radiology review by treatment arm and EML4-ALK gene fusion variant - ALK Variant Evaluable Population

EML4-ALK gene fusion variant[b]	Crizotinib (N=70)		Chemotherapy (N=78)[a]	
	Patients with variant, n (%)	ORR (CR + PR) n (%) (95% CI)[c]	Patients with variant, n (%)	ORR (CR + PR) n (%) (95% CI)[c]
V1	19 (27.1)	16 (84.2) (60.4, 96.6)	20 (25.6)	9 (45.0) (23.1, 68.5)
V2	5 (7.1)	5 (100) (47.8, 100)	6 (7.7)	2 (33.3) (4.3, 77.7)
V3a	1 (1.4)	0 NA	1 (1.3)	1 (100) (2.5, 100)
V3a/b	3 (4.3)	3 (100) (29.2, 100)	5 (6.4)	3 (60.0) (14.7, 94.7)
No rearrangement	42 (60.0)	30 (71.4) (55.4, 84.3)	46 (59.0)	20 (43.5)(28.9, 58.9)

Source: Section 14.2, Tables 14.2.8.2 and 14.2.8.3.
Abbreviations: ALK=anaplastic lymphoma kinase; CI=confidence interval; CR=complete response; EML4=echinoderm microtubule-associated protein-like 4; n/N=number of patients; NA=not applicable; ORR=objective response rate; PR=partial response.
[a] Only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.
[b] Variants V4, V5a, V6, and V7 were not detected.
[c] Using exact method based on F distribution.

2.3.4. PK/PD Modelling

As recommended by the CHMP, the MAH conducted an Exposure-Response (ER) analysis of efficacy endpoints for crizotinib study A8081014 (PMAR-EQDD-A808a-sNDA-319). The objectives of this ER analysis were:

- To perform crizotinib ER analysis of selected efficacy endpoints (Objective Response Rate [ORR], Progression-free survival [PFS] that is the only primary endpoint of the study and overall survival [OS]).

- To evaluate effect modifiers (interactions between covariates and exposure) in these ER analyses of crizotinib efficacy.

Methods

Model assumptions were made based on data from 2 previous studies in which 3 exposure measures were analysed: C_{trough} (average crizotinib trough concentration), mC_{trough} (average metabolite trough concentration) and $C_{avg,ss}$ (population model predicted steady-state average crizotinib concentration). The 2 previous studies were the following: Study A8081005 and Study A8081007.

Also in study A8081014 ER analysis, 3 sets of exposure measures were used:

- Arithmetic mean of observed steady-state (≥ Cycle 2 Day 1; cycle length is 21 days) trough value (C_{trough}) for crizotinib up to 5 cycles of crizotinib treatment or at the time of data cut-off.
- Arithmetic mean of observed steady-state (≥ Cycle 2 Day 1) trough value (mC_{trough}) for PF-06260182 up to 5 cycles of crizotinib treatment or at the time of data cut-off.
- Predicted average steady-state concentration values ($C_{avg,ss}$) for crizotinib, based on steady-state clearance from the population PK model and the average total daily dose. This exposure measure was only planned to be used in the analysis if at least 20% of patients had a missing crizotinib C_{trough} value.

The exposure measure for the crizotinib metabolite was based only on observed concentrations since a population PK model was not available for this metabolite.

Analyses were performed using generalized linear models and Cox proportional hazards models. Cox regression models were used for time-to-event endpoints. All potential confounders were included in each of the logistic regression and the Cox regression models. The following covariates were reported: Race group (Asian vs. Non-Asian), Baseline body weight (BWT), Baseline creatinine clearance (BCCL), gender (male vs. female), Age, Baseline ECOG Performance Status (PS) (0 vs. ≥ 1), PPI use (yes/no), CYP3A Inhibitor use (CYP3A Inh), CYP3A inducer use (CYP3A Ind), Baseline sum of longest lesion diameters (SLD), Actual total dose/number of days on treatment (Dose/day).

Logistic regression models were used for binary endpoints.

A modelling approach was used to control for potential confounders, and explore potential effect modifiers. The potential effect modifiers were evaluated individually including interactions between the potential effect modifiers and the exposure metric. No detailed model building for interactions was planned or done.

In order to estimate the model predictability for ORR, the residual deviance was used as the primary measure of model fit. Moreover diagnostics were assessed using plot of observed and predicted response versus exposure to evaluate the predictive performance for the model for ORR.

Results

In the Study A8081014, 340 patients were included in the dataset, 171 in the crizotinib arm, 169 in the chemotherapy arm (pemetrexed/carboplatin or pemetrexed/cisplatin).

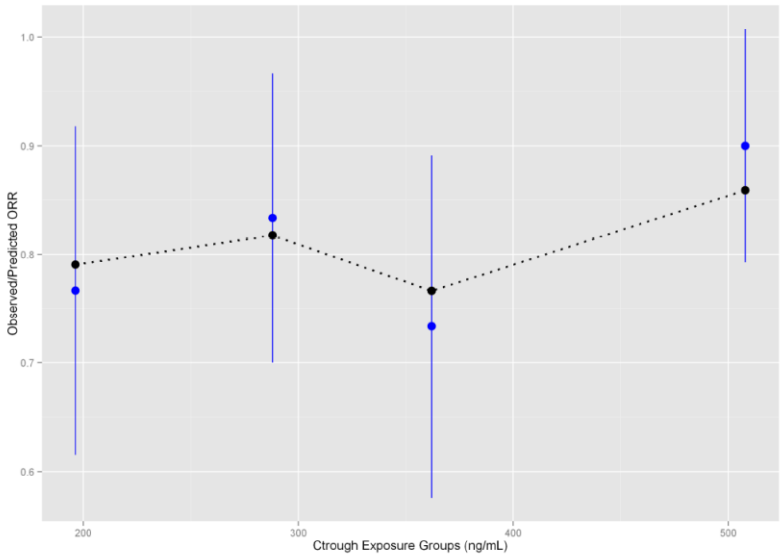
Approximately linear relationship was shown between crizotinib C_{trough} and the average metabolite C_{trough} (mC_{trough}). The Pearson correlation coefficient of the 2 exposure measures was 0.83. Approximately linear relationship was shown also between average crizotinib C_{trough} and population PK predicted crizotinib exposure ($C_{avg,ss}$). The Pearson correlation coefficient of the 2 exposure measures was 0.85.

In the population modelling analysis report (PMAR) the ER relationship between each efficacy endpoints - ORR, PFR and OS – and the exposure measures - C_{trough}, mC_{trough} and predicted $C_{avg,ss}$ was analysed. No statistically significant exposure-response relationship, e.g. p-value>0.05, was found for any of the exposure measures.

ER relationship of each model changed after adjusting for potential confounders. This indicates that there was a degree of confounding with the ER relationship in the unadjusted model. However, in most cases no statistically significant interaction was observed between the measures of exposure and the potential effect modifiers.

Statistically significant relationships were detected when analysing all the exposure measures - $log(C_{trought})$, $log(mC_{trought})$ and $log(C_{avg,ss})$ - with concomitant proton pump inhibitor (PPI) usage in the ORR results.

Observed and average model-predicted ORR tended to increase with increasing exposure, as shown in the below figure.



Blue = observed objective response rates with 95% confidence intervals. Black = average model-based predictions by crizotinib C_{trough} exposure quantiles (range in ng/mL) - Quantile Group 1 (Q1): (139, 248); Quantile Group 2 (Q2): (>248, 316);Quantile Group 3 (Q3): (>316, 404); Quantile Group 4 (Q4): (>404, 872). (ePharmacology Artifact ID, 8648044)

Figure 1: Observed and average model-predicted objective response rates for average crizotinib C_{trough}.

The increase in ORR with increasing exposure was larger in patients using PPIs than in patients with no PPI use.

Cox regression analysis showed that higher exposures corresponded to numerically longer PFS for all 3 exposure measures. For this endpoint, the ER relationship was not statistically significant (p-value>0.05) for all 3 exposure measures. There were no statistically significant effect modifiers of the ER relationship for PFS for any of the exposure metrics.

Cox regression analysis of OS showed that higher exposures corresponded to numerically longer event times for all 3 exposure measures. However, none of the exposure measures were statistically significant (p-value>0.05) exposure-response effect for OS. Statistically significant relationships were detected also when analysing log (C_{trough}) and co-administrations of a CYP3A4 inhibitor in the OS analysis. This data indicates that use of CYP3A4 inhibitor is an effect modifier of the ER relationship. In this analysis, higher exposure corresponded to lower hazard, and thus longer OS.

Additional ER analyses (study A8081014 and study A8081007) were conducted by the MAH.

ER analyses for Study A8081014

Univariate covariate analysis and stepwise covariate selection for ER (efficacy) relationship in previously untreated patients with ALK-positive NSCLC were conducted. The datasets, sets of exposure and covariates used in these analyses were also reported in PMAR-EQDD-A808a-sNDA-319 (see above). The analyses were conducted for ORR, PFS, and OS using logistic regression models for ORR and Cox regression models for PFS and OS.

The following table summarizes the comparison ER estimates between full models (PMAR-EQDD-A808a-sNDA-319) and stepwise backward covariate selection final models.

Table 5: Comparison of ER estimates between full models and stepwise backward covariate selection final models (study 1014)

Response	Exposure Measure	Model	Covariate	Slope Estimate[1]	95 % CI
ORR	$\log(C_{trough})$	Full	all	0.485	-1.051, 2.021
		Final	none	0.393	-0.836, 1.621
	$\log(mC_{trough})$	Full	all	0.381	-0.768, 1.530
		Final	none	0.176	-0.757, 1.108
	$\log(C_{avg,ss})$	Full	all	0.950	-0.343, 2.244
		Final	none	0.903	-0.053, 1.860
PFS	$\log(C_{trough})$	Full	all	-0.600	-1.263, 0.064
		Final	SLD	-0.548	-1.182, 0.086
	$\log(mC_{trough})$	Full	all	-0.349	-0.860, 0.162
		Final	SLD	-0.340	-0.821, 0.140
	$\log(C_{avg,ss})$	Full	all	-0.654	-1.375, 0.067
		Final	SLD	-0.919*	-1.514, -0.325
OS	$\log(C_{trough})$	Full	all	-1.138	-2.331, 0.055
		Final	Asian, BWT, ECOG	-1.307*	-2.387, -0.227
	$\log(mC_{trough})$	Full	all	-0.664	-1.538, 0.210
		Final	Asian, BWT	-0.915*	-1.762, -0.069
	$\log(C_{avg,ss})$	Full	all	-0.663	-1.682, 0.356
		Final	Asian, ECOG	-0.835*	-1.555, -0.114

[1] log(hazard ratio) for exposure; * p<0.05
Abbreviations: Asian = Race group for Asian vs. non-Asian; BWT= Baseline body weight; CI = confidence interval; ECOG= Baseline ECOG Performance Status; Full = full model including all covariates ; . Final = final model based on stepwise selected covariates and exposure measure; SLD= Baseline sum of lesion diameters

Logistic regression for ORR showed similar numerical trends for exposure across all models.

There was no statistically significant ER relationship for ORR and no statistically significant covariates were retained in the model through stepwise selection for any of the exposure measures.

For PFS, Cox regression models showed similar numerical trends for exposure across all models. The analysis showed that final model for $\log(C_{avg,ss})$ which included baseline SLD as the only covariate was statistically significant. Baseline SLD was consistently included in the final model for all 3 exposure measures.

Cox regression models for OS showed similar numerical trends for exposure for all models. The analysis showed that final model for all 3 exposure measures was statistically significant. Significant covariates included Asian race, BWT and baseline ECOG PS in the stepwise selection analyses.

OS data were immature as only 22% of the patients with a crizotinib C_{trough} have reached the survival endpoint and the median survival time was not achieved (as of the data cut-off).

ER analyses for Study A8081007

In order to evaluate if trends in the crizotinib ER relationship for previous clinical studies were similar to those with Study 1014, data from Study 1007 were used for a stepwise covariate selection procedure to evaluate the ER relationship for ORR, PFS and OS. Study 1007 is a pivotal randomized phase 3 study which had a similar study design to 1014. The ER analyses using full models (including covariates and modifiers) for Study A8081007 was provided in a previous variation procedure II/0005/G which received a commission decision on 29 January 2014.

The set of covariates used in Study A8081007 differed slightly from those used in Study A8081014. Covariates baseline brain metastases (BBM) and baseline ALT were included in analyses for Study A8081007 but not for Study A8081014, and CYP3A inhibitor use was included in analyses for Study A8081014 but not for Study A8081007. Only log transformed $C_{avg, ss}$ was included in the analyses as three exposure measures C_{trough}, mC_{trough} and $C_{avg, ss}$ tended to give similar results.

The Table below summarizes the exposure-response estimates between full models and stepwise backward covariate selection models.

Table 6: Comparison of ER estimate between full models and stepwise backward covariate selection models, study A8081007

Response	Exposure Measure	Model	Covariate	Slope Estimate[1]	95 % CI
ORR	$\log(C_{avg,ss})$	Full	all	0.674	-0.531, 1.880
		Final	none	0.928	-0.053, 1.909
PFS	$\log(C_{avg,ss})$	Full	all	-0.109	-0.985 0.767
		Final	BBM, PPI, SLD	-0.429	-1.166, 0.308
OS	$\log(C_{avg,ss})$	Full	all	-0.591	-1.578, 0.397
		Final	ECOG, SLD	-0.809*	-1.615, -0.003

[1] log(hazard ratio) for exposure; * $p<0.05$

Abbreviations: BBM= baseline brain metastases; CI = confidence interval; ECOG= Baseline ECOG Performance Status; Full = full model including all covariates ; . Final = final model based on stepwise selected covariates and exposure measure; SLD= Baseline sum of lesion diameters

Logistic regression for ORR showed similar numerical trends for exposure for the full and final models and are similar to those observed in Study A8081014.

There was no statistically significant ER relationship for ORR and no statistically significant covariates were retained in the model through stepwise selection for any of the exposure measures. For PFS, Cox regression models showed similar numerical trends for exposure for the full and final models and were similar to those seen in Study A8081014. The analysis showed that final model for $\log(C_{avg,ss})$ which included baseline SLD as the only covariate was not statistically significant.

Cox regression for OS showed similar numerical trends in exposure for the full and final models and were similar to those observed in Study A8081014. The analyses showed a statistically significant ER relationship with OS for the final model. The final model for $\log(C_{avg,ss})$ and OS included baseline SLD and baseline ECOG as covariates.

Similarly to Study A8081014, the OS data were immature because the median survival time was not achieved indicating that a majority of patients were censored by the data cut-off.

2.3.5. Discussion on clinical pharmacology

Greater than proportional increases in crizotinib AUC and Cmax were observed over the 200-300 mg BID dose in patients (during the initial MA). Consequently, multiple-dose pharmacokinetics of steady-

state trough concentration following 250 mg BID crizotinib cannot be precisely predicted by single-dose. To investigate steady-state trough plasma concentration values following 250 mg BID crizotinib during repeated treatment cycles, the MAH submitted the results of the phase 3, randomized, open-label study A8081014.

The PK method and sample timing were considered appropriate and in line with information reported in the Xalkori SmPC.

The analysis of pre-dose concentrations indicates that crizotinib and its active moieties, PF-06260182, reach the steady-state plasma concentrations within the first cycle after repeated oral administration of crizotinib 250 mg BID. Asian patients appeared to exhibit slightly higher $C_{trough, ss}$ mean for crizotinib and PF-06260182 than non-Asian patients confirming a slightly higher systemic exposure in Asian patients. However, the geometric mean ratios of PF-06260182 to crizotinib $C_{trough, ss}$ were similar between Asian and non-Asian patients.

One of the secondary objectives of the A8081014 study was to evaluate the PK of crizotinib, including its active moieties, using PopPK methods and explore correlations between PK and response.

The demographic characteristics were well balanced between the 2 randomized treatment arms but they were relatively less balanced across the four exposure quantiles for a few variables (eg, gender, baseline body weight, Asian race, proton pump inhibitor [PPI] usage, SLD) which necessitates a modelling approach to adjust for the potential confounders in order to appropriately assess the ER relationship.

Only numerical trends in the overall ER relationship could be observed in the ER study: i) logistic regression analysis showed that higher exposure corresponded to numerically higher ORR for all the 3 exposure measures; ii) Cox regression analysis showed that higher exposure corresponded to numerically higher PFS for all the exposure measures analysed, and iii) Cox regression of OS showed that higher exposure corresponded to numerically longer event times for all the exposure measures analysed. Because OS data are immature, the analysis of the OS data is limited.

The evaluation of interactions between covariate and exposure modifiers shows that the increase in ORR with increasing exposure was larger in patients using PPIs than in patients with no PPI use. This finding may suggest that a complex interaction occurs. Previous PopPK analysis indicated that PPIs decreased crizotinib Ka when concomitantly administered. Yet, co-administration with PPIs has no clinically relevant effect on exposure to crizotinib. Also, CYP3A4 inhibitor use is an effect modifier of the ER relationship given that higher exposure corresponds to lower hazard, and thus longer OS. However it is difficult to properly adjust for many covariates in logistic and Cox regression models when there is limited number of evaluable events in subgroups with different covariates for endpoint.

Additional exposure-response analyses in studies A8081014 and A8081007 were conducted by the MAH. The univariate covariate analysis and stepwise covariate selection in Study A8081014 showed no statistically significant covariates for ORR, while all covariates reported as statistically significant for OS and PFS (i.e. SLD, Asian, BWT and ECOG) were intrinsic factors.

Regarding the exposure-response analysis in study A8081007, differently from what done in study A8081014, “CYP3A inhibitor use” covariate was not included. However, consistently with results reported for study A8081014, also in this case the only covariates statistically significant were intrinsic factors (i.e. ECOG and SLD).

One of the secondary endpoint was the analysis of the correlation between ALK gene fusion variants (either no rearrangement or one of the specific rearrangements V1, V2, V3a, V3b, V3a/b, V4, V5a, V6, V7) and outcome measures. However, the number of patients with each ALK gene fusion variant

detected using the PCR test was too small to draw any valid conclusions with respect to outcome measures.

2.3.6. Conclusions on clinical pharmacology

Results of the pharmacokinetic assessment of plasma concentrations (based on sparse sampling) in Study A8081014 and of a pharmacokinetic/pharmacodynamics (PK/PD) analysis for efficacy endpoints in Study A8081014 were consistent with those from previous studies of Xalkori. No changes to the SmPC are warranted.

2.4. Clinical efficacy

This extension of indication for the first-line treatment of ALK-positive advanced NSCLC patients is supported by one single pivotal phase III study A8081014 and updated OS results of Studies A8081005 A8081001, originally submitted to support the Xalkori initial Marketing Authorisation.

2.4.1. Dose response study

No new dose-response studies have been performed.

2.4.2. Main study

Study A8081014: ***Phase 3, randomized, open-Label study of the efficacy and safety of crizotinib versus pemetrexed/cisplatin or pemetrexed/carboplatin in previously untreated patients with non-squamous carcinoma of the lung harbouring a translocation or inversion event involving the anaplastic lymphoma kinase (ALK) gene locus***

Methods

Study participants

Female or male patients, 18 years of age or older, were eligible if they had locally advanced recurrent or metastatic non-squamous NSCLC based on histological or cytological diagnosis.

ALK-positive status was determined by the Abbott Molecular IUO test performed by a central laboratory under US FDA Investigational Device Exemption (IDE).

Patients were required to have tumours with measurable disease according to RECIST (version 1.1) and an ECOG PS of 0-2.

Patients must have had no prior systemic treatment for locally advanced or metastatic disease with the exception of prior adjuvant chemotherapy for Stage I-III or combined modality chemotherapy-radiation for locally advanced disease, which was allowed if completed >12 months prior to documented disease progression.

Patients with brain metastases were only eligible if treated and neurologically stable with no ongoing requirement for corticosteroids for at least 2 weeks prior to randomization, and if they were not taking any medications contraindicated by protocol exclusion criteria.

Any major surgeries must have been completed at least 4 weeks prior to initiation of study treatment, while at least 2 weeks were required for any prior radiation (except palliative) or minor surgeries/procedures. In case of palliative radiation (≤10 fractions), it must have been completed 48 hours prior to crizotinib therapy commencing. In addition, an adequate organ function was required.

Patients previously exposed to therapy directly targeting ALK and with baseline severe medical conditions (i.e., ongoing congestive heart failure, cardiac dysrhythmias Grade≥2, history of extensive disseminated/bilateral or known presence of Grade 3/4 interstitial fibrosis or interstitial lung disease) were excluded from the study.

Treatments

All patients were required to take folic acid, 350-1000 µg orally daily and to receive Vitamin B12, 1000 µg (1 injection IM or as required by local standard of care/regulations) for seven days prior to randomization, starting approximately 7 days before beginning treatment.

Crizotinib arm:

Crizotinib, 250 mg BID, was taken orally on a continuous daily dosing schedule. Cycles were defined in 21-day periods to facilitate scheduling of visits and assessments. Patients were required to continue with folic acid, 350-1000 µg orally on a daily basis through completion of the first cycle only (up to 3 weeks).

It was allowed to continue crizotinib treatment as assigned beyond the time of RECIST-defined disease progression, as assessed by Independent Radiology Review (IRR), at the discretion of the investigator if the patient was perceived to be experiencing clinical benefit.

Chemotherapy arm:

The chemotherapy regimen (cisplatin or carboplatin combined with pemetrexed) was chosen by the investigator after randomization. The maximum number of chemotherapy treatment cycles allowed was 6.

Pemetrexed/Cisplatin or Pemetrexed/Carboplatin*:*

Pemetrexed, 500 mg/m^2, was administered IV over 10 minutes or according to institutional administration timing on Day 1 of a 21-day cycle, in combination with Cisplatin (75 mg/m^2) or Carboplatin (AUC 5 or 6 mg.min/mL), administered approximately 30 minutes after the end of pemetrexed infusion.

Patients were also required to continue to take folic acid (350-1000 µg orally daily) until 3 weeks after the last dose of pemetrexed, and to receive Vitamin B12 (1000 µg every 9 weeks) until discontinuation of chemotherapy.

Premedication with corticosteroid (e.g. dexamethasone, 4 mg given twice daily) was required the day before, the day of, and the day after pemetrexed dosing, in order to reduce potential cutaneous reactions.

After 6 cycles patients were to continue in the study without further treatment, having ongoing tumour assessments until RECIST-defined disease progression as determined by IRR.

In case of progression of disease, patients were allowed to cross-over to receive crizotinib treatment.

In both treatment arms, following the discontinuation of study treatment, survival status was to be collected every 2 months until death or until 18 months after the randomization of the last patient.

Objectives

The primary study objective was to demonstrate the crizotinib superior efficacy in terms of prolonged PFS compared to first-line chemotherapy with either pemetrexed/cisplatin or pemetrexed/carboplatin in patients with previously untreated ALK-positive advanced non-squamous NSCLC.

As secondary objectives, additional measures of clinical efficacy (ORR, OS, DCR, TTP and TTR), the safety and tolerability compared to chemotherapy, the crizotinib PK profile, the correlation of ALK gene fusion variants to outcome measures, the Patient-Reported Outcomes (PRO) and the health care resource utilization (HCRU) were also investigated in the trial.

Outcomes/endpoints

The primary endpoint was PFS based on RECIST 1.1, with disease progression events assessed by IRR. PFS was defined as the time from the date of randomization to the date of the first documentation of objective tumor progression (by IRR) or death on study due to any cause, whichever occurred first.

The efficacy secondary endpoints assessed were:

-ORR (determined by IRR) was defined as the percentage of patients with CR or PR according to RECIST Version 1.1, as determined by IRR, relative to the FA population;

- OS was defined as the time from randomization to the date of death due to any cause.#;

- Disease control rate (DCR) at 12 weeks was defined as the percentage of patients with CR, PR, or stable disease at 12 weeks according to RECIST Version 1.1, as determined by IRR, relative to the FA population;

- times to overall, intracranial and extracranial progression (TTP, IC-TTP, EC-TTP), the rate of OS at 1 year and 18 months, duration of response (DR), and time to tumour response (TTR).

As additional secondary endpoints, safety, PK/PD, patient-reported outcomes (PRO) and health care resource utilization (HCRU) were evaluated.

Sample size

Considering that a total of 229 PFS events in the two arms, using a 1-sided log-rank test at a significance level of 0.025, is required to detect a 50% improvement in PFS (from 6 to 9 months) with 85% power, a total sample size of 294 patients is required, assuming non-uniform accrual over approximately 25 months and follow-up of at least 8 months after the last patient is randomized. To account for events being censored, for example due to potential discordance between the investigators and independent radiology review, approximately 40 extra patients were planned to be enrolled for a total sample size of 334 patients (167 in each treatment arm).

Randomisation

Patients were randomized in a 1:1 ratio based on a random permutated block design using a centralized Interactive Voice Response System (IVRS)/website to receive either crizotinib or chemotherapy.

The randomization was stratified by Eastern Cooperative Oncology Group performance status (ECOG PS) (0-1 or 2), race (Asian or non-Asian), and baseline brain metastases (presence or absence).

Patients randomized to chemotherapy with disease progression as assessed by IRR were permitted to cross-over to crizotinib treatment provided that relevant safety screening criteria for crizotinib were met.

Statistical methods

Primary efficacy analysis

PFS was analysed in the full analysis (FA) population defined as defined all patients who were randomized with study drug assignment designated according to the initial randomization. This was the primary population for evaluating all efficacy endpoints.

Estimates of the PFS curves were obtained from the Kaplan-Meier method and were displayed graphically. Differences in PFS between treatment arms were analysed by the log rank test stratified for baseline factors. The median event time (and other quartiles) and corresponding 2-sided 95% CI were provided for each treatment arm. Additionally, for each treatment arm the median PFS and corresponding 2-sided 95% CI were provided for each level of the stratification variables. The Cox regression model, stratified for baseline stratification factors, was fitted. The estimated hazard ratio and 2-sided 95% CI was provided.

Secondary and sensitivity analyses of the primary endpoint

The potential influences of the stratification factors and other baseline patient characteristics were evaluated by Cox proportional hazard models. As secondary analyses for PFS an unstratified log-rank test and Cox regression model was used. PFS based on the investigator assessment was summarized for subgroups: 1) the patients randomized to crizotinib; 2) patients randomized to chemotherapy; 3) patients randomized to chemotherapy who crossed over to receive crizotinib, beginning from the first day of crizotinib treatment. The total event disagreement rate between PFS based on IRR and the investigator assessment of tumour data was calculated.

Secondary efficacy analyses

One-year and 18-month survival probabilities were based on the Kaplan-Meier method. Differences in OS between treatment arms were analysed by a 1-sided log-rank test stratified for baseline stratification factors. Estimates of the OS curves obtained from the Kaplan-Meier method were presented. Analysis of OS was also performed by treatment group. The Cox regression model, stratified for baseline stratification factors, was fitted. The estimated hazard ratio and its 95% CI was provided. In order to take into account that in case of progression of disease, patients were allowed to receive crizotinib treatment the rank preserving structural failure time model (RPSFTM) was used as a sensitivity analysis.

ORR was summarized for each treatment arm along with the corresponding exact 2-sided 95% CI using a method based on the F-distribution. ORR between the 2 treatment arms was compared using a 2-sided Cochran-Mantel-Haenszel test stratified for baseline stratification factors and a 2-sided unstratified test (e.g., Pearson). Treatment difference of ORR and its 95% CI based on the normal distribution were provided. Analysis of ORR was also performed by treatment group. DCR at Week 12 was analysed similarly as described for ORR.

Best overall response was summarized by treatment arm.

TTR was summarized by descriptive statistics in the subgroup of responders (CR and PR) and in the subgroup of the patients randomized to chemotherapy who crossed over to receive crizotinib based on investigator assessment of response using descriptive statistics.

DR was summarized for the subgroup of responders (CR and PR) and in in the subgroup of the patients randomized to chemotherapy who crossed over to receive crizotinib based on investigator assessment of response using using the Kaplan-Meier method. The median event time (if appropriate) and 2-sided 95% CI for the median for each treatment arm were provided.

TTP, IC-TTP and EC-TTP analysed for subgroups of patients with and without brain metastases at baseline. Differences between treatment arms were analysed by the unstratified log rank test. Estimates of the curves obtained from the Kaplan-Meier method were presented.

All patients from the FA population who completed a baseline and at least 1 post-baseline PRO assessment prior to cross-over or end of randomized study treatment were included in the PRO evaluable population used for the analysis of change from baseline scores and TTD in patient-reported pain in chest, dyspnea and cough.

The study was designed to have an interim analysis and a final analysis for the primary endpoint. The interim analysis was planned after 103 (45%) PFS events, with the aim to allow early stopping of the study for futility, to assess safety, and to allow for sample size re-estimation based on the method outlined by Cui et al (1999). The O'Brien-Fleming stopping boundary was used for efficacy and the Rho (rho=1.5) stopping boundary (non-binding was used for futility). Both Type I and II error rates was preserved. The final analysis has been conducted after achievement of the pre-specified 229 events.

The original Statistical Analysis Plan (SAP) was amended twice. The main changes included in Version 2.0 (dated 22 January 2013) were the removal of the second interim analysis of efficacy/futility for PFS and the postponement of the planned first interim analysis to after 45% instead of 35% of PFS events.

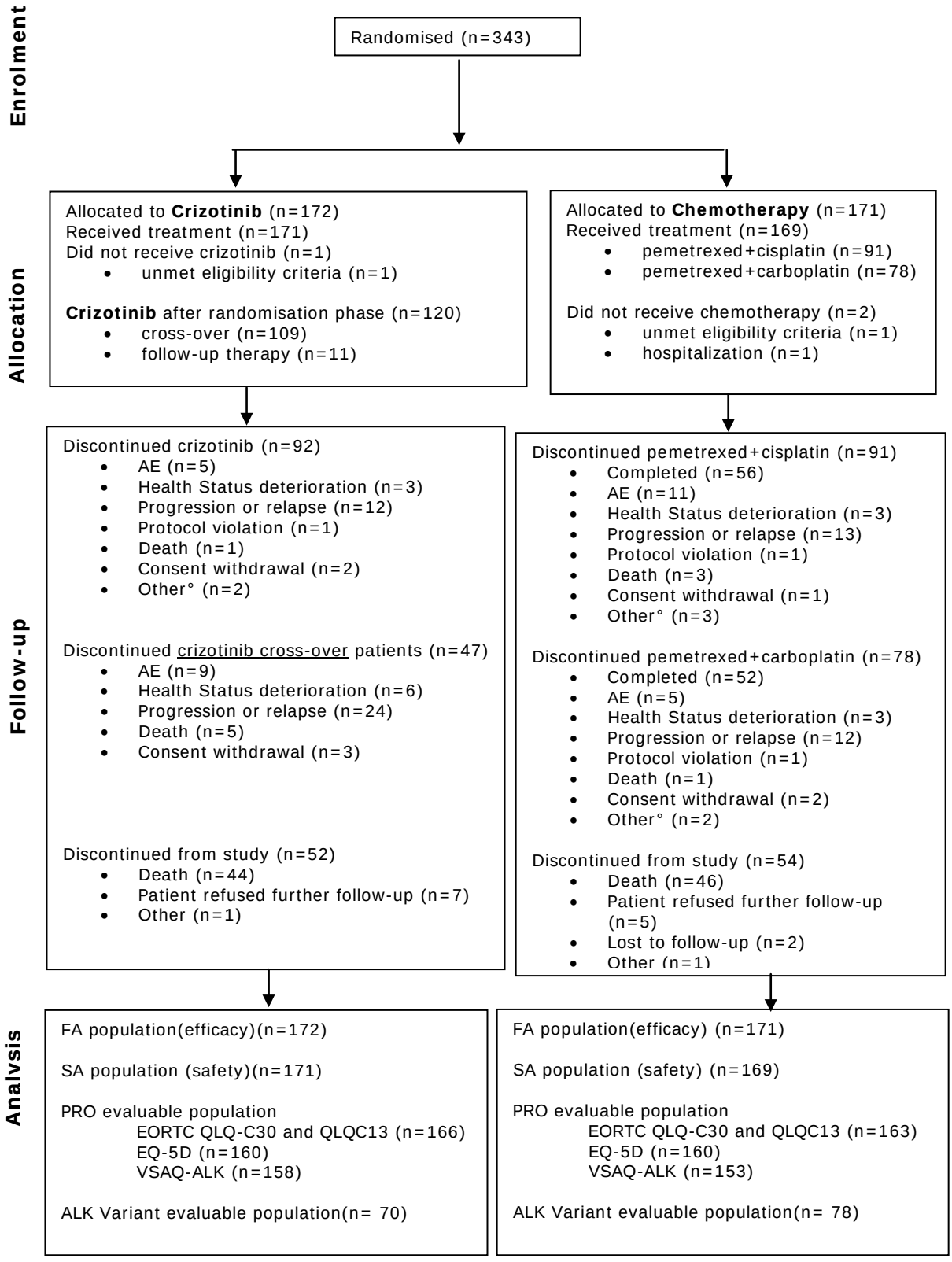
In the amended SAP Version 2.1 (dated 14 February 2014), endpoints and statistical analyses to evaluate treatment activity in patients with or without brain metastases were added.

Additional changes to planned analyses that were implemented after the database snapshot included:

- Analysis of PFS, ORR, OS and AEs by type of chemotherapy individually (pemetrexed + cisplatin or pemetrexed + carboplatin).
- Evaluation of ORR, TTR and DR for cross-over patients in the "Response Evaluation" population, defined as all patients with an adequate baseline disease assessment (at the time of cross-over) and at least 1 post-cross-over assessment or who discontinued the study.

Results

Participant flow



Recruitment

Three-hundred forty three (343) patients were randomised from January 2011 to July 2013. Overall, the study was conducted at 169 sites in 31 countries. The study is ongoing, but closed to enrolment and patients continue to be followed for safety and OS.

Conduct of the study

The original study protocol (dated 31 May 2010) was amended 8 times, including 1 countries specific amendment.

Table 7: summary of main changes implemented with each protocol amendment

Amendment number	Version Date	Summary of main changes
1	03 Aug 2010	Additional safety monitoring language for pneumonitis; Clarification of vitamin supplement administration in the crizotinib arm
2	20 Dec 2010	Further clarification on dose modifications for drug-related toxicities; Introduction of SAE reporting requirements for drug-induced liver injury; Clarification of carboplatin dosing when using IDMS method for serum creatinine estimation.
3 (United Kingdom and France specific)	21 Feb 2011	Clarification of adequate contraceptives in response to MHRA request; Introduction of list of medications that may prolong QT interval and recommendation to avoid these in response to AFSSAPS request; Increased frequency of ophthalmologic examinations for patients enrolled in France in response to AFSSAPS request.
4	10 Jun 2011	Explanation of the formation and remit of the Sponsor's Internal Oncology Business Unit-Safety Data Monitoring Committee (IOBU-SDMC); Further clarification of the liver function tests to be performed for suspected Hy's Law cases; Introduction of baseline and on-study urinalysis by dipstick and microscopy after request from Korean Health Authority; Introduction of dipstick urinalysis at baseline for all patients; Introduction of safety monitoring for a very uncommon AE of renal cyst on crizotinib therapy; Clarification that crizotinib capsules had to be administered orally; Clarification related to exclusion of interstitial lung disease; Addition of end stage renal disease on hemodialysis to exclusion criterion 17; Other typographical corrections.
5	22 May 2012	Introduction of Indian Health Authority-requested imposition of upper 65-year age limit and ophthalmologic examinations every cycle; Introduction of French Health Authority requirement for the Sponsor to discuss patient management on a case-by-case basis with the investigator in the case of treatment-related Grade 2 increases in ALT with normal total bilirubin levels, discontinuing crizotinib for treatment-related Grade 3 or 4 ALT elevations, and the introduction of the Fibro Test in patients with baseline values of ALT/AST between 3-<5 x ULN; Reduced schedule of tumour assessments every 12 weeks instead of every 6 weeks in patients with central radiology review determined progressive disease who were continuing on crizotinib therapy as a cross-over patient or because overall clinical benefit was observed while on crizotinib; Removal of second interim analysis for efficacy in response to regulatory health authority feedback and change first interim analysis for safety and futility to occur at 45% instead of 35% PFS events; Allowance for sample size re-estimation at the interim analysis; addition of DCR at 12 weeks and time to tumour response as secondary endpoints.
6	06 Sep 2012	Addition of ECG and PK time points around the expected T_{max}; Introduction of centralized blinded manual review of ECG tracings in all subsequent patients randomized to the crizotinib arm at the request of European CHMP made upon review of the MAA; For male patients only, introduction of prospective hypogonadism laboratory testing and bone mineral density and muscle mass assessments by DXA scan in response to observations made by Weickhardt et al, 2012
7	17 May 2013	In response to an Australian ethics committee request, addition of definition of TTR analysis to the secondary efficacy endpoints; Correction of inconsistencies across the protocol.
8	19 Dec 2013	Addition of secondary objectives, endpoints and statistical analyses related to the evaluation of intracranial antitumour activity.

AFSSAPS= French Agency for the Safety of Health Products; DXA= dual energy X-ray absorptiometry; IDMS=isotope dilution mass spectrometry; MHRA= Medicines and Healthcare Products Regulatory Agency;

Protocol Amendment 8 was implemented after the data cut-off date for the submitted CSR.

Significant protocol deviations, mainly related to failure to obtain informed consent (12.2%) and treatment administration (11.7%), were registered in 41.1% of patients. During the course of the study, 3 Protocol Deviation Alert Letters (i.e. reminder to perform pregnancy testing, to select and confirm use of appropriate contraception, and to repeat ALT and total bilirubin laboratory test when symptomatic or within 7 days for crizotinib-treated patients with Grade 2 ALT elevation) were sent to Investigators.

Baseline data

A summary of baseline demographic and disease characteristics by treatment arm for the FA population in Study 1014 is reported in the following tables:

Table 8: Demographic Characteristics by Treatment Arm in Study 1014 (Full Analysis Population)

	Crizotinib (N=172)	Chemotherapy (N=171)
Sex, n (%)		
Male	68 (39.5)	63 (36.8)
Female	104 (60.5)	108 (63.2)
Age, years		
N	172	171
Mean (SD)	50.94 (11.9)	52.89 (13.1)
Median (Range)	52.0 (22-76)	54.0 (19-78)
Age category, n (%)		
<65 years	149 (86.6)	139 (81.3)
<45 years	56 (32.6)	44 (25.7)
45-<55 years	52 (30.2)	46 (26.9)
55-<65 years	41 (23.8)	49 (28.7)
≥65 years	23 (13.4)	32 (18.7)
Race, n (%)		
White	91 (52.9)	85 (49.7)
Black	0	4 (2.3)
Asian	77 (44.8)	80 (46.8)
Japanese	14 (8.1)	18 (10.5)
Korean	30 (17.4)	26 (15.2)
Chinese	27 (15.7)	32 (18.7)
Other Asian	6 (3.5)	4 (2.3)
Other	4 (2.3)	2 (1.2)
Smoking classification, n (%)		
Never smoked	106 (61.6)	112 (65.5)
Ex-smoker	56 (32.6)	54 (31.6)
Smoker	10 (5.8)	5 (2.9)

Source: Study 1014 CSR Table 14.1.2.1.1.1 and Table 14.1.2.1.2.1
Note: Chemotherapy group includes pemetrexed/cisplatin and pemetrexed/carboplatin
Abbreviations: CSR=clinical study report, n/N=number of patients; SD=standard deviation

Table 9: Summary of Baseline Disease Characteristics in Study 1014 (Full Analysis Population)

Parameter	Number (%) of Patients	
	Crizotinib) (N=172)	Chemotherapy (N=171)
Measurable Disease Present[a]		
No	2 (1.2)	3 (1.8)
Yes	170 (98.8)	168 (98.2)
Disease Stage		
Locally advanced	4 (2.3)	3 (1.8)
Metastatic	168 (97.7)	168 (98.2)
Histological Classification		
Adenocarcinoma	158 (91.9)	159 (93.0)
Acinar adenocarcinoma	12 (7.0)	11 (6.4)
Papillary adenocarcinoma	5 (2.9)	10 (5.8)
Bronchioloalveolar carcinoma	2 (1.2)	3 (1.8)
Solid adenocarcinoma with mucin production	10 (5.8)	9 (5.3)
Signet ring adenocarcinoma	11 (6.4)	16 (9.4)
Adenocarcinoma not otherwise specified	118 (68.6)	110 (64.3)
Large cell carcinoma	3 (1.7)	8 (4.7)
Adenosquamous carcinoma	5 (2.9)	1 (<1.0)
Other[b]	6 (3.5)	3 (1.8)
ECOG PS[c]		
0	58 (33.7)	47 (27.5)
1	105 (61.0)	117 (68.4)
2	9 (5.2)	7 (4.1)
Brain Metastases		
Present	45 (26.2)	47 (27.5)
Absent	127 (73.8)	124 (72.5)
Had Prior Systemic Therapy[d]	12 (7.0)	13 (7.6)
Neoadjuvant	2 (16.7)	2 (15.4)
Adjuvant	10 (83.3)	9 (69.2)
Curative	1 (8.3)	0
Locally advanced	2 (16.7)	2 (15.4)

Source: Study 1014 CSR Table 14.1.2.2.2.1, Table 14.1.2.2.3, Table 14.1.2.4.1, Table 14.1.2.5.1; Table 14.4.2.2.1.

Abbreviations: CSR=clinical study report, ECOG PS=Eastern Cooperative Oncology Group performance status; N=number of patients

a At least 1 target lesion ≥2 cm for X-ray or at least 1 target lesion ≥1 cm for spiral CT or clinical examination or at least 1 lymph node target lesion with shortest diameter ≥1.5 cm, based on investigator tumor assessment.

b Other includes: non-squamous NOS p63 negative, codominant acinar and papillary pattern*, adenocarcinoma NOS*, non-squamous cell carcinoma, mucinous adenocarcinoma*, and middle to large cell carcinoma in the crizotinib arm; sarcomatoid carcinoma, mixed acinar and focal papillary*, and acinar and papillary adenocarcinoma* in the chemotherapy arm (Study 1014 Clinical Study Report Table 16.2.4.2).
*Recategorized as adenocarcinoma in subset analyses of adenocarcinoma versus non-adenocarcinoma.

c Baseline used the Cycle 1 Day 1 value; if Cycle 1 Day 1 value was missing, then baseline used the screening value.

d A patient could report more than 1 setting for prior systemic therapy. Percentages for the types of prior systemic therapy are based on the total number of patients who had a prior systemic therapy.

Numbers analysed

Overall, 343 patients (172 randomized to crizotinib and 171 randomized to chemotherapy) were included in the FA population. At the time of the final PFS analysis, 120 (70.2%) patients randomized to the chemotherapy arm received subsequent crizotinib treatment (109 patients through the crossover process and 11 patients as subsequent follow up therapy).

Outcomes and estimation

The median duration of study treatment was 47.4 weeks in the crizotinib arm and 18 weeks in the chemotherapy group for which a maximum of 6 cycles was permitted, with median relative dose intensities of 98.9% for crizotinib and 94.4-96.3% across the individual chemotherapy agents (i.e., pemetrexed, cisplatin, carboplatin).

Primary endpoint

Progression Free Survival

Table 10: Progression-Free Survival Based on Independent Radiology Review by Treatment Arm in Study 1014 (Full Analysis Population)

Response Parameter	Crizotinib (N=172)	Chemotherapy (N=171)
Number with event, n (%)	100 (58.1)	137 (80.1)
Type of event, n (%)		
Objective progression	89 (51.7)	132 (77.2)
Death without objective progression	11 (6.4)	5 (2.9)
Number censored, n (%)	72 (41.9)	34 (19.9)
Reason for censorship, n (%)		
No adequate baseline assessment	0	0
No on-study disease assessments	0	2 (1.2)
Given new anticancer treatment prior to tumor progression	12 (7.0)	6 (3.5)
Unacceptable gap (>14 weeks) between PD or death to the most recent prior adequate assessment	0	2 (1.2)
Lost to follow-up	0	0
Withdrew consent for follow-up	3 (1.7)	6 (3.5)
No scans/data available	1 (<1.0)	0
In follow-up for progression	56 (32.6)	18 (10.5)
Probability of being event free at Month 6[a], % (95% CI)[b]	69.9 (62.1. 76.3)	60.7 (52.6. 67.9)
Probability of being event free at Month 12[a], % (95% CI)[b]	47.8 (39.5, 55.7)	16.1 (10.5, 22.8)
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI)[c]		
25%	5.4 (4.0, 6.8)	4.0 (2.8, 5.3)
50%	10.9 (8.3, 13.9)	7.0 (6.8, 8.2)
75%	NR (15.7, NR)	10.8 (9.5, 11.2)
Crizotinib Arm vs Chemotherapy Arm		
Hazard ratio[d] (95% CI)	0.454 (0.346, 0.596)	
p-value[e]	<0.0001	

Note: Chemotherapy arm includes data before cross-over to crizotinib.
Abbreviations: CI=confidence interval; CSR=clinical study report; ECOG PS=Eastern Cooperative Oncology Group performance status; HR=hazard ratio; N/n=Number of patients; NR=not reached; PD=progressive disease
a Estimated from the Kaplan-Meier curve.
b Calculated using the normal approximation to the log transformed cumulative hazard rate.
c Based on the Brookmeyer and Crowley method.
d Based on the Cox proportional hazards model stratified by ECOG PS score, race, and brain metastases. Assuming proportional hazards, an HR less than 1 indicates a reduction in hazard rate in favor of crizotinib.
e 1-sided p-value from the log-rank test stratified by ECOG PS, race, and brain metastases.

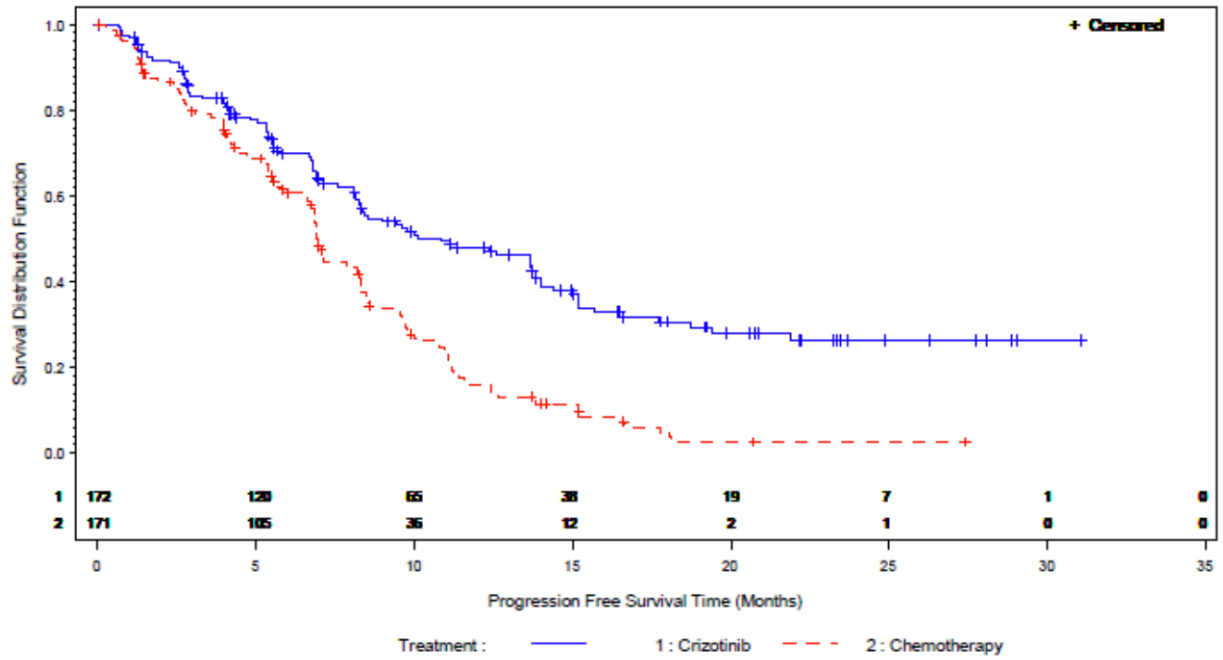
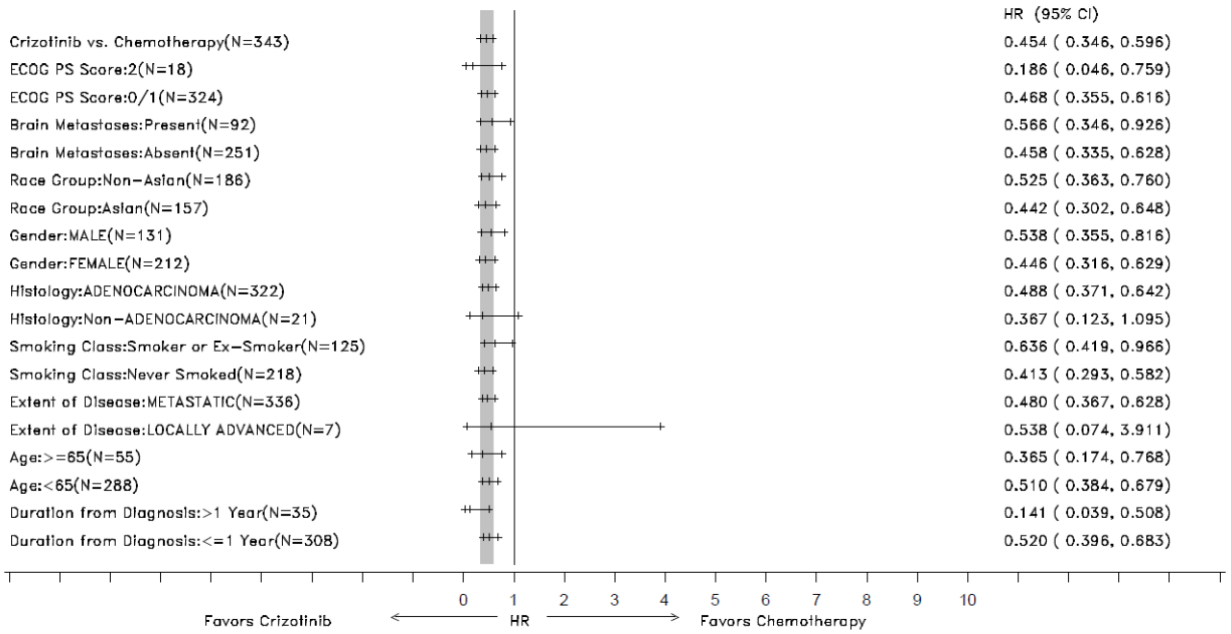


Figure 2: Kaplan-Meier Plot of Progression-Free Survival Based on Independent Radiology Review by Treatment Arm in Study 1014 (Full Analysis Population)

Comparison of PFS by Treatment Group (SA Population)



Abbreviations: CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; N=number of patients; PS=performance status

Figure 3: Forest Plot of Progression-Free Survival - Full Analysis Population

Secondary endpoints

Overall Survival and Survival Probabilities at 1 year and 18 months

The median duration of follow-up for OS was 17.4 months for patients randomized to crizotinib and 16.7 months for those in the chemotherapy group.

Table 11: Summary of Overall Survival by Treatment Arm in Study 1014 (Full Analysis Population)

Response Parameter	Crizotinib (N=172)	Chemotherapy (N=171)
Number of deaths, n (%)	44 (25.6)	46 (26.9)
Number censored, n (%)	128 (74.4)	125 (73.1)
Patient remains on follow-up	119 (69.2)	115 (67.3)
Patient no longer being followed	2 (1.2)	3 (1.8)
Withdrew consent for follow-up	7 (4.1)	5 (2.9)
Lost to follow-up	0	2 (1.2)
12-Month Survival Probability,[a] % (95% CI)[b]	83.5 (76.7, 88.5)	78.6 (71.3, 84.2)
18-Month Survival Probability,[a] % (95% CI)[b]	68.6 (59.5, 76.1)	67.3 (58.1, 74.9)
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI)[c]		
25%	15.5 (12.5, 26.5)	14.9 (8.8, 23.0)
50%	NR	NR
75%	NR	NR
Crizotinib Arm vs Chemotherapy Arm		
Hazard ratio[d] (95% CI)	0.821 (0.536, 1.255)	
p-value[e]	0.1804	

Note: The chemotherapy arm includes events before and after cross-over to crizotinib for those patients who crossed over to receive crizotinib treatment.
Abbreviations: CI=confidence interval; CSR=clinical study report; HR=hazard ratio; N/n=number of patients; NR=not reached.
a Estimated from the Kaplan-Meier curve.
b Calculated using the normal approximation to the log transformed cumulative hazard rate.
c Based on the Brookmeyer and Crowley method.
d Based on the Cox Proportional hazards model stratified by ECOG PS, race, and brain metastases. Assuming proportional hazards, an HR less than 1 indicates a reduction in hazard rate in favor of the crizotinib arm.
e 1-sided p-value from the log-rank test stratified by ECOG PS, race, and brain metastases

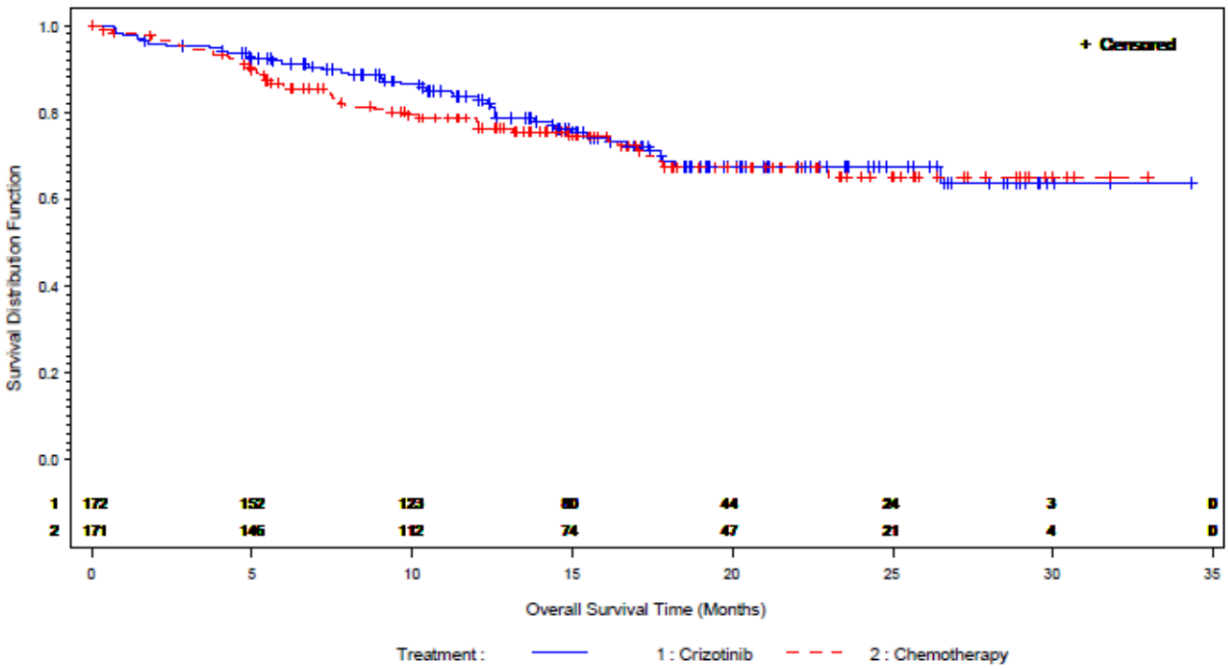


Figure 4: Kaplan-Meier Plot of Study 1014 Overall Survival by Treatment Arm (Full Analysis Population)

Objective Response Rate and Disease Control Rate

Data for best overall response, ORR and DCR are shown in the table below:

Table 12: Objective response-related endpoints based on IRR by treatment arm in Study 1014 (FA population)

Efficacy Parameter	Crizotinib (N=172)	Chemotherapy (N=171)
Best Response, n (%)		
CR	3 (1.7)	2 (1.2)
PR	125 (72.7)	75 (43.9)
SD	29 (16.9)	63 (36.8)
PD	8 (4.7)	21 (12.3)
Early death[a]	4 (2.3)	4 (2.3)
Indeterminate[b]	3 (1.7)	6 (3.5)
ORR (CR + PR), n (%)	128 (74.4)	77 (45.0)
[95% CI][c]	(67.2, 80.8)	(37.4, 52.8)
SD duration (months)[d], n (%)		
0 to <3 months	11 (37.9)	12 (19.0)
3 to <6 months	5 (17.2)	15 (23.8)
6 to <9 months	4 (13.8)	15 (23.8)
9 to <12 months	1 (3.4)	15 (23.8)
≥12 months	8 (27.6)	6 (9.5)
Treatment comparison (vs chemotherapy)		
Treatment difference in ORR rate[e] (95% CI[e])	29.4 (19.5, 39.3)	
p-value[f]	<0.0001	
Treatment comparison (vs chemotherapy)		
Risk ratio[g] (95% CI of risk ratio[g])	1.664 (1.379, 2.007)	
p-value[g]	<0.0001	
DCR (CR+PR+SD) at 12 weeks, n (%)[95% CI][c]	135 (78.5) (71.6, 84.4)	117 (68.4) (60.9, 75.3)
Treatment comparison (vs chemotherapy)		
Treatment difference in DCR rate[e] (95% CI[e])	10.1 (0.8, 19.4)	
p-value[f]	0.0381	

Source: Study 1014 CSR Table 14.2.1.1, Table 14.2.2

Note: Chemotherapy arm only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.

Abbreviations: CI=confidence interval; CR=complete response; CSR=clinical study report; DCR=disease control rate; ND=analysis not done; N/n=number of patients; ORR=objective response rate; PD=progressive disease (or objective progression); PR=partial response; SD=stable disease.

a Early death was death within 42 days (6 weeks) from randomization and prior to having sufficient evaluations for overall response.

b Indeterminate is assigned when a patient has only a baseline assessment, or response assessment of SD at an interval <6 weeks and has no subsequent disease evaluation, or when all overall response evaluations were assessed as indeterminate (SAP in Study 1014 CSR Section 16.1.9) .

c Using exact method based on F-distribution.

d % was based on the number of SD patients.

e Calculated based on a normal distribution.

f p-value was from a 2-sided Pearson chi-square test.

g Calculated from 2-sided Cochran-Mantel-Haenszel (CMH) test stratified by ECOG PS score, brain metastases, race.

Duration of Response and Time to Tumour Response

Table 13: Duration of Response and Time to Tumour Response based on Independent Radiology Review by arm in Study 1014 (FA population; objective responders only)

Response Parameter	Crizotinib (N=172)	Chemotherapy[a] (N=171)
Number of patients with objective response (CR + PR), n (%)[b]	128 (74.4)	77 (45.0)
With subsequent disease progression or death	70 (54.7)	68 (88.3)
Without subsequent disease progression or death	58 (45.3)	9 (11.7)
Kaplan-Meier Estimates of Duration of Response		
Median, weeks (95% CI)[c]	49.0 (35.1, 60.0)	22.9 (18.0, 25.1)
Time to Tumor Response		
Median, weeks (range)[d]	6.1 (2.7-41.4)	12.1 (5.1-36.7)
Time category, n (%)		
0 to <6	24 (18.8)	11 (14.3)
6 to <12	81 (63.3)	24 (31.2)
12 to <18	15 (11.7)	22 (28.6)
18 to <24	5 (3.9)	8 (10.4)
≥24	3 (2.3)	12 (15.6)

Source: Study 1014 CSR Table 14.2.4.1 and Table 14.2.4.2
Note: Duration of response was the time from the date of first documentation of CR or PR to the date of first documentation of objective progression or death due to any cause.
Note: Time to tumor response is the time from the randomization date to the first documentation of objective tumor response (CR or PR).
Abbreviations: CI=confidence interval; CR=complete response; PR=partial response; CSR=clinical study report; n/N=number of patients
a Only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.
b Denominator (N) for DR and TTR is number of responders in the FA population.
c Based on the Brookmeyer and Crowley method.
d Calculation based on descriptive statistics

Time to Progression (Overall, Intracranial and Extracranial)

A summary of data for time to progression endpoints, overall and for extracranial (new or progression of existing extracranial lesions) and intracranial (new or progression of existing brain metastases) TTP is shown in the table below.

Table 14: Time to Progression endpoints (Overall, Extracranial, Intracranial) based on Independent Radiology Review in Study 1014 (FA population)

	Overall TTP		EC-TTP		IC-TTP	
	Crizotinib (N=172)	Chemo-therapy (N=171)	Crizotinib (N=172)	Chemo-therapy (N=171)	Crizotinib (N=172)	Chemo-therapy (N=171)
No. with event, n (%)	89 (51.7)	132 (77.2)	71 (41.3)	119. (69.6)	25 (14.5)	26 (15.2)
No. censored, n (%)	83 (48.3)	39 (22.8)	101 (58.7)	52 (30.4)	147 (85.5)	145 (84.8)
Probability of being event-free[a]						
at Month 6 (95% CI)[b]	74 (66.3, 80.2)	62.7 (54.5, 69.9)	78.5 (71.0, 84.2)	65.4 (57.0, 72.5)	93.5 (87.4, 96.7)	92.8 (86.9, 96.1)
at Month 12 (95% CI)[b]	51.2 (42.4, 59.3)	16.7 (10.9, 23.5)	59.1 (50.1, 67.0)	19.1 (12.6, 26.6)	83.3 (74.3, 89.4)	74.2 (61.8, 83.1)
Kaplan-Meier estimates of time to event (months)						
50% quartile (95% CI)[c]	13.6 (8.5, 15.0)	7.0 (6.8, 8.3)	15.2 (12.6, 21.9)	7.2 (6.9, 8.5)	NR	17.8 (13.9, NR)
Versus chemotherapy						
Hazard ratio[d]	0.441		0.387		0.595	
95% CI of hazard ratio	(0.335, 0.582)		(0.286, 0.524)		(0.338, 1.048)	
P-value[e]	<0.0001		<0.0001		0.0347	

Source: Study 1014 CSR Table 14.2.9.1, Table 14.2.9.3 and Table 14.2.9.5
Note: The chemotherapy arm includes events before crossover to crizotinib only.
Abbreviations: CI=confidence interval; CSR=clinical study report; EC-TTP=extracranial time to progression; IC-TTP=intracranial time to progression; n/N=number of patients; NR=not reached; TTP=time to progression.
a Estimated from the Kaplan-Meier curve.
b Calculated using the normal approximation to the log transformed cumulative hazard rate.
c Based on the Brookmeyer and Crowley method.
d Based on the Cox Proportional hazards model. Assuming proportional hazards, a hazard ratio <1 indicates a reduction in hazard rate in favor of crizotinib.
e 1-sided p-value from the unstratified log-rank test.

Efficacy Endpoints in Crossover Patients

In the chemotherapy arm, 109 (63.7%) patients crossed over to receive crizotinib treatment. The median time from randomization to the chemotherapy arm until the start of crizotinib treatment was 33.3 weeks (range: 3 to 97 weeks).

Table 15: Crossover from Chemotherapy to Crizotinib – Full Analysis Population

	Chemotherapy (N=171)
Patients who discontinued treatment, n (%)	169 (98.8)
Patients who discontinued the study but never received treatment, n (%)	2 (1.2)
Crossed over to receive crizotinib treatment, n (%)	
Yes	109 (63.7)
No	62 (36.3)
Reason for crossover to crizotinib, n (%)	
IRR assessed PD[a]	109 (100)
Time to crossover to receive crizotinib treatment[b], weeks	
n	109
Mean (SD)	36.0 (20.5)
Median	33.3
Range	3.4-97.0

Table 16: Efficacy Endpoints-Crossover Patients

Response Parameter	Crizotinib Crossover Patients N=109
Progression-Free Survival (PFS)	
Number with event, n (%)	34 (31.2)
Objective progression	29 (26.6)
Death without objective progression	5 (4.6)
Number censored, n (%)	75 (68.8)
Kaplan-Meier estimates of time to event (months)	
Median (95% CI)[a]	7.9 (5.4, 14.3)
Objective Response Rate (ORR)[b]	
Number of response evaluable patients	61
Best response, n (%)	
CR	0
PR	33 (54.1)
SD	10 (16.4)
PD (objective progression)	12 (19.7)
Early death	2 (3.3)
Indeterminate	4 (6.6)
Objective response rate (CR + PR), n (%)	33 (54.1)
95% exact CI[c]	(40.8, 66.9)
Time to Tumor Response, weeks[b]	
Number of patients with an event	33
Median (range)[e]	10.1 (2.0-23.6)
Duration of Response[b]	
Number of response evaluable patients	61
Patients with objective response (CR or PR), n (%)[d]	33 (54.1)
With subsequent progression or death	15 (45.5)
Without subsequent progression or death	18 (54.5)
Kaplan-Meier estimates of duration of response (weeks)	
Median (95% CI)[a]	48.7 (18.4, 62.1)

Source: Study 1014 CSR Table 14.2.5.7.5c, Table 14.2.1.4c, Table14.2.4.1c, Table 14.2.4.2c
Abbreviations: CI=confidence interval; CR=complete response; CSR=clinical study report; N/n=Number of patients; PD=progressive disease; PR=partial response; SD=stable disease.

a Based on the Brookmeyer and Crowley method.
b Endpoints assessed in Response Evaluable crossover patients.
c Using exact method based on F distribution.
d Percentage is based on the number of patients with objective response (CR or PR).
e Calculation based on descriptive statistics.

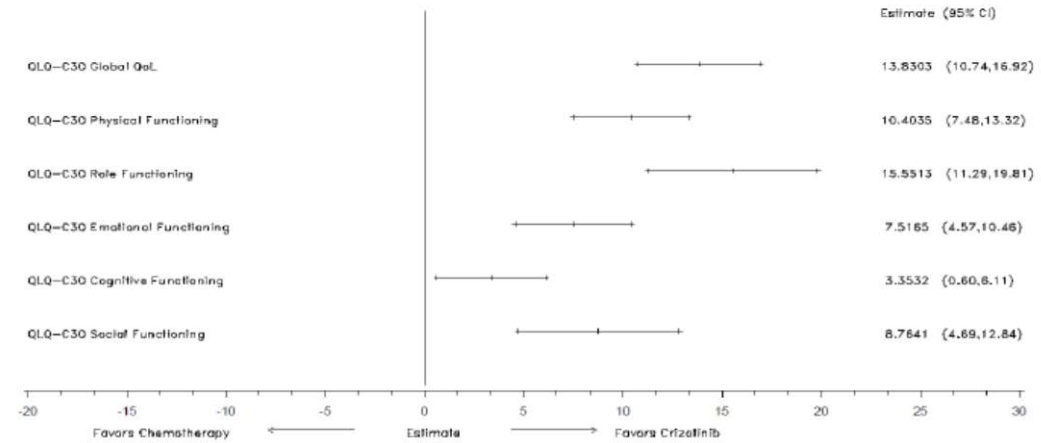
Patient- Reported Outcomes (PROs)

Patient-reported symptoms and global QOL were collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). A total of 166 patients in the crizotinib arm and 163 patients in the chemotherapy arm had completed the EORTC QLQ-C30 and LC13 questionnaires at baseline and at least 1 post baseline visit.

Significantly greater improvement in global QOL was observed in the crizotinib arm compared to the chemotherapy arm (overall difference in change from baseline scores 13.8; p value <0.0001).

A clinically meaningful (≥10-point) improvement from baseline was observed in the crizotinib arm at Cycles 9 and 10, while clinically meaningful (≥10-point) deterioration was observed in the chemotherapy arm on Cycle 1 Day 7.

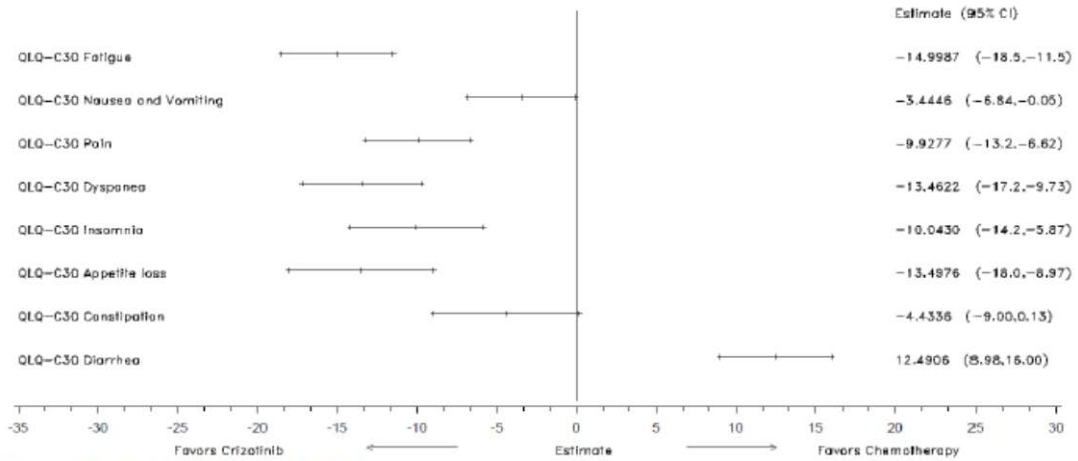
A Forest plot of crizotinib vs chemotherapy for the overall estimated difference in change from baseline scores in global quality of life and functioning domains is provided below:



Source: Section 14.5, Figure 14.5.9.1.
From a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction, and baseline EORTC QLQ-C30 subscale baseline score.
Abbreviations: CI=confidence interval; EORTC=European Organization for the Research and Treatment of Cancer; PRO=patient-reported outcome; QLQ-C30=Quality of Life Questionnaire-Core 30.

Figure 5: Forest Plot of crizotinib versus chemotherapy overall differences in change from baseline scores in QLQ-C30 domains-PRO evaluable population

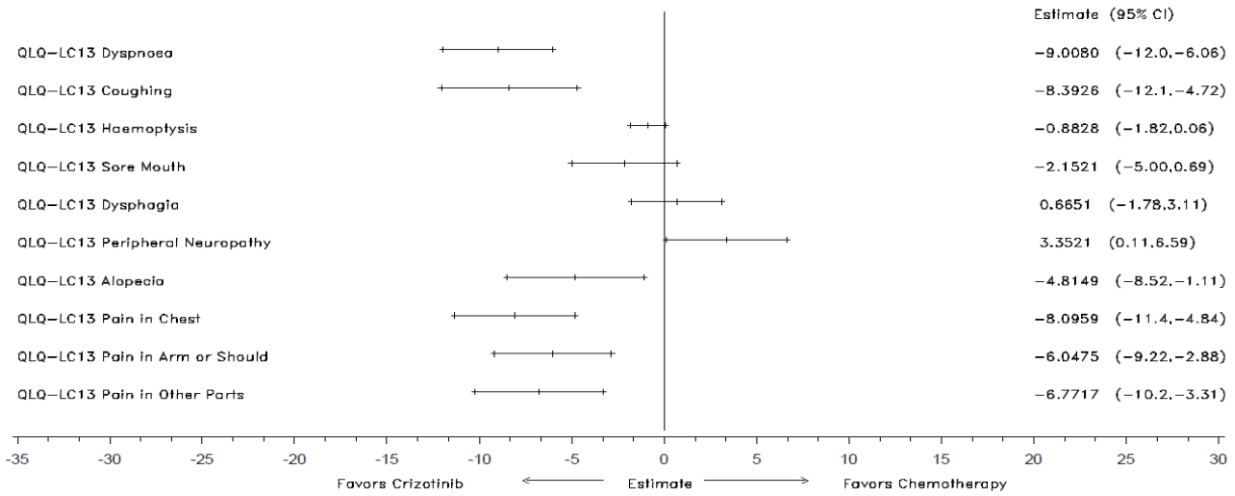
Considering the EORTC QLQ-C30 symptoms, a Forest plot of the overall difference in change from baseline scores in the crizotinib and chemotherapy arms is shown in the following figure:



Source: Section 14.5, Figure 14.5.9.2.
From a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction and baseline EORTC QLQ-C30 subscale baseline score.
Abbreviations: CI=confidence interval; EORTC=European Organization for the Research and Treatment of Cancer; PRO=patient-reported outcome; QLQ-30=Quality of Life Questionnaire-Core 30.

Figure 6: Forest Plot of crizotinib versus chemotherapy overall differences in change from baseline scores in QLQ-C30 symptoms-PRO evaluable population

The Forest plot of overall differences in change from baseline scores in QLQ-LC13 symptoms by arm is reported below:



Source: Study 1014 CSR Figure 14.5.9.3
Note: From a repeated measures mixed-effects model with an intercept term, treatment, treatment-by-time interaction and baseline EORTC QLQ-LC13 subscale baseline score.
Note: QLQ-LC13 Pain in Arm or "Should" is equal to Pain in Arm or "Shoulder.
Abbreviations: CI=confidence interval; CSR=clinical study report; EORTC=European Organization for the Research and Treatment of Cancer; QLQ-13=Quality of Life Questionnaire-Supplement Module for Lung Cancer (LC13).

Figure 7: Forest Plot of crizotinib versus chemotherapy overall differences in change from baseline scores in QLQ-LC13 symptoms-PRO evaluable population

Time to Deterioration (TTD) was prespecified as the first occurrence of a ≥10-point increase in scores from baseline in symptoms of pain in chest, cough, or dyspnoea as assessed by EORTC QLQ-LC13.

Results of composite endpoint TTD in pain, dyspnoea or cough are reported in the following table:

Table 17: Summary of Time to Deterioration in Pain (in Chest), Dyspnea, or Cough by treatment arm in Study 1014 (PRO evaluable population)

	Crizotinib (N=166)	Chemotherapy (N=163)[a]
Number with event, n (%)	111 (66.9)	123 (75.5)
Number censored, n (%)	55 (33.1)	40 (24.5)
Reason for censorship, n (%):		
No deterioration	55 (33.1)	40 (24.5)
Probability of being event-free at Month 6[b] (95% CI)[c]	36.9 (29.3, 44.5)	19.7 (13.0, 27.4)
Kaplan-Meier estimates of time to event, months		
25% quartile (95% CI)[d]	0.3 (0.3, 0.5)	0.3 (0.3, 0.3)
50% quartile (95% CI)[d]	2.1 (0.8, 4.2)	0.5 (0.4, 0.7)
75% quartile (95% CI)[d]	16.7 (7.7, NR)	2.9 (1.5, NR)
Versus chemotherapy		
Hazard ratio[e]	0.591	
95% CI of hazard ratio	(0.452, 0.773)	
p-value[f]	0.0002	

Source: Section 14.5, Table 14.5.2.2.1.
Abbreviations: CI=confidence interval; n/N=number of patients; NR=not reached; PRO=patient-reported outcome.
PRO evaluable patients with either a missing baseline or follow-up symptom values are not included in summary.

[a] Only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.
[b] Estimated from the Kaplan-Meier curve.
[c] Calculated using the normal approximation to the log transformed cumulative hazard rate.
[d] Based on the Brookmeyer and Crowley method.
[e] Based on the Cox Proportional hazards model. Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of crizotinib.
[f] Two-sided p-value from the unstratified log-rank test.

The individual component symptoms included in the composite endpoint have been also analysed separately. A significantly longer TTD was registered in dyspnoea with crizotinib in comparison to chemotherapy (7.6 months versus 1.4 months, HR: 0.548, 95% CI: 0.404, 0.744, Hochberg-adjusted log-rank 2-sided p-value=0.0005).

Regarding the EQ-5D questionnaire, the results of the within patients analyses showed a statistically significant (p-value <0.05) improvement from baseline in EQ-5D VAS general health status scores in the crizotinib arm (Cycles 3 to 16 and 18 to 21) and no statistically significant change from baseline in the chemotherapy arm over the first 6 cycles. A statistically significant (p-value <0.05) greater improvement was observed in EQ-5D VAS general health status scores in the crizotinib arm compared to the chemotherapy arm.

In the VSAQ-ALK questionnaire, in response to the first question ("*Have you experienced any visual disturbances?*"), 33% to 67% of patients reported experiencing a visual disturbance in the crizotinib arm and 13% to 21% in the chemotherapy arm. In both treatment arms, the majority of patients (73%-100% with crizotinib and >60% with chemotherapy) who reported experiencing a visual disturbance had an event frequency of >1 day per week. In the crizotinib arm, visual disturbances were reported as occurred in the morning by 38% to 63% of patients and as occurred in the evening by 56% to 86% of patients. Most patients reported each event lasting ≤1 minute in both arms. The most commonly experienced visual disturbances were appearance of shimmering/flashing/trailing

lights, streamers/strings/floaters, and overlapping shadows/after images in the crizotinib arm, and hazy/blurry vision in the chemotherapy group. For most patients with a visual disturbance at each cycle in the crizotinib arm, visual effects were reported as not at all or a little bothersome, and no or minimal impact (scores 0 to 3) on daily activities at each cycle was indicated.

Ancillary analyses

Several secondary and sensitivity analyses for both primary and secondary endpoints were conducted.

In particular, pre-specified sensitivity analyses were conducted to assess the impact of cross-over on OS, specifically, for the potentially confounding effects of subsequent crizotinib treatment (n=120 patients) in the chemotherapy arm and of subsequent platinum-based chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) (n= 21 patients) in the crizotinib arm. With the Rank-Preserving Structural Failure Time Model (RPSFTM), two approaches (i.e, the Wilcoxon and log-rank tests) were used to derive parameters to correct for cross-over. After adjusting for cross-over, the HRs for OS were 0.604 (95% CI: 0.265, 1.420) and 0.674 (95% CI: 0.283, 1.483) based on the Wilcoxon and log-rank tests, respectively.

Kaplan-Meier plots of OS after adjusting for cross-over by RPSFTM using the Wilcoxon and log-rank tests are presented below:

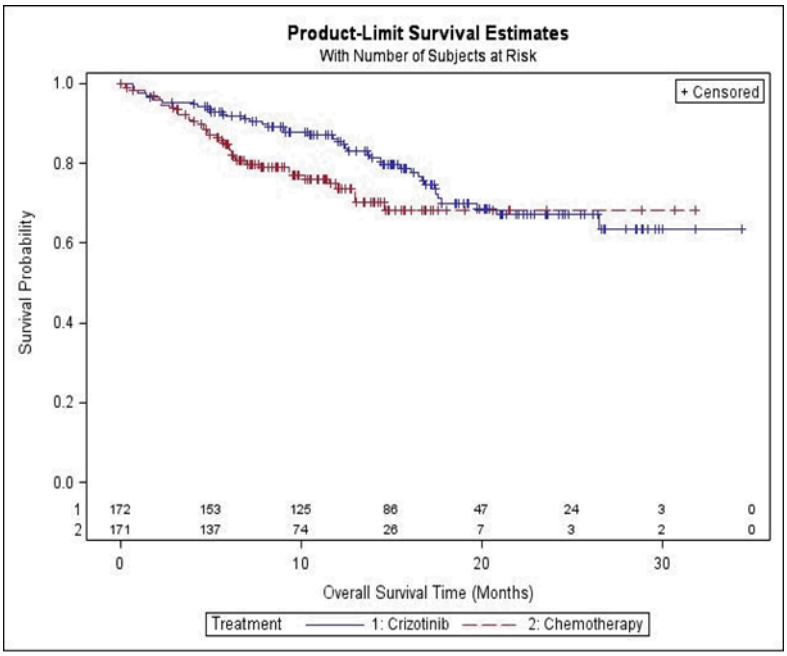


Figure 8: Kaplan-Meier Plot of Overall Survival by Treatment Arm: After Adjusting for Crossover by RPSFTM Using the Wilcoxon Test - Study 1014

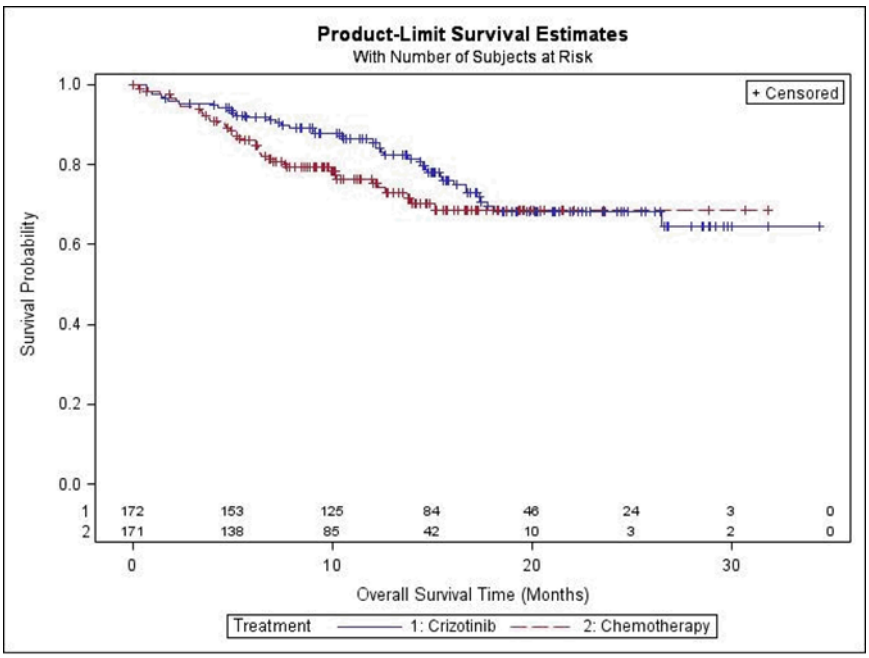


Figure 9: Kaplan-Meier Plot of Overall Survival by Treatment Arm: After Adjusting for Crossover by RPSFTM Using the Log-Rank Test - Study 1014

Further to the CHMP request, the MAH has performed additional sensitivity analyses for Study 1014, to estimate the effect of crizotinib on OS in the presence of crossover, using the two-stage and the IPE methods.

The two-stage model (Latimer and Abrams, 2014), with Log-normal distribution for OS was applied to two sets of analyses: an analysis unadjusted for the differences in patient's characteristics between crossover and non-crossover patients and an analysis that take into account for differences in patients characteristics.

The Iterative Parameter Estimation (IPE) method (Branson and Whitehead 2002) was conducted to adjust for the impact of crossover from chemotherapy to crizotinib and from crizotinib to chemotherapy and estimate the treatment effect for OS in Study 1014.

Table 18: Summary of overall survival analyses for study 1014 based on data at the time of final PFS analysis

Method of Analysis	Parametric Model	Adjusted for Crossover	Analysis Details	Hazard Ratio (95% CI)[1]	1-sided p-value[2]
Primary	NA	No	NA	0.821 (0.536, 1.255)	0.1804.
RPSFTM	NA	Yes†	Using Wilcoxon test	0.604 (0.265, 1.420)	NR
			Using Log-rank test	0.674 (0.283, 1.483)	NR
2-stage	Log-normal	Yes‡	Not adjusted for covariates	0.610 (0.395, 0.942)	0.0123
			Adjusted for baseline Smoking Status and ECOG PS at PD by IRR (ECOG PS imputation #1)	0.649 (0.421, 1.000)	0.0242
			Adjusted for baseline Smoking Status and ECOG PS at PD by IRR (ECOG PS imputation #2)	0.624 (0.405, 0.963)	0.0158
IPE	Weibull	Yes†	Adjusted for baseline ECOG PS, baseline Brain Metastases and baseline Smoking Status	0.626 (0.395, 0.992)	0.0230
	Log-normal			0.633 (0.401, 1.000)	0.0251
	Log-Logistic			0.571 (0.349, 0.935)	0.0130
	Exponential			0.674 (0.432, 1.051)	0.0408

Abbreviations: NA= Not applicable; NR=Not Reported; HR= Hazard Ratio; RPSFTM=Rank Preserving Structural Failure Time Model; IPE=Iterative Parameter Estimation; ECOG PS=Eastern Cooperative Group Performance Status; PD=Progressive Disease

† Adjusted for crossover (from randomized chemotherapy to crizotinib) and (from randomized crizotinib to chemotherapy [only pemetrexed/cisplatin or pemetrexed/carboplatin])

‡ Adjusted for crossover (from randomized chemotherapy to crizotinib)

[1] Based on the Cox model stratified for ECOG PS (0-1, 2), race group (Asian, Non-Asian) and presence of brain metastases (present, absent)

[2] Based on 1-sided log-rank test, stratified for race group, Baseline ECOG PS and Baseline brain metastases

Summary of main study

The following table 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).

Table 19: Summary of Efficacy for trial A8081014

Title: Phase 3, Randomized, Open-Label Study of the Efficacy and Safety of Crizotinib Versus Pemetrexed/Cisplatin or Pemetrexed/Carboplatin in Previously Untreated Patients With Non-Squamous Carcinoma of the Lung Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus		
Study identifier	A8081014	
Design	Open-label, multicenter, randomized, Phase 3 study	
	Duration of main phase:	until disease progression, unacceptable toxicity, death or patient consent withdrawal
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable

Hypothesis	Superiority		
Treatments groups	crizotinib		250 mg BID, continous daily dosing schedule, 172 patients randomized
	chemotherapy		Pemetrexed 500 mg/m^2 IV + Cisplatin 75 mg/m^2 IV, every 3 weeks Pemetrexed 500 mg/m^2 IV + Carboplatin AUC 5-6 mg ml/min, every 3 weeks Maximum 6 cycles 171 patients randomized
Endpoints and definitions	Primary endpoint	PFS	Time from the date of randomization to the date of the first documentation of objective tumour progression (by IRR) or death on study due to any cause, whichever occurred first.
	Secondary endpoints	OS	Time from randomization to the date of death due to any cause
		ORR	Percentage of patients with CR or PR according to RECIST 1.1, as determined by IRR.
		TTR	Time from randomization to first documentation of objective tumour response (CR or PR), as determined by IRR.
		DR	Time from the first documentation of objective tumour response (CR or PR), as determined by IRR, to the first documentation of objective tumour progression or to death due to any cause, whichever occurred first.
		DCR	Percentage of patients with CR, PR or stable disease at 12 weeks according to RECIST 1.1, as determined by IRR.
		TTP	Time from randomization to first documentation of objective tumour progression, as determined by IRR.
		IC-TTP	Time from randomization to first documentation of objective intracranial disease progression, based on either new brain metastases or progression of existing brain metastases, as determined by IRR.
		EC-TTP	Time from randomization to first documentation of objective extracranial disease progression, based on either new extracranial lesions or progression of existing extracranial lesions, as determined by IRR.
		PRO	TTD in pain in chest, dyspnea and cough as the time from randomization to the earliest date the patient's scale scores showed a 10-point or greater increase after baseline in any of these 3 symptoms.
Data cutoff date	30 November 2013		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Full Analysis population

Descriptive statistics and estimate variability	Treatment group	crizotinib	chemotherapy
	Number of subject	172	171
	Primary endpoint		
	PFS (IRR) N. with events n(%)	100 (58.1)	137 (80.1)
	Median PFS months (95% CI)	10.9 (8.3, 13.9)	7.0 (6.8, 8.2)
	Stratified Hazard Ratio (95% CI)	0.45 (0.346, 0.596)	
	p-value (1-sided stratified Log-Rank Test)	<0.0001	
	Secondary endpoints		
	OS N. with events n(%)	44 (25.6)	46 (26.9)
	Median OS months (95% CI)	Not reached	Not reached
	Stratified Hazard Ratio (95% CI)	0.82 (0.536, 1.255)	
	p-value (1-sided stratified Log-Rank Test)	0.18	
	ORR (CR+PR) n(%)	128 (74.4)	77 (45.0)
	Risk ratio (%) (95% CI) (2-sided CMH chi-square test stratified)	1.66 (1.379, 2.007)	
	p-value (2-sided Pearson chi-square test)	<0.0001	
	TTR median weeks range	 6.1 (2.7-41.4)	 12.1 (5.1-36.7)
	Duration of Response median weeks (95% CI)	 49.0 (35.1, 60.0)	 22.9 (18.0, 25.1)
	DCR (CR+PR+ SD) n(%) (95% CI)	 135 (79) (72, 84)	 117 (68) (61, 75)
	p-value (2-sided Pearson chi-square test)	0.038	
	TTP n (%) Median months (95% CI)	 89 (51.7) 13.6 (8.5, 15.0)	 132 (77.2) 7.0 (6.8, 8.3)
	Hazard Ratio (95% CI)	0.44 (0.33, 0.58)	

	p-value (1-sided unstratified Log-Rank Test)	<0.0001	
	IC-TTP n (%) Median months (95% CI)	 25 (14.5) Not reached	 26 (15.2) 17.8 (13.9, ...)
	Hazard Ratio (95% CI)	0.59 (0.338, 1.048)	
	p-value (1-sided unstratified Log-Rank Test)	0.034	
	EC-TTP n (%) Median months (95% CI)	 71 (41.3) 15.2 (12.6, 21.9)	 119 (69.6) 7.2 (6.9, 8.5)
	Hazard Ratio (95% CI)	0.38 (0.286, 0.524)	
	p-value (1-sided unstratified Log-Rank Test)	<0.0001	

Analysis performed across trials (pooled analyses and meta-analysis)

Non-adenocarcinoma histology

Further to a CHMP request in the context of variation EMEA/H/C/002489/II/0004, a subgroup efficacy and safety analysis in patients with adenocarcinoma and non-adenocarcinoma histology has been submitted, including Study A8081014 (before cross-over) and Study A8081005.

A summary of efficacy results by histology groups in both studies are reported in the following table:

Table 20: Summary of efficacy results by treatment arm and histology group

	Adenocarcinoma			**Non-adenocarcinoma**		
	Study 1014		**Study 1005**	**Study 1014**		**Study 1005**
	crizotinib	**Chemo therapy[d]**	**crizotinib**	**crizotinib**	**Chemo therapy[d]**	**crizotinib**
PFS[a]						
N of patients	**161**	**161**	**856**	**11**	**10**	**45**
Number with event, n(%) • Objective PD • Death without PD	92 (57.1) 82 (50.9) 10 (6.2)	127 (78.9) 123 (76.4) 4 (2.5)	594 (69.4) 512 (59.8) 82 (9.6)	8 (72.7) 7 (63.6) 1 (9.1)	10 (100) 9 (90) 1 (10)	37 (82.2) 33 (73.3) 4 (8.9)
Probability of being event free • 6 months° (95% CI) • 12 months° (95% CI)	 71.4 (63.5, 77.9) 49.5 (40.9, 57.6)	 62.8 (54.5, 70.1) 17.3 (11.3, 24.4)	 62.3 (58.8, 65.6) N/A	 44.4 (13.6, 71.9) 22.2 (3.4, 51.3)	 30.0 (7.1, 57.8) 0.0	 43.4 (28.2, 57.5) N/A
KM estimate of time to event (months) Quartiles (95% CI)• • 50%	 **11.3** (8.3, 14.0)	 **7.1** (6.8, 8.3)	 **9.1** (7.7, 10.2)	 **5.6** (4.2, 11.1)	 **4.2** (2.6, 6.9)	 **5.6** (4.1, 8.3)
Hazard ratio (95% CI) p-value[#]	0.488 (0.371, 0.642) <0.0001			0.367 (0.123, 1.095) 0.0310		

ORR[b]						
Best overall response, n(%) • CR • PR • SD • PD • Early death • Indeterminate	 3 (1.9) 117 (72.7) 27 (16.8) 8 (5.0) 4 (2.5) 2 (1.2)	 2 (1.2) 69 (42.9) 60 (37.3) 20 (12.4) 4 (2.5) 6 (3.7)	 11 (1.3) 425 (52.9) 240 (28.1) 78 (9.1) 34 (4.0) 40 (4.7)	 0 8 (72.7) 2 (18.2) 0 0 1 (9.1)	 0 6 (60.0) 3 (30.0) 1 (10.0) 0 0	 0 20 (44.4) 11 (24.4) 10 (22.2) 2 (4.4) 2 (4.4)
Objective Response Rate (CR+PR), n(%)	120 (**74.5**)	71 (**44.1**)	463 (**54.2**)	8 (**72.7**)	6 (**60.0**)	20 (**44.4**)
SD duration (months) • 0 to <3 months • 3 to <6 months • 6 to <9 months • 9 to <12 months • ≥12 months	 11 (40.7) 4 (14.8) 4 (14.8) 1 (3.7) 7 (25.9)	 12 (20.0) 14 (23.3) 15 (25.0) 13 (21.7) 6 (10.0)	 61 (25.4) 73 (30.4) 31 (12.9) 14 (5.8) 61 (25.4)	 0 1 (50.0) 0 0 1 (50.0)	 0 1 (33.3) 0 2 (66.7) 0	 3 (27.3) 6 (54.5) 0 1 (9.1) 1 (9.1)
Treatment difference ORR (95% CI) p-value"	30.435 (20.2, 40.6) <0.0001			12.727 (-27.5, 52.9) 0.6594		
OS[c]						
Number of deaths, n(%)	39 (24.2)	40 (24.8)	468 (54.7)	5 (45.5)	6 (60.0)	34 (75.6)
Survival probability • 6 months° (95% CI) • 12 months° (95% CI) • 18 months° (95% CI)	 N/A 83.8 (76.7, 88.9) 69.8 (60.5, 77.4)	 N/A 81.3 (74.0, 86.7) 69.2 (59.6, 76.9)	 81.9 (79.2, 84.4) 67.2 (63.9, 70.3) N/A	 N/A 80.0 (40.9, 94.6) 57.1 (21.7, 81.5)	 N/A 40.0 (12.3, 67.0) 40.0 (12.3, 67.0)	 75.6 (60.2, 85.6) 52.9 (37.3, 66.2) N/A
KM estimate of time to event (months) Quartiles (95% CI) • 50%	 NR	 NR	 22.0 (19.9, 24.3)	 18.2 (16.1, NR)	 8.1 (5.4, NR)	 13.2 (9.0, 22.3)
Hazard ratio (95% CI) p-value[#]	0.943 (0.607, 1.466) 0.397			0.509 (0.151, 1.720) 0.134		

Table made by the Assessor. Source: Studies A8081014/A8081005 Report (Adenocarcinoma and Nonadenocarcinoma) Table 6, Table 7, Table 8.

[a] For Study 1014, data based on independent radiology review assessment using the FA population. For Study 1005, data based on investigator tumour assessment using the ALK+ by IUO safety analysis population.

[b] Best overall response data for Study 1014is based on IRR assessment using the FA population, and best overall response data for Study 1005 is based on the investigator tumour assessment using the ALK+ by IUO response evaluable population.

[c] For Study 1014, data from the FA population; for Study 1005, data from the ALK+ by IUO SA population.

[d] PFS and ORR: only includes data before cross-over to crizotinib; OS:includes event before and after cross-over.

° estimated from the Kaplan-Meier curve.

● based on the Brookmeyer and Crowley Method

CI= confidence interval; n= number of patients; NR= not reached.

[a] estimated from Kaplan-Meier curve. [b] Calculated using the normal approximation to the log transformed cumulative hazard rate. [c]

[#]1-sided p-value from the unstratified log-rank test.

" p-value is from a 2-sided Pearson chi-square test.

In study A8081005, information is available from 45 response-evaluable patients with previously treated non adenocarcinoma NSCLC (including 22 patients with SCC). Partial responses were observed in 20 of 45 patients with non-adenocarcinoma NSCLC for an ORR of 44%, and 9 of 22 patients with SCC NSCLC for an ORR of 41%, both of which were less than the ORR reported in Study A8081005 (54%) for all patients (see SmPC section 5.1).

Elderly population

Of the 171 patients treated with crizotinib in randomised Phase 3 Study A8081014, 22 (13%) were 65 years or older. Of 109 patients treated with crizotinib who crossed over from chemotherapy arm, 26

(24%) were 65 years or older. Of the 172 patients treated with crizotinib in randomised Phase 3 Study A8081007, 27 (16%) were 65 years or older. Of the 154 patients in Study A8081001, 22 (14%) were 65 years or older. Of the 1063 patients in Study A8081005, 173 (16%) were 65 years or older. The frequency of adverse reactions was generally similar for patients <65 years of age and patients ≥65 years of age with the exception of oedema and constipation, which were reported with greater frequency (≥15% difference) in Study A8081014 among patients treated with crizotinib ≥65 years of age. No patients in the crizotinib arm of randomised Phase 3 Studies A8081007 and A8081014, and single arm Study A8081005 were >85 years. There was one patient >85 years old out of 154 patients in single-arm Study A8081001 (see SmPC section 5.1).

Supportive studies

As supportive to the crizotinib efficacy in ALK-positive advanced NSCLC patients, updated OS results from study 1005 (phase 2, open-label, single arm study of crizotinib in ALK-positive advanced NSCLC patients who had been treated with at least 1 prior treatment) and study 1001 (open-label, single arm study of crizotinib in advanced malignancies, including a cohort with ALK-positive advanced NSCLC) have been submitted.

In particular, in this submission OS data have been updated (data cut-off date 30 November 2013) based on the 905 previously treated patients with ALK-positive (by the IUO) in the SA population for study 1005, and based on 154 patients in the ALK-positive advanced NSCLC cohort in the SA population for study 1001.

As of the data cut-off date, the median duration of treatment was 47.0 weeks (range 0.1 to 192 weeks) in Study 1005 and 56.9 weeks (range 0.7 to 267 weeks) in Study 1001.

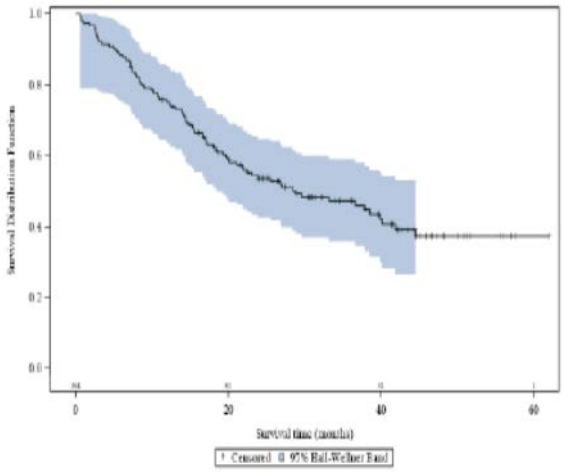
Table 21: OS in patients with ALK-positive NSCLC in studies 1005 and 1001 (SA population)

	Crizotinib 250 mg BID	
Overall Survival	**Study 1005 ALK-positive by IUO N=905**	**Study 1001 ALK-positive by Local Test N=154**
Number of deaths , n (%)	504 (55.7)	83 (53.9)
Number censored, n (%)	401 (44.3)	71 (46.1)
Reason for censorship		
Patient remains in follow-up[a]	338 (37.3)	24 (15.6)
Patient no longer being followed for survival	2 (<1.0)	47 (30.5)[b]
Withdrew consent for follow-up	46 (5.1)	--
Lost to follow-up	15 (1.7)	--
Survival probability at Month 6[c] (95% CI)[d]	81.6 (78.9, 84.0)	88.3 (82.1, 92.5)
Survival probability at Month 12[c] (95% CI)[d]	66.5 (63.3, 69.5)	75.2 (67.6, 81.3)
Kaplan-Meier estimates of time to event (Month)		
Quartiles (95% CI)[e]		
25%	8.5 (7.5, 9.7)	12.3 (8.4, 15.4)
50%	21.5 (19.3, 23.6)	28.9 (21.1, 40.1)
75%	NR (43.7, NR)	NR

Source: SCE Section 2.7.3.6.3, Study 1005, Table 14.2.6.1a; SCE Section 2.7.3.6.2, Study 1001, Table 13.4.3.1
Abbreviations: ALK=anaplastic lymphoma kinase; BID=twice daily; CI=confidence interval; IUO=investigational-use only; n/N=number of patients; NR=not reached.

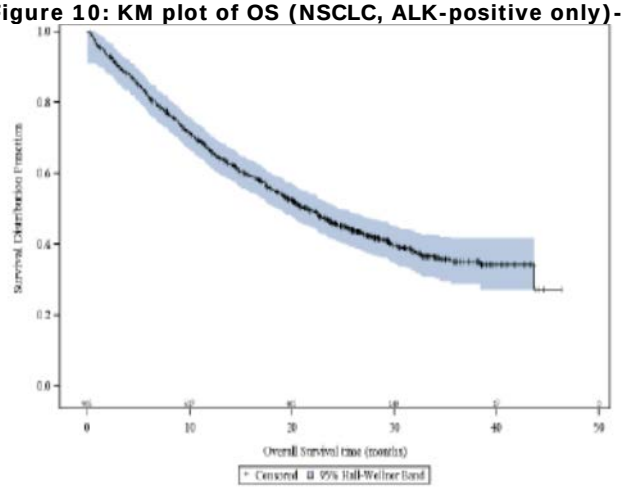
[a] In follow-up as of data cut-off. Patients in follow-up include patients still on treatment.
[b] Patients no longer being followed for survival may include patients who have completed the required 1year follow-up according to protocol.
[c] Estimated from the Kaplan-Meier curve.
[d] Calculated using the normal approximation to the log transformed cumulative hazard rate.
[e] Based on the Brookmeyer and Crowley method.

The median duration of follow-up was 28.2 months (95% CI: 27.4, 29.2) in Study 1005 and 39.4 months (95% CI: 32.2, 42.7) in Study 1001. The Kaplan-Meier plots for OS in Study 1001 and Study 1005 are presented below:



Source: Study 1001, SCE Section 2.7.3.6.2, Appendix 2, Figure 14.3
Abbreviations: ALK=anaplastic lymphoma kinase; NSCLC=non-small cell lung cancer.

Figure 10: KM plot of OS (NSCLC, ALK-positive only)- Study 1001 (SA population)



Source: Study 1005, SCE Section 2.7.3.6.3, Appendix 3, Figure 14.2.3.1a
Abbreviations: ALK=anaplastic lymphoma kinase, IUO=investigational use only

Figure 11: KM plot of OS (ALK-positive by IUO test) - Study 1005 (SA population)

A comprehensive view of the latest available OS results across the crizotinib development program, including studies 1014, 1007, 1005 and 1001, is shown in the Table below:.

Table 22: Overall Survival Summary in Studies 1014, 1007, 1005 and 1001 at the time of latest reporting

	Crizotinib 250 mg BID			
	Study 1014 (N=172)[a]	Study 1007 (N=173)[a]	Study 1005 (N=905)[a]	Study 1001 (N=154)[a]
Patient Population	**Previously untreated (ALK-positive NSCLC)**	**Previously treated (ALK-positive NSCLC)**	**Previously treated (ALK-positive NSCLC by IUO)**	**Previously untreated (N=22) Previously treated (N=132) (ALK-positive NSCLC)**
Duration of treatment, med (range)[b], weeks	47.4 (1.9-148.9)	31.0 (1.3-110.1)	47.0 (0.1-191.7)	56.9 (0.7-267.3)
Duration of follow-up, med (95% CI)[c] months	17.4 (15.7, 19.3)	12.2 (11.0, 13.4)	28.2 (27.4, 29.2)	39.4 (32.2, 42.7)
Number of deaths, n (%)	44 (25.6)	49 (28.3)	504 (55.7)	83 (53.9)
Number censored, n (%)	128 (74.4)	124 (71.7)	401 (44.3)	71 (46.1)
Patient remains in follow-up	119 (69.2)	118 (68.2)	338 (37.3)	24 (15.6)
Patient no longer being followed for survival	2 (1.2)	2 (1.2)	2 (<1.0)	47 (30.5)
Other[d]	7 (4.1)	4 (2.3)	61 (6.8)	0
Kaplan-Meier median OS (months) (95% CI)[e]	NR	20.3 (18.1, NR)	21.5 (19.3, 23.6)	28.9 (21.1, 40.1)
6-Month OS Probability[f], % (95% CI)[g]	NA	86.8 (80.4, 91.2)	81.6 (78.9, 84.0)	88.3 (82.1, 92.5)
12-Month OS Probability[f], % (95% CI)[g]	83.5 (76.7, 88.5)	69.5 (60.6, 76.8)	66.5 (63.3, 69.5)	75.2 (67.6, 81.3)
18-Month OS Probablility	68.6 (59.5, 76.1)	NA	NA	NA
Crizotinib vs Chemotherapy[h]				
Hazard ratio (95% CI)[i]	0.821 (0.536, 1.255)	1.021 (0.677, 1.540)	NA	NA
P-value[j]	0.1804	0.5394	NA	NA
Adjusted for crossover[k]				
Hazard ratio (95% CI)[i, l]	0.604 (0.265, 1.420)	0.831 (0.356, 1.347)	NA	NA
Hazard ratio (95% CI)[i, m]	0.674 (0.283, 1.483)	NA	NA	NA

Source: Study 1014 CSR Table 14.2.6.1.1, 14.2.6.5, 14.4.1.1.3, Study 1007 CSR Table 14.2.6.1.1, 14.2.6.5, Table 14.4.1.1.3.1, Table 14.2.6.1.1; SCE Appendix 3 [Study 1005] Table 14.2.6.5a, Table 14.4.1.1a, Table 14.2.6.1a; SCE Appendix 2 [Study 1001] Table 13.3.1.1b, Table 13.3.2.2b, Table 13.4.5.4, Table 13.4.3.1. Technical Report for Evaluating the Impact of Follow-up Therapy on Overall Survival in Study 1007 at the Time of Interim Overall Survival Analysis, Appendix 1: Output from Sensitivity Analyses for RPSFT (Module 5.3.5.1 [1007 Supplemental Submission]); Technical Report for Evaluating the Impact of Crossover on Overall Survival in Study A8081014 (Module 5.3.5.1).
Note: Time of latest reporting is the data cutoff date: 30 November 2013 for Studies 1014, 1005, and 1001 and 30 March 2012 for Study 1007.
Abbreviations: ALK+=anaplastic lymphoma kinase positive; BID=twice daily; CI=confidence interval; IUO=investigational use only; med=median; N/n=number of patients; NA=not applicable; NR=not reached; NSCLC=non-small cell lung cancer; OS=overall survival.
a. The Full Analysis set (all randomized patients) was used for all summaries for Studies 1014 and 1007, except for duration of treatment, where the Safety set was used. The Safety set was used for all summaries in Studies 1005 and 1001.
b. Based on descriptive statistics.
c. Based on the reverse Kaplan-Meier method with 95% CIs based on the Brookmeyer and Crowley Method.
d. Includes withdrawal of consent (Studies 1014, 1007, 1005) and lost to follow-up (Studies 1007 and 1005).
e. Based on the Brookmeyer and Crowley method.
f. Estimated from the Kaplan-Meier method.
g. Calculated using the normal approximation to the log transformed cumulative hazard function.
h. Study 1014: pemetrexed/cisplatin or pemetrexed/carboplatin; Study 1007: pemetrexed or docetaxel.
i. Based on the Cox Proportional hazards model stratified by ECOG PS, Race, and Brain Metastases in Study 1014 and stratified by ECOG PS, Brain Metastases, and Prior EGFR TKI treatment in Study 1007.
j. 1-sided p-value from the log-rank test stratified by ECOG PS, Race, and Brain Metastases in Study 1014 and stratified by ECOG PS, Brain Metastases, and Prior EGFR TKI treatment in Study 1007.
k. Using the Rank Preserving Structural Failure Time model.
l. Based on the Wilcoxon test used to derive the parameters to correct for crossover in Study 1014. Based on both the log-rank and Wilcoxon tests to derive the parameters to correct for crossover in Study 1007, where the 2 test statistics are combined into a single statistic through the variance-covariance matrix.
m. Based on the log-rank test used to derive parameters to correct for crossover in Study 1014.

2.4.3. Discussion on clinical efficacy

Design and conduct of studies

The pivotal trial for this application for an extension of indication is a phase III study (A8081014) designed as an open-label, randomized, 2-arm, international, multicentre trial to assess the efficacy and safety of crizotinib alone versus first-line chemotherapy, i.e., pemetrexed/cisplatin or pemetrexed/carboplatin in patients with advanced non-squamous NSCLC whose tumours harbour ALK fusions.

The primary objective was to demonstrate that crizotinib is superior to first-line chemotherapy, pemetrexed/cisplatin or pemetrexed/carboplatin, in prolonging PFS. Secondary objectives notably included OS, ORR, DCR, and QoL. A total of 343 patients were randomized in the study.

Overall, the eligibility criteria are acceptable. The enrolment was restricted to patients with non-squamous histology, which is acceptable taking into account the expected incidence of ALK mutations

according to histology, and furthermore it allowed selecting pemetrexed-based chemotherapy as the comparator. The PI has been updated to reflect the inclusion and exclusion criteria regarding the squamous cell carcinoma histology (see sections 4.4 and 5.1 of the SmPC).

The patient population was adequately selected on the basis of the diagnostic test Vysis ALK Break Apart FISH.

ECOG PS 2 patients were poorly represented, while patients with brain metastases (asymptomatic and stable) were adequately represented, which is important taking into account the frequency expected in the target population. Prior (neo-)adjuvant chemotherapy was allowed, provided that DFS was > 12 months. Overall, about 7% of the patients had received prior systemic treatment, balanced in the two arms.

The combination of pemetrexed-based with cisplatin or carboplatin is deemed an adequate control arm in the target population, also considering the results observed in the 1007 trial, in which pemetrexed performed better than docetaxel. Pemetrexed is currently approved as monotherapy for the maintenance treatment in patients whose disease has not progressed immediately following platinum-pemetrexed combination (since September 2011 in EU, see EPAR Alimta), and therefore the inclusion of this option in the control arm would have strengthened the adequacy of the control arm. The MAH argued that the ORR reported with maintenance pemetrexed after 4 cycles induction chemotherapy in studies JMEN and PARAMOUNT were low (6.8% and 3%, respectively), however it is not known whether allowing maintenance pemetrexed would have impacted the results, due to a delay in the occurrence of progression in the control arm. It is acknowledged that maintenance treatment with pemetrexed as monotherapy was not considered a standard approach when the study was designed.

In principle, the selection of PFS as the primary endpoint is considered acceptable in this early setting. Since all patients in the control arm were allowed to receive crizotinib at progression, OS results are expected to be confounded. The choice to allow systematic one-way cross-over is justified based on ethical reasons. An additional possible source of bias is the prospect for both investigators' and patients' in the control arm to have access to a targeted treatment. This is much more relevant taking into account that this was an open-label study with PFS as the primary endpoint. To control for the risks of bias, the primary PFS analysis was based on Independent Radiology Review (IRR).

The evaluation of global quality of life, and more particularly the time to deterioration in symptoms (pain in chest, dyspnoea, or cough), based on validated and widely used PRO instruments, was among the secondary endpoints. The statistical methods for the analysis of Time to deterioration (TTD) in patient-reported pain in chest, dyspnoea, and cough are considered adequate, including the use of the Hochberg procedure to adjust for multiple comparisons. Completion of EORTC QLQ-C30 and QLQ-LC13 was requested at days 1, 7 and 15 of cycle 1, and day 1 of the subsequent cycles, and at the end of treatment.

Efficacy data and additional analyses

Study A8081014 was a worldwide study. Overall, a sufficient number of EU patients has been enrolled. Baseline demographic and disease characteristics were balanced between crizotinib and chemotherapy arm.

A clinically meaningful benefit in terms of PFS by IRR has been observed, with a 3.9 months difference in median PFS and HR of 0.454 (95% CI 0.346, 0.596). The curves show an early separation (at the time of the first assessment) which augments over time. At month 12, the probability of being event free was 47.8 (95% CI 39.5, 55.7) and 16.1 (95% CI 10.5, 22.8) for crizotinib and chemotherapy, respectively.

Submitted OS data are still too immature to draw any conclusion. Furthermore, as mentioned above, the systematic one-way cross-over is expected to confound the interpretation of OS results. At the data cut-off of the present analysis (30 November 2013), very few patients who had progressed in the crizotinib arm had crossed to another systemic treatment post-progression, mainly due to the possibility to continue crizotinib beyond progression.

When using PFS as primary endpoint for confirmatory studies, there is a risk that the tumour's drug resistance profile is affected by therapy which might be of relevance for the activity of next-line therapies. Based on study design, no information on PFS of treatments received post-progression (PFS2), including crizotinib, can be provided. Therefore, the potential impact of first line crizotinib on next line therapies cannot be evaluated. In addition, no safety and efficacy data are available on re-treatment with crizotinib of patients who received crizotinib in previous lines of therapy. However, for patients progressing after first-line crizotinib there are at present therapeutic options which were not available at the time of study conduction.

In addition, the benefit in terms of PFS observed in patients who crossed to crizotinib after progression in the control arm is consistent to what has been observed in Study 1007, which is re-assuring.

ORR was much higher in the crizotinib arm, responses were in general more profound and durable (more than twice longer than in the control arm). Time to tumour response was shorter in the crizotinib arm. Interestingly, in the chemotherapy arm responses were observed up to 24 weeks, with 26% of the responses observed from week 18 onwards. This observation raises questions on the adequacy of the control arm and the choice to have a maximum of 6 cycles of chemotherapy without allowing maintenance with pemetrexed as monotherapy. However, in this regard, it should be noted that in the PARAMOUNT study, on which the approval of pemetrexed as monotherapy for the maintenance treatment immediately following platinum-pemetrexed combination was based, only a limited number of objective responses (4.1%) were reported. In addition, although cross-study comparisons have limitations, patients with ALK-positive advanced NSCLC randomized to crizotinib in Study 1014 had longer median PFS (10.9 months) than patients with unselected advanced NSCLC with a complete response, partial response, or stable disease during induction treatment in either JMEN study (7.7 months, as measured from the start of induction treatment) or PARAMOUNT study (6.9 months, as measured from the start of induction treatment).

Treatment with crizotinib was associated with a statistically significant longer Time to Deterioration in Pain (in Chest), Dyspnoea, or Cough, with a median TTD of 2.1 vs 0.5 months, with an HR: 0.591. A sensitivity analysis excluding Cycle 1 day 7 and day 15 from the TTD assessment showed no impact on the overall results, with a median TTD (pain in chest, dyspnea, or cough) of 4.3 months (95% CI: 2.8, 7.6) in the crizotinib arm and 1.7 months (95% CI: 1.4, 2.1) in the chemotherapy arm. Nevertheless, due to the study design (open-label, collection of questionnaires at day 7 and 15 of cycle 1 despite the differences in the treatment characteristics, and the trend to late responses in the control arm) these results might overestimate the benefit, especially in the long-run.

Descriptive statistics by treatment arm were reported for the change from baseline for each of the QLQ-C30 and QLQ-LC13 multiple-item and single-item scale scores, and EQ-5D VAS scores. Overall a benefit in favour of crizotinib has been observed for all domains and all the symptoms' scores analysed, with the exception of diarrhoea and peripheral neuropathy for which a statistically significant deterioration was observed in the crizotinib arm compared with the chemotherapy arm.

A number of sensitivity and subgroup analyses have been provided that overall support the results of the primary analysis of PFS and do not raise any particular concern for any of the subgroups analysed.

The overall disagreement rate between IRR and Investigator assessment was not negligible. Nevertheless, overall there were no major differences in the PFS results by IRR or by investigators.

The analysis of TTP based on the presence/absence of brain metastases at baseline does not seem to show any meaningful differences, thus supporting a potential benefit of crizotinib in both subgroups. This finding is consistent with PFS subgroup analyses.

A number of subgroup and sensitivity analyses, pre-specified in the protocol, were conducted, including the use of the Rank Preserving Structural Failure Time Model (RPSFTM) to adjust OS analyses for cross-over.

As requested by the CHMP, the MAH also performed additional OS sensitivity analyses (i.e. IPE and two-stage methods) to explore different methods with different assumptions.

In all analysis set, the results of two-stage methods are consistent with those obtained by RPSFTM. In particular, the results show a significant improvement in OS in favour of crizotinib with HRs ranging from 0.610 to 0.649 and 1-sided p-values ranging from 0.0123 to 0.0242 for the Log-normal model without or with covariates and methods of missing data imputation. Results from the IPE method suggested an improved OS with crizotinib compared to chemotherapy (i.e. HRs ranging from 0.571 to 0.674). The observed improvement was statistically significant for all parametric models explored with the IPE method (1-sided p-values ranging from 0.0130 to 0.0251), with the exception of the Exponential model that was to be considered to best fit to the data (1-sided p-value = 0.0408). In any case, results from the exponential model were in line with those coming from the remaining sensitivity analyses to correct for crossover.

Considering the various analyses presented, the treatment effect estimates of crizotinib on OS in presence of cross-over remain overall consistent, reassuring on the robustness of the primary analysis results.

Further to the CHMP request, the MAH provided available data in patients with non-adenocarcinoma histology. The subgroups in studies 1007 and 1014 were too small to draw reliable conclusions. Of note, no patients with SCC histology were randomized in the crizotinib arm in Study 1007 and no patients with SCC were enrolled in Study 1014 due to pemetrexed-based regimen being used as a comparator.

2.4.4. Conclusions on the clinical efficacy

A clinically meaningful benefit in terms of PFS has been observed in favour of crizotinib, which is supported by consistent results from a number of pre-specified sensitivity analyses. Subgroup analyses did not raise particular concern for any of the subgroups analysed. The primary analysis of OS is supported by different sensitivity analyses adjusted for cross-over conducted by the MAH. Results in terms of ORR, Duration of Response, Time to Progression and Time to Tumour Response support the high activity of crizotinib in the patient population enrolled in the pivotal study, which adequately reflects the target population expected in the real-life setting. PROs showed a benefit in favour of crizotinib for most domains and symptoms, although the results may overestimate the true benefit due to the study design. Although the control arm could have included the option for maintenance treatment with pemetrexed, the magnitude of benefit observed in terms of PFS and other secondary endpoints is considered sufficient to provide reassurance on the benefit of crizotinib in this setting.

2.5. Clinical safety

The safety profile of crizotinib in ALK positive pre-treated advanced NSCLC patients is mainly characterised by ADRs in the SOC *eye disorders* (vision disorder), *gastrointestinal disorders* (vomiting, diarrhoea, nausea, constipation) , *general disorders* (oedema, fatigue), *hepatobiliary disorders* (elevated transaminases) and *nervous system disorders* (dizziness, neuropathy).

For the Xalkori extended indication in the treatment of previously untreated ALK-positive advanced NSCLC patients, data from the pivotal randomised phase 3 study 1014 and cumulative supportive safety data from 6 additional studies in ALK+ advanced NSCLC and other advanced cancers patients, have been submitted.

Overall, safety data of 2044 patients treated with crizotinib and of 340 patients who received chemotherapy have been provided.

Patient exposure

Details of the 7 clinical studies contributing to safety are reported in the table below:

Table 23: Summary of clinical studies included in the safety review

Study title or dataset ***Status***	**Study design**	**Treatment**	**Safety data provided**
Studies in ALK-positive NSCLC			
A8081014 Phase 3, Randomized, Open-Label Study of the Efficacy and Safety of Crizotinib vs Pemetrexed/Cisplatin or Pemetrexed/Carboplatin in Previously Untreated Patients with Non-Squamous Carcinoma of the Lung Harboring a Translocation or Inversion Event Involving the ALK Gene Locus *Ongoing*	Open-label, multicenter, randomized, 2 arms	*Crizotinib:* 250 mg BID *Chemotherapy:* pemetrexed, 500 mg/m^2 carboplatin or cisplatin 21-day cycles	All safety data
A8081007 Phase 3, Randomized, Open-Label Study of the Efficacy and Safety of crizotinib vs Standard of Care Chemotherapy (Pemetrexed or Docetaxel) in Patients with Advanced NSCLC Harboring a Translocation or Inversion Event Involving the ALK gene locus *Ongoing*	Open-label, multicenter, randomized, 2 arms	*Crizotinib:* 250 mg BID *Chemotherapy:* Pemetrexed 500 mg/m^2 Day 1 of 21-day cycles or Docetaxel 75 mg/m^2 Day 1 of 21-day cycles	Grade 3/4 AEs, Grade 5 AEs, SAEs, permanent discontinuation
A8081005 Phase 2, Open-Label, Single-Arm Study of the Efficacy and Safety of crizotinib in Patients with Advanced NSCLC harboring a Translocation or Inversion Involving the *ALK* gene locus *Ongoing*	Open-label, multicenter, single arm	*Crizotinib:*250 mg BID 21-day cycles	Grade 3/4 AEs, Grade 5 AEs, SAEs, permanent discontinuation
A8081001 Phase 1 Safety, Pharmacokinetic and Pharmacodynamic Study of crizotinib administered orally to Patients with Advanced Cancer *Ongoing*	Open-label, multicenter, single arm	*Crizotinib:* ALK-positive NSCLC RP2D cohort 250 mg BID 28-day cycles	Grade 3/4 AEs, Grade 5 AEs, SAEs, permanent discontinuation
		Crizotinib: Other RP2D cohorts 250 mg BID 28-day cycles (21-day cycles in2 groups)	SAEs, permanent discontinuation
A8081029	Open-label,	*Crizotinib:* 250 mg BID	SAEs

Phase 3, Randomized, Open-Label Study of the Efficacy and Safety of Crizotinib vs Pemetrexed/Cisplatin or Pemetrexed/Carboplatin in Previously Untreated East Asian Patients with Non-Squamous Carcinoma of the Lung Harboring a Translocation or Inversion Event Involving the ALK Gene Locus *Ongoing*	multicenter, randomized, 2 arms	*Chemotherapy:* pemetrexed, 500 mg/m^2 carboplatin or cisplatin 21-day cycles	
Studies in advanced cancer			
A8081013 Phase 1B Open-Label Study of the Safety and Clinical Activity of Crizotinib in Tumours with Genetic Events Involving the ALK Gene Locus *Ongoing*	Open-label, multicenter, single arm	*Crizotinib:*250 mg BID 21-day cycles	Grade 3/4 AEs, Grade 5 AEs, SAEs, permanent discontinuation
A8081012 Phase 1 Study to evaluate the Effect of Hepatic Impairment on the Pharmacokinetics and Safety of Crizotinib in Advanced Cancer Patients *Ongoing*	Open-label, multicenter, single arm Hepatic Impairment: Normal Mild Moderate Severe	*Crizotinib* 250 mg BID, 200 mg BID, or 250 mg QD 28-day cycles	SAEs

The number of patients exposed to crizotinib by clinical study is reported in the Table below:

Table 24: Patient exposure (cut-off date of 30 November 2013)

	Patients exposed to the proposed dose range	Patients with long term* safety data	
		≥6 months	≥12 months
Controlled studies			
A8081014[a]	171 + 109°	122	76
A8081007[a]	172	130	83
A8081029[a]	81 + 15°		
Single arm studies			
A8081005[a]	1063	718	475
A8081001[b]	358	123	86
A8081013	44		
A8081012	31		

[a] ALK+ NSCLC patients; [b] Including 154 ALK+ NSCLC patients; °crossed over from chemotherapy arm; * In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

In addition, 11,659 patients were cumulatively exposed to crizotinib from post-marketing experience (PSUR#5: 26 February 2013-25 August 2014).

In the pivotal phase III study, the median duration of treatment was 47.4 weeks in the crizotinib arm compared with 18.0 weeks in the chemotherapy group, with a similar median overall relative dose intensity per cycle across the 4 drugs (crizotinib: 98.9%; pemetrexed: 95.8%; cisplatin: 96.3%; carboplatin: 94.4%). The median number of cycles started was 16 (1-50) in the crizotinib arm and 6 (1-6) in the chemotherapy group, reflecting the maximum number of cycles permitted. In the crizotinib arm, 84 (49.1%) patients required a dosing interruption, and in 66 (38.6%) patients at least 1 dose reduction was needed. These rates were lower for the chemotherapy treatments (at least 1 dose interruption: 0.6%-5.5%; at least 1 dose reduction: 9.5%-9.9%). However, 36 (21.3%) patients had at least 1 cycle delay of the chemotherapy regimen.

Among the 109 patients who crossed over from the chemotherapy group in study 1014, the median duration of crizotinib treatment based on active dosing days was 22.6 weeks, with a median number of 8 cycles started. Around 57% of crossing over patients were still on-treatment at the time of data cut-

off. A dose interruption and a dose reduction was requested in 38 (34.9%) and 36 (33%) patients, respectively.

Baseline demographic and disease characteristics in Study 1014 are shown in the tables below:

Table 25: Demographic Characteristics by Study Treatment in Study 1014-SA Population

Variable	Crizotinib (N=171)	Pemetrexed + Cisplatin (N=91)	Pemetrexed + Carboplatin (N=78)	Total (N=340)
Sex, n (%)				
Male	67 (39.2)	30 (33.0)	33 (42.3)	130 (38.2)
Female	104 (60.8)	61 (67.0)	45 (57.7)	210 (61.8)
Age, years				
Mean (SD)	50.9 (11.9)	50.8 (11.6)	55.4 (14.1)	51.9 (12.5)
Median	52.0	53.0	56.0	53.0
Range	22-76	19-75	19-78	19-78
Age category, n (%)				
<45 years	56 (32.7)	27 (29.7)	16 (20.5)	99 (29.1)
45-<55 years	52 (30.4)	26 (28.6)	20 (25.6)	98 (28.8)
55-<65 years	41 (24.0)	28 (30.8)	21 (26.9)	90 (26.5)
≥65 years	22 (12.9)	10 (11.0)	21 (26.9)	53 (15.6)
Race, n (%)				
White	90 (52.6)	53 (58.2)	32 (41.0)	175 (51.5)
Black	0	3 (3.3)	0	3 (0.9)
Asian	77 (45.0)	35 (38.5)	45 (57.7)	157 (46.2)
Japanese	14 (8.2)	7 (7.7)	11 (14.1)	32 (9.4)
Korean	30 (17.5)	25 (27.5)	1 (1.3)	56 (16.5)
Chinese	27 (15.8)	2 (2.2)	30 (38.5)	59 (17.4)
Other Asian	6 (3.5)	1 (1.1)	3 (3.8)	10 (2.9)
Other	4 (2.3)	0	1 (1.3)	5 (1.5)
Smoking classification, n (%)				
Never smoked	106 (62.0)	63 (69.2)	47 (60.3)	216 (63.5)
Ex-smoker	56 (32.7)	27 (29.7)	27 (34.6)	110 (32.4)
Smoker	9 (5.3)	1 (1.1)	4 (5.1)	14 (4.1)

Source: Study 1014 CSR Tables 14.1.2.1.1.2 and 14.1.2.1.2.2.
Abbreviations: n/N=number of patients; SD=standard deviation.

Table 26: Baseline Disease Characteristics by Study Treatment in Study 1014-SA Population

Variable	Crizotinib N=171	Chemotherapy N=169	Pemetrexed + Cisplatin N=91	Pemetrexed + Carboplatin N=78
Disease Stage				
Locally advanced	4 (2.3)	3 (1.8)	2 (2.2)	1 (1.3)
Metastatic	167 (97.7)	166 (98.2)	89 (97.8)	77 (98.7)
Histological Classification				
Adenocarcinoma	158 (92.4)	157 (92.9)	87 (95.6)	70 (89.7)
Large cell carcinoma	3 (1.8)	8 (4.7)	2 (2.2)	6 (7.7)
Adenosquamous carcinoma	5 (2.9)	1 (0.6)	0	1 (1.3)
Other	5 (2.9)	3 (1.8)	2 (2.2)	1 (1.3)
ECOG PS at baseline, n (%)[a]				
0	57 (33.3)	46 (27.2)	29 (31.9)	17 (21.8)
1	105 (61.4)	117 (69.2)	61 (67.0)	56 (71.8)
2	9 (5.3)	6 (3.6)	1 (1.1)	5 (6.4)

Source: 1014 CSR Tables 14.1.2.2.2.2 and 14.1.2.4.2.
Abbreviations: ECOG PS=Eastern Cooperative Oncology Group performance status; N=number of patients.
a. Baseline was using the Cycle 1 Day 1 value, unless it was missing then baseline used the Screening value.

Patients who crossed over from chemotherapy to receive crizotinib were generally comparable with those in the 2 randomized treatment arms, with the exception of a higher percentage of Asian (56.0%) versus White (42.2%).

Adverse events

All AEs were coded using MedDRA Version 16.1 and summarized by MedDRA System Organ Class and preferred term. Severity grading for AEs was consistent with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; Version 4.0 for Studies 1014, 1007, 1005, 1013, 1029, and 1012, and Version 3.0 for Study 1001).

In order to avoid underestimation of medical conditions, certain PTs were analysed in aggregate using clustered terms.

A summary of all-causality and treatment-related AEs registered by treatment arm in Study 1014 is shown in below tables:

Table 27: Summary of Treatment-Emergent AEs in Study 1014 by treatment arm (All-Causality and Treatment-Related) - SA Population

Number of patients, n (%)[b]	Crizotinib (N=171)		Chemotherapy (N=169)[a]	
	All Causality n (%)	Treatment Related n (%)	All Causality n (%)	Treatment Related n (%)
With AEs	170 (99.4)	168 (98.2)	168 (99.4)	157 (92.9)
With SAEs[c]	58 (33.9)	18 (10.5)	47 (27.8)	15 (8.9)
With Grade 3 or 4 AEs	97 (56.7)	60 (35.1)	87 (51.5)	66 (39.1)
With Grade 5 AEs	20 (11.7)	0	4 (2.4)	0
With AEs associated with:				
Permanent discontinuation[d]	21 (12.3)	8 (4.7)	24 (14.2)	14 (8.3)
Dose reduction	11 (6.4)	9 (5.3)	14 (8.3)	14 (8.3)
Temporary discontinuation	70 (40.9)	59 (34.5)	58 (34.3)	51 (30.2)

Source: Study 1014 CSR Tables 14.3.1.2.1.1 and 14.3.1.3.1.1.
Abbreviations: AE=adverse event; n/N=number of patients; SAE=serious adverse event.
a. Only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.
b. Patients are counted only once per treatment in each row.
c. According to the investigator assessment.
d. AEs associated with permanent discontinuation are based on the Adverse Event case report form page; the AE may not be the patient's primary reason for discontinuation, as documented on the End of Treatment case report form and summarized in Study 1014 CSR Table 14.1.1.3.2.

The All-Causality AEs reported with an incidence of ≥10% of patients in either treatment arm and ≥5% absolute difference between groups are listed in the table below:

Table 28: All-Causality AEs by treatment arm in ≥10% of patients and with a ≥5% absolute difference between treatment arms (All Cycles) in Study 1014- SA population

MedDRA Preferred Term or CLUSTERED TERM	Crizotinib (N=171) n (%)	Chemotherapy (N=169)[a] n (%)
VISION DISORDER	122 (71.3)	16 (9.5)
Diarrhoea	105 (61.4)	22 (13.0)
EDEMA	83 (48.5)	21 (12.4)
Vomiting	78 (45.6)	60 (35.5)
Constipation	74 (43.3)	51 (30.2)
ELEVATED TRANSAMINASES	61 (35.7)	22 (13.0)
UPPER RESPIRATORY INFECTION	55 (32.2)	21 (12.4)
ABDOMINAL PAIN	45 (26.3)	20 (11.8)
Dysgeusia	45 (26.3)	9 (5.3)
Headache	37 (21.6)	25 (14.8)
Pyrexia	32 (18.7)	18 (10.7)
DIZZINESS	31 (18.1)	17 (10.1)
Pain in extremity	27 (15.8)	12 (7.1)
BRADYCARDIA	23 (13.5)	1 (0.6)
Dyspepsia	23 (13.5)	4 (2.4)
Fatigue	49 (28.7)	65 (38.5)
NEUTROPENIA	36 (21.1)	51 (30.2)
STOMATITIS	24 (14.0)	34 (20.1)
Asthenia	22 (12.9)	41 (24.3)
ANEMIA	15 (8.8)	54 (32.0)
LEUKOPENIA	12 (7.0)	26 (15.4)
THROMBOCYTOPENIA	2 (1.2)	31 (18.3)

Source: Study 1014 CSR Table 14.3.1.10.1.1.1.
MedDRA version 16.1 coding dictionary applied.
Unshaded terms occurred at a higher frequency in the crizotinib arm than in the chemotherapy arm; shaded terms occurred at a higher frequency in the chemotherapy arm than in the crizotinib arm.
Abbreviations: N/n=number of patients; MedDRA=Medical Dictionary for Regulatory Activities
a. Only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.

Grade 3/4 all-causality AEs were reported in 97 (56.7%) patients in the crizotinib arm and 87 (51.5%) patients in the chemotherapy group. Those reported in 2% of patients in either treatment arm with at least a 2-fold difference between arms are listed in the table below:

Table 29: Grade 3/4 All-Causality AEs by treatment arm in ≥2% of patients and with at least a 2-fold difference between treatment arms (All Cycles) in Study 1014-SA Population

MedDRA Preferred Term or CLUSTERED TERM	Crizotinib (N=171) n (%)	Chemotherapy (N=169)[a] n (%)
ELEVATED TRANSAMINASES	24 (14.0)	4 (2.4)
Decreased appetite	4 (2.3)	1 (0.6)
Diarrhoea	4 (2.3)	1 (0.6)
Electrocardiogram QT prolonged	4 (2.3)	0
LEUKOPENIA	3 (1.8)	9 (5.3)
Hyponatremia	1 (0.6)	4 (2.4)
ANEMIA	0	15 (8.9)
THROMBOCYTOPENIA	0	11 (6.5)

Source: Study 1014 CSR Table 14.3.1.2.11.1.2.
Unshaded terms occurred at a higher frequency in the crizotinib arm than in the chemotherapy arm; shaded terms occurred at a higher frequency in the chemotherapy arm than in the crizotinib arm.
MedDRA version 16.1 coding dictionary applied.
Abbreviations: n/N=number of patients; MedDRA=Medical Dictionary for Regulatory Activities.
a. Only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.

A total of 168 (98.2%) patients in the crizotinib arm and 157 (92.9%) patients in the chemotherapy group had treatment-related AEs (TRAEs). A summary of the most common (≥10% of patients) TRAEs by treatment arm is reported below:

Table 30: Treatment- Related Adverse Events by Treatment Arm in ≥10% of patients (All Cycles) in Study 1014- SA population

MedDRA Preferred Term or CLUSTERED TERM	Crizotinib (N=171) n (%)	Chemotherapy (N=169)[a] n (%)
VISION DISORDER	120 (70.2)	7 (4.1)
Diarrhoea	98 (57.3)	15 (8.9)
Nausea	86 (50.3)	94 (55.6)
Vomiting	68 (39.8)	53 (31.4)
ELEVATED TRANSAMINASES	59 (34.5)	20 (11.8)
Constipation	55 (32.2)	34 (20.1)
EDEMA	54 (31.6)	11 (6.5)
Dysgeusia	41 (24.0)	8 (4.7)
Fatigue	41 (24.0)	55 (32.5)
Decreased appetite	38 (22.2)	51 (30.2)
NEUTROPENIA	36 (21.1)	50 (29.6)
ABDOMINAL PAIN	33 (19.3)	11 (6.5)
DIZZINESS	23 (13.5)	7 (4.1)
BRADYCARDIA	20 (11.7)	0
NEUROPATHY	20 (11.7)	29 (17.2)
STOMATITIS	17 (9.9)	27 (16.0)
Rash	16 (9.4)	18 (10.7)
Asthenia	14 (8.2)	34 (20.1)
LEUKOPENIA	11 (6.4)	26 (15.4)
ANEMIA	4 (2.3)	46 (27.2)
THROMBOCYTOPENIA	1 (0.6)	30 (17.8)

Source: Study 1014 CSR Table 14.3.1.3.11.1.2.
MedDRA version 16.1 coding dictionary applied.
Abbreviations: N/n=number of patients; MedDRA=Medical Dictionary for Regulatory Activities.
a. Only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.

The Grade 3/4 TRAEs reported in ≥2% of patients are listed in the following table:

Table 31: Grade 3/4 Treatment-Related AEs in ≥2% of patients by MedDRA preferred or clustered terms (All Cycles) in Study 1014- SA Population

Adverse Events MedDRA Preferred Term or CLUSTERED TERM	Crizotinib N=171 n (%)	Chemotherapy N=169[a] n (%)
ELEVATED TRANSAMINASES	23 (13.5)	4 (2.4)
NEUTROPENIA	18 (10.5)	26 (15.4)
Fatigue	4 (2.3)	1 (0.6)
Vomiting	3 (1.8)	5 (3.0)
LEUKOPENIA	3 (1.8)	9 (5.3)
PULMONARY EMBOLISM	2 (1.2)	4 (2.4)
ANEMIA	0	14 (8.3)
THROMBOCYTOPENIA	0	11 (6.5)

Source: Study 1014 CSR Table 14.3.1.3.11.1.2.
Table ordered by descending frequency of AEs occurring in total numbers of patients in crizotinib column.
MedDRA version 16.1 coding dictionary was applied.
Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; n/N=number of patients.
a. Only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.

Among the 109 patients in the chemotherapy arm who crossed over to receive crizotinib, the most common all-causality AEs were vision disorder (57.8%), nausea (47.7%), diarrhoea (46.8%), edema (39.4%), Vomiting (35.8%), and elevated transaminases (34.9%). The treatment-related AEs commonly reported were vision disorder (52.3%), diarrhoea (42.2%), nausea (42.2%), vomiting (32.1%) and elevated transaminases (32.1%). Forty-three out of the 109 patients (39.5%) reported Grade 3/4 all-causality AEs that were considered treatment-related in 36 (33%) of them, mainly in terms of elevated transaminases (12.8%) and neutropenia (11%).

Adverse events of Special Interest in Study 1014
AEs of special interest, all-causality and treatment-related, were summarized overall and also followed a 3-tier approach, on which basis they were classified into 1 of 3 tiers:

- Tier-1: pre-specified events or clusters of events of clinical importance, described in a list in the product's Safety Review Plan maintained by the Sponsor.
- Tier-2: not Tier-1 but "common" events, reported by at least 10% of patients for all grades in any treatment arm and by at least 5% of patients for Grade 3, 4, or 5 combined.
- Tier-3: events that were neither Tier-1 nor Tier-2.

Tier 1 all-causality AEs of special interest that occurred statistically significantly (2-sided p-value <0.05) more frequently in the crizotinib arm compared with the chemotherapy arm (before cross-over) were constipation, diarrhea, elevated transaminases and hepatotoxicity, and bradycardia. In the chemotherapy arm, the Tier 1 all-causality AE of special interest occurred more frequently compared with the crizotinib arm was leukopenia. These comparisons were not adjusted for multiplicity or the longer duration of study treatment in the crizotinib arm.

To account for this difference between arms, exposure adjusted incidence rates (per 1,000 person-years) were calculated. Person-years of exposure was calculated as the sum of individual patient-years at risk, which is the sum of time to onset for patients with the event, time to 28 days after last dose for patients alive without the event, or time to death for patients who died within 28 days after the last dose without the event, divided by 365.25. Incidence rates were calculated as the total number of patients with events relative to person-years exposure.

Results of this exposure-adjusted analysis are summarized in the table below.

Table 32: Summary of Person-Year Exposure and Exposure-Adjusted Incidence Rates for Treatment-Emergent Adverse Events for Individual and Clustered MedDRA Preferred Terms of Special Interest (All-Causality) in Study 1014-SA Population

MedDRA Preferred Term or Cluster	Crizotinib (N=171)			Chemotherapy (N=169)[a]			Difference (crizotinib – chemotherapy)			
	n	Person-year	Incidence rate per 1000 person-years	n	Person-year	Incidence rate per 1000 person-years	Incidence rate difference	Lower limit 95% CI	Upper limit 95% CI	2-sided p-value
BRADYCARDIA	23	157.6	145.9	1	54.0	18.5	127.4	57.57	197.24	0.0003
Constipation	74	114.4	646.7	46	41.5	1108.1	-461.4	-813.83	-108.87	0.0103
Diarrhoea	105	76.8	1367.4	21	48.9	429.4	938.0	618.43	1257.62	<0.0001
DIZZINESS	31	151.4	204.8	15	50.5	297.1	-92.3	-259.09	74.41	0.2778
Dysgeusia	45	134.8	333.8	9	51.7	174.1	159.7	9.94	309.55	0.0366
DYSPNOEA	29	166.7	173.9	24	48.8	491.4	-317.4	-523.96	-110.91	0.0026
EDEMA	83	111.5	744.5	19	51.0	372.8	371.8	139.91	603.58	0.0017
Electrocardiogram QT prolonged	10	171.6	58.3	3	53.7	55.9	2.4	-70.49	75.22	0.9493
ELEVATED TRANSAMINASES	61	133.9	455.4	21	47.8	439.1	16.4	-203.45	236.21	0.8839
HEPATOTOXICITY	2	182.6	11.0	0	54.2	0.0	11.0	-4.23	26.14	0.1573
Hypokalaemia	6	177.9	33.7	8	53.0	150.9	-117.2	-225.20	-9.18	0.0335
INTERSTITIAL LUNG DISEASE	2	182.6	11.0	0	54.2	0.0	11.0	-4.23	26.14	0.1573
LEUKOPENIA	12	171.8	69.8	26	47.8	544.2	-474.4	-687.22	-261.48	<0.0001
Nausea	95	87.3	1088.8	97	24.8	3917.0	-2828.2	-3637.84	-2018.51	<0.0001
NEUROPATHY	35	153.6	227.9	24	50.1	479.3	-251.4	-457.53	-45.34	0.0168
NEUTROPENIA	36	150.7	238.8	51	42.6	1197.0	-958.2	-1295.84	-620.53	<0.0001
PULMONARY EMBOLISM	11	175.8	62.6	11	52.4	209.8	-147.3	-276.66	-17.86	0.0257
Syncope	1	182.6	5.5	1	54.1	18.5	-13.0	-50.75	24.77	0.5001
UPPER RESPIRATORY INFECTION	55	133.3	412.6	16	50.9	314.2	98.4	-90.25	287.05	0.3066
VISION DISORDER	122	51.1	2389.1	15	50.7	295.9	2093.2	1643.56	2542.75	<0.0001
Vomiting	78	107.5	725.6	57	41.2	1382.2	-656.7	-1049.97	-263.36	0.0011

Source: Study 1014 CSR Table 14.3.1.11.1.
MedDRA version 16.1 coding dictionary applied.
Some Low Level Terms were mapped to a common medical terminology for reporting.
Abbreviations: CI=confidence interval; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients.
a. Only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.

The exposure adjusted incidence rates were statistically significantly higher in the crizotinib arm for all-causality bradycardia, diarrhoea, dysgeusia, oedema, and vision disorder.

Tier 1 Grade 3, 4, or 5 all-causality AEs of special interest that occurred statistically significantly (2-sided p-value <0.05) more frequently in the crizotinib arm compared with the chemotherapy arm (before cross-over) were Electrocardiogram QT prolonged, and elevated transaminases and hepatotoxicity no Tier 1 Grade 3, 4, or 5 all-causality AEs of special interest occurred more frequently in the chemotherapy arm than in the crizotinib group.

Tier-2 TRAEs of special interest reported more frequently with crizotinib were visual impairment, abdominal pain, oedema peripheral, dysgeusia and dizziness, while in the chemotherapy arm anemia, asthenia, platelet count decrease and decreased appetite were mostly registered. The only treatment-related Grade ≥3 occurred was anaemia in the chemotherapy arm.

Based on the current crizotinib safety data, an internal clinical and safety review was done to determine ADRs likely associated with crizotinib. The list of crizotinib ADRs reported in Study 1014 is presented in the following table:

Table 33: Crizotinib ADRs by SOC and severity-Frequency of All-Causality AEs in Study 1014- SA Population

SOC Adverse Reaction	Frequency[b]	Number (%) of Patients – All-Causality Adverse Events: Crizotinib N=171 All Grades	Crizotinib N=171 Grades 3/4	Chemotherapy N=169[a] All Grades	Chemotherapy N=169[a] Grades 3/4
Blood and Lymphatic System Disorders					
Neutropenia[c]	Very Common	36 (21.1)	19 (11.1)	51 (30.2)	26 (15.4)
Leukopenia[c]	Common	12 (7.0)	3 (1.8)	26 (15.4)	9 (5.3)
Metabolism and Nutritional Disorders					
Decreased appetite	Very Common	51 (29.8)	4 (2.3)	57 (33.7)	1 (0.6)
Nervous System Disorders					
Dysgeusia	Very Common	45 (26.3)	0	9 (5.3)	0
Neuropathy[c]	Very Common	35 (20.5)	2 (1.2)	38 (22.5)	0
Dizziness[c]	Very Common	31 (18.1)	0	17 (10.1)	2 (1.2)
Eye Disorders					
Vision Disorder[c]	Very Common	122 (71.3)	1 (0.6)	16 (9.5)	0
Cardiac Disorders					
Bradycardia[c]	Very Common	23 (13.5)	2 (1.2)	1 (0.6)	0
Electrocardiogram QT prolonged	Common	10 (5.8)	4 (2.3)	3 (1.8)	0
Syncope[d]	Uncommon	1 (0.6)	1 (0.6)	2 (1.2)	2 (1.2)
Respiratory, Thoracic and Mediastinal Disorders					
Interstitial Lung Disease[c]	Common	2 (1.2)	1 (0.6)	1 (0.6)	0
Gastrointestinal Disorders					
Diarrhoea	Very Common	105 (61.4)	4 (2.3)	22 (13.0)	1 (0.6)
Nausea	Very Common	95 (55.6)	2 (1.2)	99 (58.6)	3 (1.8)
Vomiting	Very Common	78 (45.6)	3 (1.8)	60 (35.5)	5 (3.0)
Constipation	Very Common	74 (43.3)	3 (1.8)	51 (30.2)	0
Dyspepsia	Very Common	23 (13.5)	0	4 (2.4)	0
Hepatobiliary Disorders					
Elevated Transaminases[c]	Very Common	61 (35.7)	24 (14.0)	22 (13.0)	4 (2.4)
Blood alkaline phosphatase increased	Common	4 (2.3)	0	2 (1.2)	0
Skin and Subcutaneous Tissue Disorders					
Rash	Very Common	18 (10.5)	0	19 (11.2)	0
Renal and Urinary Disorders					
Renal Cyst[c]	Common	8 (4.7)	0	1 (0.6)	0
General Disorders and Administration Site Conditions					
Edema[c]	Very Common	83 (48.5)	1 (0.6)	21 (12.4)	1 (0.6)
Fatigue	Very Common	49 (28.7)	5 (2.9)	65 (38.5)	4 (2.4)

Source: Study 1014 CSR Tables 14.3.1.2.9.4.1 and 14.3.1.5.1.1.

CTCAE Version 4.0.

Of note, there were no cases of Hepatic failure in Study 1014; across clinical trials with crizotinib, Hepatic failure was uncommonly (<1%) observed.

Abbreviations: ADR=adverse drug reaction; SOC=system organ class

a. Only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.
b. Based on the frequency in the crizotinib arm of Study 1014. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), or very rare (<1/10,000).
c. Includes Preferred Terms reported within the CLUSTERED TERMS.
d. Syncope was added to the ADR list in in the Pfizer reference product label after the 1007 supplemental regulatory submission (March 2014_Crizotinib_2 5 Clinical Overview_CDS_Syncope).

Review of selected safety events across clinical studies

The following selected events were reviewed because considered associated or potentially correlated to crizotinib, or were newly identified:

- **Hepatotoxicity**

Increases to Grade 3 or 4 ALT or AST elevation were observed in 184 (11%) and 93 (6%) of patients, respectively. Seventeen (1%) patients required permanent discontinuation from treatment associated

with elevated transaminases. In randomised Phase 3 Study 1014, increases to Grade 3 or 4 ALT or AST elevations were observed in 15% and 8% of patients receiving crizotinib versus 2% and 1% of patients receiving chemotherapy. In randomised Phase 3 Study 1007, increases to Grade 3 or 4 ALT or AST elevations were observed in 18% and 9% of patients receiving crizotinib and 5% and <1% of patients receiving chemotherapy.

Drug-induced hepatotoxicity with fatal outcome occurred in less than 0.5% of 1669 patients treated with crizotinib across clinical trials.

Transaminase elevations generally occurred within the first 2 months of treatment. Across studies with crizotinib in patients with ALK-positive NSCLC, median time to onset of increased Grade 1 or 2 transaminases was 23 days. Median time to onset of increased Grade 3 or 4 transaminases was 43 days.

Across studies with crizotinib in patients with ALK-positive NSCLC (N=1669), dose reductions associated with transaminase elevations occurred in 74 (4%) patients. Seventeen (1%) patients required permanent discontinuation from treatment.

There have been no fatal cases reported in Study 1014 or new fatal cases in the other clinical studies since the last regulatory submission.

Potential Drug-Induced Liver Injury Cases

Across studies 1014, 1007, 1005 and 1001, a total of 20 ALK-positive NSCLC crizotinib-treated patients have been identified with ALT and/or AST ≥3 x ULN and total bilirubin ≥2 x ULN, including 4 patients in the Study 1014, 11 patients described in previous regulatory submissions, and 5 new cases from Studies 1005 and 1001.

Cases were determined to be potentially consistent with drug-induced hepatotoxicity, if significant liver injury occurred during administration of crizotinib, and if there was no plausible alternative explanation for the observed event, or if the investigator or the Sponsor considered crizotinib to be a reasonably likely cause of the observed liver injury, despite the presence of plausible alternative explanations.

Out of the total 20 patients with adverse events and/or laboratory test results suggestive of drug-induced liver injury, 8 were considered to meet Hy's Law criteria.

- **Interstitial Lung Disease / Pneumonitis**

Across studies in patients with ALK-positive NSCLC (N=1669), 49 (3%) patients treated with crizotinib had any grade ILD, 18 (1%) patients had Grade 3 or 4, and 8 (<1%) patients had fatal outcome.

Independent Review Committee (IRC) review of ILD/Pneumonitis

In order to evaluate potential cases of pneumonitis associated with crizotinib, all Grade ≥3 respiratory AE/SAEs plus any-grade Pneumonitis, Interstitial lung disease, and Radiation pneumonitis AE/SAEs were reviewed by an Independent Review Committee (IRC).

As per the current IRC review (July 2014 IRC Report), there were a total of 20 patients (3 from the original review, 6 from the second review, 9 from the third review and 2 from the current review, 1 from study 1005 and 1 from study 1014) with events of de novo ILD/Pneumonitis possibly related to crizotinib.

The mean onset of crizotinib induced ILD from the time the drug was started was 82 days. In 17 of 20 patients de novo ILD/Pneumonitis occurred before 100 days (average time 29 days).

Overall for the 4 studies, based on the IRC review, the incidence of crizotinib induced ILD was 1.2% (1.2% for Caucasian and 1.2% for Asian). However, the incidence rate is 1.4% also taking into account 3 possibly treatment-related respiratory events based on investigator's assessment of the 25 patients with insufficient data for the IRC to make an assessment.

To date, the IRC did not identify any chemotherapy-treated patients with de novo ILD/Pneumonitis.

- **QT Interval Prolongation**

Across studies in patients with ALK-positive advanced NSCLC, QTcF (corrected QT by the Fridericia method) ≥ 500 msec was recorded in 32 (2.1%) of 1560 patients and a maximum increase from baseline in QTcF ≥ 60 msec was observed in 76 (5.0%) of 1520 patients. All-causality Grade 3 or 4 Electrocardiogram QT prolonged was reported in 25 (1.5%) out of 1669 patients

- **Bradycardia**

In studies with crizotinib in patients with ALK-positive advanced NSCLC, all-causality bradycardia was experienced by 205 (12%) of 1669 patients treated with crizotinib. A total of 242 (15%) patients had a pulse rate <50 bpm.

- **Vision Disorder**

In studies in patients with ALK-positive advanced NSCLC (N=1669), all-causality vision disorder, most commonly visual impairment, photopsia, vision blurred, and vitreous floaters, was experienced by 1038 (62%) of 1669 patients treated with crizotinib. Ninety-five percent of these patients had events that were mild in severity. Seven (0.4%) patients had temporary treatment discontinuation and 2 (0.1%) patients had a dose reduction associated with vision disorder. There were no permanent discontinuations associated with vision disorder for any of the 1669 patients treated with crizotinib.

- **Gastrointestinal Events**

Across studies in patients with ALK-positive advanced NSCLC, nausea (57%), diarrhoea (54%), vomiting (51%), and constipation (43%) were the most commonly reported all-causality gastrointestinal events. Median times to onset for nausea and vomiting were 4 days.

In clinical studies with crizotinib, events of gastrointestinal perforations were reported. There were reports of fatal cases of gastrointestinal perforation during post-marketing use of crizotinib.

- **Neuropathy**

All-causality neuropathy (including cases of burning sensation, dysaesthesia, formication, gait disturbance, hyperaesthesia, hypoaesthesia, hypotonia, motor dysfunction, muscle atrophy, muscular weakness, neuralgia, neuritis, neuropathy peripheral, neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, peroneal nerve palsy, polyneuropathy, sensory disturbance, skin burning sensation), was experienced by 419 (25%) out of 1669 patients treated with crizotinib.

- **Neutropenia and Leukopenia**

Across studies in patients with ALK-positive advanced NSCLC (N=1669), Grade 3 or 4 neutropenia was observed in 207 (12%) patients treated with crizotinib. Median time to onset of any grade neutropenia was 87 days. Neutropenia was associated with dose reduction or permanent treatment discontinuation for 4% and <1% of patients, respectively. Less than 0.5% of patients experienced febrile neutropenia in clinical studies with crizotinib.

Across studies in patients with ALK-positive advanced NSCLC (N=1669), Grade 3 or Grade 4 leukopenia was observed in 48 (3%) patients. Median time to onset of any grade leukopenia was 85 days.

Leukopenia was associated with a dose reduction for <0.5% of patients, and no patients permanently discontinued crizotinib treatment associated with leukopenia.

In clinical studies of crizotinib in patients with ALK-positive advanced NSCLC, shifts to Grade 3 or 4 decreases in leukocytes and neutrophils were observed at frequencies of 4% and 14%, respectively.

- **Renal Cyst**

All-causality complex renal cysts were experienced by 50 (3%) of 1669 patients treated with crizotinib.

- **Oedema**

Oedema (including cases of face oedema, generalised oedema, local swelling, localised oedema, oedema, oedema peripheral, and periorbital oedema) is a very common ADR reported in 49% of patients across studies in patients with ALK-positive advanced NSCLC.

- **Syncope**

Across studies, syncope has been reported in 3% of patients and is considered as a common ADR.

Update of the list of adverse drug reactions (ADRs) on the basis of the pooled safety data

In the crizotinib SmPC, Section 4.8, undesirable effects, all causality frequency data for all listed ADRs has been updated with the larger data set that includes 1669 ALK positive advanced NSCLC patients from the pooled data of 4 clinical studies (Studies 1001, 1005, 1007 and 1014). All the 4 studies are ongoing. The cut-off date for summary of the pooled data was 30 November 2013. The frequencies of the ADR terms were categorized according to the Council for International Organizations of Medical Sciences (CIOMS Working Group III-V) convention.

An overview of the changes in ADR frequencies and categories is presented in the table below. The ADRs are ordered first by system organ class (SOC).

Table 34: Updated list of adverse drug reactions based on data from studies 1001, 1005, 1007 and 1014

System Organ Class	ADR Term	Frequency (%)	Comments
Blood and Lymphatic System Disorders	Neutropenia[a]	21.9	365/1669 = 21.9%
	Anaemia[b]	15.0	250/1669 = 15.0%
	Leukopenia[c]	14.8	247/1669 = 14.8% The frequency category has been updated to Very common from Common.
Metabolism and Nutrition Disorders	Decreased appetite	29.8	498/1669 = 29.8%
	Hypophosphataemia	5.6%	93/1669 = 5.6%
Nervous System Disorders	Neuropathy[d]	25.1	419/1669 = 25.1%
	Dysgeusia	21.1	352/1669 = 21.1%
Eye Disorders	Vision disorder[e]	62.2	1038/1669 = 62.2%
Cardiac Disorders	Dizziness[f]	25.2	421/1669 = 25.2% The term has been retained in the most relevant SOC related to the target organ.
	Bradycardia[g]	12.3	205/1669 = 12.3% The frequency category has been updated to Very common from Common.
	Electrocardiogram QT prolonged	3.7	62/1669 = 3.7% The term has been retained in the most relevant SOC related to the target organ.
	Syncope	2.5	41/1669 = 2.5% The term has been retained in the most relevant SOC related to the target organ.
Respiratory, Thoracic and Mediastinal Disorders	Interstitial lung disease[h]	2.9	49/1669 = 2.9%
Gastrointestinal Disorders	Nausea	56.5	943/1669 = 56.5%
	Diarrhea	54.3	906/1669 = 54.3%
	Vomiting	50.7	847/1669 = 50.7%
	Constipation	43.1	720/1669 = 43.1%
	Abdominal pain*[i]	20.7	345/1669 = 20.7%
	Dyspepsia	8.2	137/1669 = 8.2%
	Gastrointestinal perforation[j]	0.2	3/1669 = 0.2%
Hepatobiliary Disorders	Elevated transaminases[k]	32.0	534/1669 = 32.0% The clustered term has been retained in the most relevant SOC related to the target organ.
	Blood alkaline phosphatase increased	6.6	110/1669 = 6.6% The PT has been retained in the most relevant SOC related to the target organ.
	Hepatic failure	0.3	5/1669 = 0.3%
Skin and Subcutaneous Tissue Disorders	Rash	12.8	213/1669 = 12.8% The frequency category has been updated to Very common from Common.
Renal and Urinary Disorders	Renal cyst[l]	3.0	50/1669 = 3.0%
General Disorders and Administration Site Conditions	Edema[m]	48.8	814/1669 = 48.8%
	Fatigue	29.8	497/1669 = 29.8%

Serious adverse event/deaths/other significant events

Study 1014

The most common SAEs registered in study 1014 are reported in the table below:

Table 35: Most common (≥2%) SAEs by treatment arm (All Causality and Treatment-Related) in Study 1014- SA Population

	Crizotinib	Chemotherapy

	(N=171)		(N=169)[a]	
	All-Causality n (%)	Treatment-Related n (%)	All-Causality n (%)	Treatment-Related n (%)
Any SAEs	58 (33.9)	18 (10.5)	47 (27.8)	15 (8.9)f
Disease progression	15 (8)	-	1 (0.6)	-
Dyspnoea	7 (4.1)	1 (0.6)	4 (2.4)	-
Pulmonary embolism	5 (2.9)	-	7 (4.1)	2 (1.2)
Nausea	3 (1.8)	3 (1.8)	1 (0.6)	1 (0.6)
Oesophagitis	3 (1.8)	3 (1.8)	-	-
Diarrhoea	2 (1.2)	2 (1.2)	1 (0.6)	1 (0.6)
Renal cyst	2 (1.2)	2 (1.2)	-	-
Vomiting	2 (1.2)	2 (1.2)	4 (2.4)	4 (2.4)
Dehydration	-	-	2 (1.2)	2 (1.2)
Febrile neutropenia	-	-	2 (1.2)	2 (1.2)
General health deterioration	-	-	2 (1.2)	2 (1.2)
Pyrexia	1 (0.6)	1 (0.6)	2 (1.2)	2 (1.2)
Oesophageal ulcer	1 (0.6)	1 (0.6)	-	-
Drug-induced liver injury	1 (0.6)	1 (0.6)	-	-
Interstitial lung disease	1 (0.6)	1 (0.6)	-	-
Pneumonitis	1 (0.6)	1 (0.6)	-	-

[a] Only includes data before cross-over to crizotinib for those patients who crossed over to receive crizotinib treatment

All-causality SAEs were registered in 34 (31.2%) out of the 109 crossing over patients. The most frequently reported (≥2% patients) events were Disease progression (14 patients, 12.8%), elevated transaminases (3 patients, 2.8%) and Respiratory failure (3 patients, 2.8%). In 8 (7.3%) patients SAEs were considered treatment-related. The only treatment-related SAE reported in more than 1 patient was elevated transaminases (3 patients, 2.8%).

Study 1007

In 23 (13.4%) patients in the crizotinib arm, SAEs were considered treatment-related, including interstitial lung disease (4 patients, 2.3%), elevated transaminases (3 patients, 1.7%), decreased appetite, neutropenia, pneumonia and vomiting (each in 2 patients, 1.2%).

In the chemotherapy group, treatment-related SAEs were registered in 24 (14%) patients, and the most common event was neutropenia (14 patients, 8.2%). Further treatment-related SAEs occurred in ≥ 1% of patients were anemia (3 patients, 1.8%), stomatitis (3 patients, 1.8%), deep vein thrombosis (2 patients, 1.2%) and leukopenia (2 patients, 1.2%).

Study 1005

SAEs were considered treatment-related in 115 (10.8%) patients, and the most commonly (≥1%) reported were renal cyst (15 patients, 1.4%) and interstitial lung disease (14 patients, 1.3%).

Study 1001

In the ALK-positive NSCLC RP2D cohort, treatment-related SAEs were reported in 13 (8.4%) patients, most commonly in terms of elevated transaminases (3 patients, 1.9%), dyspnoea (2 patients, 1.9%), and renal cyst (2 patients, 1.9%). Among the 204 patients in the other RP2D cohort, SAEs were considered treatment-related in 13 (6.4%) patients, and the most common event was anaemia (3 patients, 1.5%).

Study 1013

Seven patients (15.9%) experienced treatment-related SAEs, such as blood creatinine phosphokinase increased, cardiac failure congestive, cerebral infarction, deep vein thrombosis, diarrhoea, interstitial lung disease, ischemia, nausea and vomiting (each 1 patient, 2.3%).

Study 1012

All-causality SAEs were reported in 19 (61.3%) of the 31 patients, and the most common events were disease progression (7 patients, 22.6%), ascites (2 patients, 6.5%), cholestasis (2 patients, 6.5%), dyspnoea (2 patients, 6.5%), hepatotoxicity (2 patients, 6.5%) and renal failure (2 patients, 6.5%). No SAEs were considered to be treatment-related.

Deaths

Study 1014

Table 36: Deaths by Treatment Arm in Study 1014-SA Population

	Crizotinib (N=171) n (%)	Chemotherapy (N=169) n (%)
Deaths from all causes	44 (25.7)	46 (27.2)
Within 28 days of last dose of study drug[a]	18 (10.5)	4 (2.4)
More than 28 days after last dose of study drug[a]	26 (15.2)	14 (8.3)
After crossover	0[b]	28 (16.6)
Deaths within 30 days of first dose of study drug	4 (2.3)	3 (1.8)
Deaths within 60 days of first dose of study drug	7 (4.1)	5 (3.0)
Cause of death[c]		
Disease under study	39 (22.8)	43 (25.4)
Study treatment toxicity	0	1 (0.6)[d]
Other[e]	5 (2.9)	2 (1.2)

Source: Study 1014 Table 14.3.2.1.2.1.
Summary of death data are based on the 'Notice of Death' case report form page.
Chemotherapy patients who crossed over to receive crizotinib treatment are included in the chemotherapy column.
Abbreviation: n=number, NA=Not applicable.

a. Deaths that occurred after crossover are not included in these categories.
b. Not applicable.
c. More than 1 cause of death may be reported.
d. Study treatment toxicity includes Pneumonitis (after crossover to crizotinib).
e. Other includes Septic shock secondary to pneumonia (2 patients), Cardiac tamponade, Sepsis (poisoning, undercooked steak), and Urinary tract infection (1 patient for each event) in the crizotinib arm; Superinfection (after crossover to crizotinib) and Death by suicide (1 patient for each event) in the chemotherapy arm (Study 1014 CSR Tables 14.3.2.1.2.1b and 14.3.2.1.2.1c).

Fatal Grade 5 all-causality AEs were reported in 20 (11.7%) patients in the crizotinib arm (including 2 patients with Grade 5 disease progression occurred >28 days after crizotinib last dose) and 4 (2.4%) patients in the chemotherapy arm (see table below).

Table 37: Grade 5 AEs Associated With Death on Study by Treatment Arm (All-Causality and Treatment-Related) in Study 1014- SA Population

	Crizotinib (N=171) n (%)		Chemotherapy (N=169)[a] n (%)	
	All-Causality	Treatment-Related	All-Causality	Treatment-Related
Any Grade 5 AE	20 (11.7)	0	4 (2.4)	0
Disease progression[b]	16 (9.4)	0	1 (0.6)	0
Septic shock	2 (1.2)	0	0	0
Acute respiratory failure	1 (0.6)	0	0	0
Diabetic ketoacidosis	1 (0.6)	0	0	0
Cardiac arrest	0	0	1 (0.6)	0
Completed suicide	0	0	1 (0.6)	0
Haemoptysis	0	0	1 (0.6)	0

Source: Study 1014 CSR Tables 14.3.1.2.11.3 and 14.3.1.3.11.3.
MedDRA version 16.1 coding dictionary applied.
Abbreviations: AE=adverse event; N/n=number of patients; MedDRA=Medical Dictionary for Regulatory Activities.
a. Only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.
b. Two patients (11941006 and 12361005) are included although the Grade 5 events of Disease progression occurred >28 days after the last dose of crizotinib (29 days and 185 days, respectively, Study 1014 CSR Tables 16.2.7.2 and 16.2.5.1.1).

After crossing-over to crizotinib treatment, 20 (18.3%) patients had Grade 5 all-causality AEs such as disease progression (14 patients), respiratory failure (3 patients), pneumonitis (1 patient), infection (1 patient), pneumonia (1 patient). Pneumonitis was the only grade 5 all-causality considered to be treatment-related.

Study 1007

In the crizotinib arm, Grade 5 all-causality AEs were reported in 30 (17.4%) patients, including 18 (10.5%) who had disease progression. events reported in more than 1 patient were interstitial disease lung (3 patients, 1.7%), and dyspnoea and death (each in 2 patients, 1.2%) patients.

Grade 5 AEs were considered treatment-related in a total of 3 (1.7%) patients, in which interstitial disease lung (2 patients, 1.2%) and arrhythmia (1 patient, 0.6%) occurred.

Regarding chemotherapy arm, 7 out of the 171 patients (4.1%) analyzed for safety had Grade 5 all-causality AEs. Disease progression (3 patients, 1.8%) was the only Grade 5 all-causality AE reported in more than 1 patient, and sepsis (1 patient, 0.6%) was the only Grade 5 AE considered treatment-related.

Study 1005

Grade 5 all-causality AEs have been registered in 221 (20.8%) patients, mostly in terms of disease progression (126 patients, 11.9%). Other frequently reported Grade 5 all-causality AEs included pneumonia (15 patients, 1.4%), respiratory failure (8 patients, 0.8%), pulmonary embolism (7 patients, 0.7%), death (7 patients, 0.7%), dyspnoea (6 patients, 0.6%), and lung infection (5 patients, 0.5%). events were considered treatment-related for a total of 13 (1.2%) patients, including death (3 patients, 0.3%), hepatotoxicity (2 patients, 0.2%), interstitial lung disease (2 patients, 0.2%), lung infection (2 patients, 0.2%), and pneumonia (2 patients, 0.2%).

Study 1001

Twenty-nine (18.8%) out of the 154 patients in the ALK-positive NSCLC RP2D cohort reported Grade 5 all-causality AEs. Disease progression (21 patients, 13.6%) and pneumonia (2 patients, 1.3%) were the only events registered in more than 1 patient. The remaining 6 patients experienced each 1 of the following Grade 5 AEs: Aspergillus infection, disseminated intravascular coagulation, lung infection, pulmonary haemorrhage, respiratory failure and subcutaneous emphysema.

Death due to disseminated intravascular coagulation (1 patient, 0.6%) was the only Grade 5 treatment-related AE.

In the Other RP2D cohort, all-causality fatal SAEs were reported in 35 (17.2%) out of 204 patients, and the most common (≥2 patients) were disease progression (25 patients), pneumonia (2 patients) and respiratory failure (2 patients). A treatment-related SAE of death (1 patient, 0.5%) was the only Grade 5 treatment-related event reported.

Study 1013

Among the 44 patients, a total of 7 (15.9%) patients had Grade 5 all-causality AEs, including Disease progression (3 patients, 6.8%), interstitial lung disease (2 patients, 24.5%), cerebral infarction (1 patient, 2.3%) and respiratory failure (1 patient, 2.3%).

Two Grade 5 AEs, interstitial lung disease (1 patient, 2.3%) and cerebral infarction (1 patient, 2.3%), were considered treatment related.

Study 1012

All-causality fatal SAEs were reported in 11 (35.5%) of the 31 patients, including disease progression (7 patients, 22.6%), cholestasis (1 patient, 3.2%), chronic hepatic failure (1 patient, 3.2%), respiratory failure (1 patient, 3.2%) and septic shock (1 patient, 3.2%). None of these events were considered to be treatment related.

Laboratory findings

In study 1014 the shift from Grade ≤2 to Grade 3/4 in haematology and chemistry laboratory results is shown in the following tables:

Table 38: Shift Table of Haematology Laboratory Results from Grade ≤2 to Grade 3/4 by treatment arm (All Cycles)-SA Population

	Crizotinib (N=171)		Chemotherapy (N=169)*	
Patients with shift from Grade ≤2 at Baseline to Grade 3/4:	**N***	**n (%)**	**N***	**n (%)**
Anemia	170	0	165	15 (9.1)
Hemoglobin increased	170	0	165	1 (0.6)
Lymphocyte count increased	170	0	165	0
Lymphopenia	170	10 (5.9)	165	19 (11.5)
Neutrophils (absolute)	170	19 (11.2)	165	26 (15.8)
Platelets	170	2 (1.2)	165	13 (7.9)
White blood cells	170	3 (1.8)	165	17 (10.3)

Source: Section 14.3, Table 14.3.4.1.5.6.4.1.
Includes unplanned laboratory test results.
CTCAE Version 4 criteria have been used.
Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; n/N=number of patients; N*=number of patients who had at least 1 on-study assessment for the parameter of interest.
* Only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.

Table 39: Shift Table of Clinical Chemistry Laboratory Results from Grade ≤2 to Grade 3/4 by treatment arm (All Cycles)-SA Population

	Crizotinib (N=171)		Chemotherapy (N=169)[a]	
Patients with shift from Grade ≤2 at Baseline to Grade 3/4:	**N***	**n (%)**	**N***	**n (%)**
Alanine aminotransferase (ALT)	170	25 (14.7)	165	3 (1.8)
Alkaline phosphatase	170	1 (0.6)	165	2 (1.2)
Aspartate aminotransferase (AST)	170	14 (8.2)	165	2 (1.2)
Bilirubin (total)	170	0	165	0
Creatinine	170	3 (1.8)	165	1 (0.6)
Hypercalcemia	170	1 (0.6)	165	0
Hyperglycemia	170	5 (2.9)[b]	165	8 (4.8)
Hyperkalemia	170	4 (2.4)	165	3 (1.8)
Hypermagnesemia	169	3 (1.8)	162	1 (0.6)
Hypernatremia	170	1 (0.6)	165	1 (0.6)
Hypoalbuminemia	170	2 (1.2)	164	1 (0.6)
Hypocalcemia	170	2 (1.2)[c]	165	2 (1.2)
Hypoglycemia	170	0	165	1 (0.6)
Hypokalemia	170	3 (1.8)	165	4 (2.4)
Hypomagnesemia	169	0	162	1 (0.6)
Hyponatremia	170	5 (2.9)	165	9 (5.5)
Hypophosphatemia	167	16 (9.6)	161	10 (6.2)

Source: Section 14.3, Table 14.3.4.1.6.6.4.1.
Includes unplanned laboratory test results.
CTCAE Version 4 criteria have been used.
Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; n/N=number of patients; N*=number of patients who had at least 1 on-study assessment for the parameter of interest.
[a] Only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.
[b] This includes Patient 11731009 whose glucose levels met the criterion for Grade 4 hyperglycemia because an incorrect unit was reported at the time of database snapshot.
[c] This includes Patient 11731009 whose calcium levels met the criterion for Grade 4 hypocalcemia because an incorrect unit was reported at the time of database snapshot.

After Protocol Amendment #6, all male patients were to undergo hypogonadism laboratory tests (i.e. total T, free T, FSH, LH) together with DXA scan. However, limited data (8 patients in the crizotinib arm and 5 patients in the chemotherapy arm for hypogonadism laboratory parameters; 2 patients in each treatment arm for DXA analysis) are available. Hypogonadism was reported for 1 (0.6%) patient in the crizotinib arm (treatment-related Grade 1), while no events were reported in the chemotherapy group.

Safety in special populations

Safety data in special groups and situations have only been provided for Study 1014.

Elderly patients

Most common all-causality and treatment related AEs by age group (< 65 years and ≥ 65 years) are reported in the following Table:

Table 40: Most Common (≥10%) Treatment Emergent All-Causality AEs (All Cycles) for Patients <65 Years of Age and Patients ≥ Years of Age by Treatment Arm-SA Population

MedDRA Preferred Term or CLUSTERED TERM	<65 Years		≥65 Years	
	Crizotinib N=149	Chemotherapy N=138	Crizotinib N=22	Chemotherapy N=31
VISION DISORDER	109 (73.2)	15 (10.9)	13 (59.1)	1 (3.2)
Diarrhoea	93 (62.4)	16 (11.6)	12 (54.5)	6 (19.4)
Nausea	83 (55.7)	85 (61.6)	12 (54.5)	14 (45.2)
EDEMA	69 (46.3)	20 (14.5)	14 (63.6)	1 (3.2)
Vomiting	68 (45.6)	54 (39.1)	10 (45.5)	6 (19.4)
Constipation	61 (40.9)	39 (28.3)	13 (59.1)	12 (38.7)
ELEVATED TRANSAMINASES	55 (36.9)	22 (15.9)	6 (27.3)	0
UPPER RESPIRATORY INFECTION	51 (34.2)	18 (13.0)	4 (18.2)	3 (9.7)
Decreased Appetite	43 (28.9)	43 (31.2)	8 (36.4)	14 (45.2)
Dysgeusia	41 (27.5)	8 (5.8)	4 (18.2)	1 (3.2)
Fatigue	41 (27.5)	50 (36.2)	8 (36.4)	15 (48.4)
ABDOMINAL PAIN	37 (24.8)	15 (10.9)	8 (36.4)	5 (16.1)
Headache	35 (23.5)	22 (15.9)	2 (9.1)	3 (9.7)
COUGH	34 (22.8)	25 (18.1)	5 (22.7)	8 (25.8)
NEUROPATHY	31 (20.8)	34 (24.6)	4 (18.2)	4 (12.9)
NEUTROPENIA	29 (19.5)	40 (29.0)	7 (31.8)	11 (35.5)
DYSPNOEA	28 (18.8)	20 (14.5)	2 (9.1)	6 (19.4)
Pyrexia	28 (18.8)	14 (10.1)	4 (18.2)	4 (12.9)
DIZZINESS	26 (17.4)	15 (10.9)	5 (22.7)	2 (6.5)
CHEST PAIN	24 (16.1)	20 (14.5)	1 (4.5)	3 (9.7)
Pain in extremity	22 (14.8)	11 (8.0)	5 (22.7)	1 (3.2)
STOMATITIS	22 (14.8)	30 (21.7)	2 (9.1)	4 (12.9)
BRADYCARDIA	19 (12.8)	1 (0.7)	4 (18.2)	0
Back pain	19 (12.8)	17 (12.3)	4 (18.2)	4 (12.9)
Dyspepsia	19 (12.8)	4 (2.9)	4 (18.2)	0
Asthenia	18 (12.1)	32 (23.2)	4 (18.2)	9 (29.0)
Insomnia	18 (12.1)	13 (9.4)	1 (4.5)	2 (6.5)
Disease progression	15 (10.1)	1 (0.7)	1 (4.5)	0
Musculoskeletal pain	15 (10.1)	7 (5.1)	0	0
Rash	15 (10.1)	17 (12.3)	3 (13.6)	2 (6.5)
ANEMIA	14 (9.4)	37 (26.8)	1 (4.5)	17 (54.8)
Dysphagia	13 (8.7)	2 (1.4)	4 (18.2)	1 (3.2)
Alopecia	11 (7.4)	16 (11.6)	1 (4.5)	1 (3.2)
Hypoalbuminaemia	11 (7.4)	1 (0.7)	3 (13.6)	1 (3.2)
Gastrooesophageal Reflux Disease	10 (6.7)	5 (3.6)	3 (13.6)	0
LEUKOPENIA	9 (6.0)	20 (14.5)	3 (13.6)	6 (19.4)
Weight decreased	8 (5.4)	4 (2.9)	3 (13.6)	2 (6.5)
Hypokalaemia	6 (4.0)	4 (2.9)	0	4 (12.9)
RENAL CYST	5 (3.4)	1 (0.7)	3 (13.6)	0
LYMPHOPENIA	4 (2.7)	4 (2.9)	3 (13.6)	0
Hyponatraemia	2 (1.3)	4 (2.9)	1 (4.5)	4 (12.9)
THROMBOCYTOPENIA	1 (0.7)	19 (13.8)	1 (4.5)	12 (38.7)

Source: SCS Appendix 2, Table 14.3.1.4.6.1.
MedDRA Version 16.1 coding dictionary applied. Adverse events presented if ≥10% in any patient category and listed in decreasing order of frequency for patients <65 years of age in the crizotinib arm.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients.

Race

There was no clear pattern in the differences between crizotinib and chemotherapy of all-causality AE frequency for Asian and non- Asian patients. However, in the crizotinib arm elevated transaminases, decreased appetite and upper respiratory infection were more frequent in Asian, while oedema was most common in non-Asian patients. In the chemotherapy group, Asian experienced more frequently decreased appetite and leukopenia, while in non-Asian dyspnoea was the most common event.

Across studies in patients with ALK positive advanced NSCLC (N=1669), the following adverse reactions were reported with an absolute difference of ≥10% in Asian patients (N=753) than in non-Asian patients (N=916): elevated transaminases, decreased appetite, neutropenia, and leukopenia. No adverse drug reactions were reported with an absolute difference of ≥15%.

Gender

The differences between crizotinib and chemotherapy of all-causality AEs were comparable among males and females to the differences reported in the overall population. However, in the crizotinib arm

elevated transaminases were more frequent in male, and nausea, neutropenia, and vomiting in female patients. Nausea was the more frequent event in chemotherapy-treated female patients.

Use in pregnancy and lactation

At the data cut-off date, 2 cases of pregnancy in females receiving crizotinib, and 2 cases of male patients who had female partners who became pregnant have been reported in clinical studies.

Both female patients (one patient in Study 1001 and one patient in Study 1005) underwent an induced abortion.

The outcome of the pregnancy for the female partners of the 2 male patients was a full-term male in one case (Study 1001) and a foetal demise at 8 weeks gestational age in the other one (Study 1001).

A case of maternal exposure during pregnancy was reported to the MAH expedited reporting database after the data cut-off date. One patient in Study 1014 became pregnant while receiving crizotinib and underwent an induced abortion at 6 weeks gestational age. No macroscopic abnormalities were seen and the condition of the foetus was normal.

Non-adenocarcinoma histology

A report on the subgroup analysis in patients with adenocarcinoma and non-adenocarcinoma histology in Study 1014 (before cross-over) and Study 1005 has been submitted.

Since the subgroup of patients with adenocarcinoma histology corresponds to the majority of the SA population (approximately 94.1% and 94.4% for Study 1014 and Study 1005, respectively), the safety analyses were limited to presentation of AEs in all patients in the safety analysis set and in the subgroup of patients with non-adenocarcinoma histology.

A summary of all-causality AEs reported in at least 10% of all patients in the crizotinib or chemotherapy arms is reported in the following Table:

Table 41: Summary of All-Causality AEs for All Patients and Non-adenocarcinoma Patients Reported in at least 10% of All Patients-SA Population

	All Patients			Nonadenocarcinoma		
	Study A8081014		Study A8081005	Study A8081014		Study A8081005
Preferred Term, n (%)	Crizotinib N=171	Chemo-therapy N=169[a]	Crizotinib N=1063	Crizotinib N=10	Chemo-therapy N=10[a]	Crizotinib N=55
VISION DISORDER	122 (71.3)	16 (9.5)	635 (59.7)	7 (70.0)	0	29 (52.7)
Diarrhoea	105 (61.4)	22 (13.0)	548 (51.6)	4 (40.0)	2 (20.0)	29 (52.7)
Nausea	95 (55.6)	99 (58.6)	599 (56.3)	4 (40.0)	9 (90.0)	31 (56.4)
EDEMA	83 (48.5)	21 (12.4)	524 (49.3)	6 (60.0)	1 (10.0)	24 (43.6)
Vomiting	78 (45.6)	60 (35.5)	558 (52.5)	3 (30.0)	1 (10.0)	26 (47.3)
Constipation	74 (43.3)	51 (30.2)	467 (43.9)	6 (60.0)	2 (20.0)	19 (34.5)
ELEVATED TRANSAMINASES	61 (35.7)	22 (13.0)	323 (30.4)	5 (50.0)	1 (10.0)	16 (29.1)
UPPER RESPIRATORY INFECTION	55 (32.2)	21 (12.4)	240 (22.6)	4 (40.0)	2 (20.0)	12 (21.8)
Decreased appetite	51 (29.8)	57 (33.7)	320 (30.1)	3 (30.0)	6 (60.0)	14 (25.5)
Fatigue	49 (28.7)	65 (38.5)	315 (29.6)	5 (50.0)	3 (30.0)	14 (25.5)
ABDOMINAL PAIN	45 (26.3)	20 (11.8)	213 (20.0)	1 (10.0)	0	11 (20.0)
Dysgeusia	45 (26.3)	9 (5.3)	211 (19.8)	4 (40.0)	1 (10.0)	5 (9.1)
COUGH	39 (22.8)	33 (19.5)	284 (26.7)	2 (20.0)	1 (10.0)	12 (21.8)
Headache	37 (21.6)	25 (14.8)	201 (18.9)	0	3 (30.0)	11 (20.0)
NEUTROPENIA	36 (21.1)	51 (30.2)	230 (21.6)	2 (20.0)	3 (30.0)	7 (12.7)
NEUROPATHY	35 (20.5)	38 (22.5)	272 (25.6)	0	1 (10.0)	17 (30.9)
Pyrexia	32 (18.7)	18 (10.7)	183 (17.2)	2 (20.0)	1 (10.0)	10 (18.2)
DIZZINESS	31 (18.1)	17 (10.1)	265 (24.9)	1 (10.0)	2 (20.0)	9 (16.4)
DYSPNOEA	30 (17.5)	26 (15.4)	271 (25.5)	3 (30.0)	1 (10.0)	13 (23.6)
Pain in extremity	27 (15.8)	12 (7.1)	127 (11.9)	4 (40.0)	0	4 (7.3)
CHEST PAIN	25 (14.6)	23 (13.6)	179 (16.8)	2 (20.0)	2 (20.0)	10 (18.2)
STOMATITIS	24 (14.0)	34 (20.1)	160 (15.1)	1 (10.0)	1 (10.0)	11 (20.0)
BRADYCARDIA	23 (13.5)	1 (0.6)	141 (13.3)	1 (10.0)	0	2 (3.6)
Back pain	23 (13.5)	21 (12.4)	173 (16.3)	1 (10.0)	2 (20.0)	9 (16.4)
Dyspepsia	23 (13.5)	4 (2.4)	73 (6.9)	2 (20.0)	0	3 (5.5)
Asthenia	22 (12.9)	41 (24.3)	149 (14.0)	2 (20.0)	2 (20.0)	4 (7.3)
Insomnia	19 (11.1)	15 (8.9)	131 (12.3)	0	0	5 (9.1)
Rash	18 (10.5)	19 (11.2)	119 (11.2)	0	2 (20.0)	6 (10.9)
Disease progression	16 (9.4)	1 (0.6)	127 (11.9)	1 (10.0)	0	9 (16.4)
ANEMIA	15 (8.8)	54 (32.0)	170 (16.0)	1 (10.0)	5 (50.0)	7 (12.7)
Arthralgia	14 (8.2)	11 (6.5)	121 (11.4)	1 (10.0)	2 (20.0)	7 (12.7)
Alopecia	12 (7.0)	17 (10.1)	58 (5.5)	1 (10.0)	2 (20.0)	4 (7.3)
LEUKOPENIA	12 (7.0)	26 (15.4)	171 (16.1)	1 (10.0)	1 (10.0)	5 (9.1)
THROMBOCYTOPENIA	2 (1.2)	31 (18.3)	67 (6.3)	0	2 (20.0)	4 (7.3)

Source: A8081014: Section 14.3, Table 14.3.1.2.11.1.2 and Table 14.3.1.2.11.1.2.1.1; A8081005: Section 14.3, Table 14.3.1.2.11.1 and Table 14.3.1.2.11.1.1.
Medical Dictionary for Regulatory Activities (MedDRA v16.1) coding dictionary applied. Clustered terms are presented using all capital letters.
[a] Only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.

A summary of treatment-related adverse events (TRAEs) reported in at least 10% of all patients receiving crizotinib is shown in the Table below:

Table 42: Summary of Treatment-Related AEs for All- Patients and No adenocarcinoma Patients Reported in at least 10% of All Patients- Crizotinib Arm-SA Population

	All Patients		Nonadenocarcinoma	
	Study A8081014	Study A8081005	Study A8081014	Study A8081005
Preferred Term, n (%)	Crizotinib N=171	Crizotinib N=1063	Crizotinib N=10	Crizotinib N=55
VISION DISORDER	120 (70.2)	608 (57.2)	7 (70.0)	28 (50.9)
Diarrhoea	98 (57.3)	499 (46.9)	3 (30.0)	28 (50.9)
Nausea	86 (50.3)	544 (51.2)	4 (40.0)	29 (52.7)
Vomiting	68 (39.8)	492 (46.3)	3 (30.0)	23 (41.8)
ELEVATED TRANSAMINASES	59 (34.5)	309 (29.1)	5 (50.0)	16 (29.1)
Constipation	55 (32.2)	357 (33.6)	5 (50.0)	17 (30.9)
EDEMA	54 (31.6)	405 (38.1)	3 (30.0)	17 (30.9)
Dysgeusia	41 (24.0)	205 (19.3)	4 (40.0)	5 (9.1)
Fatigue	41 (24.0)	218 (20.5)	4 (40.0)	10 (18.2)
Decreased appetite	38 (22.2)	224 (21.1)	2 (20.0)	7 (12.7)
NEUTROPENIA	36 (21.1)	218 (20.5)	2 (20.0)	7 (12.7)
ABDOMINAL PAIN	33 (19.3)	129 (12.1)	0	7 (12.7)
DIZZINESS	23 (13.5)	156 (14.7)	0	4 (7.3)
BRADYCARDIA	20 (11.7)	113 (10.6)	0	1 (1.8)
NEUROPATHY	20 (11.7)	136 (12.8)	0	7 (12.7)
LEUKOPENIA	11 (6.4)	160 (15.1)	1 (10.0)	4 (7.3)

Source: A8081014: Section 14.3, Table 14.3.1.3.11.1.2 and Table 14.3.1.3.11.1.2.1.1; A8081005: Section 14.3, Table 14.3.1.2.11.2 and Table 14.3.1.2.11.2.1.
Medical Dictionary for Regulatory Activities (MedDRA v16.1) coding dictionary applied. Clustered terms are presented using all capital letters.

In Study 1014, among non-adenocarcinoma population, 2 patients (20.0%) in the crizotinib arm and no patients in the chemotherapy arm had Grade 5 AEs, while a total of 15 patients (27.3%) with non-adenocarcinoma experienced Grade 5 AEs in Study 1005. Most Grade 5 events were due to disease progression.

No Grade 5 TRAEs, either in the crizotinib or in the chemotherapy arms, were reported for Study 1014, regardless of histology. In Study 1005, a total of 13 patients (1.2%) had a Grade 5 TRAE, but no patient with non-adenocarcinoma histology was included.

Discontinuation due to adverse events

Study 1014

AEs associated with temporary discontinuation were reported in 70 (40.9%) patients in the crizotinib arm and 58 (34.3%) patients in the chemotherapy group before cross-over. In 59 (34.5%) crizotinib patients and 51 (30.2%) patients in the chemotherapy arm these events were considered treatment-related. The most common all-causality and treatment-related AEs associated with temporary discontinuation are shown in the following table:

Table 43: All-Causality and Treatment-Related AEs associated with temporary discontinuation by treatment arm (≥2% of patients in either treatment arm) in Study 1014- SA Population

MedDRA Preferred Term or CLUSTERED TERM	Crizotinib (N=171)		Chemotherapy (N=169)[a]	
	All-Causality n (%)	Treatment-Related n (%)	All-Causality n (%)	Treatment-Related n (%)
ELEVATED TRANSAMINASES	22 (12.9)	22 (12.9)	6 (3.6)	6 (3.6)
NEUTROPENIA	15 (8.8)	15 (8.8)	28 (16.6)	28 (16.6)
Vomiting	8 (4.7)	8 (4.7)	3 (1.8)	3 (1.8)
Fatigue	5 (2.9)	5 (2.9)	6 (3.6)	4 (2.4)
LEUKOPENIA	3 (1.8)	3 (1.8)	5 (3.0)	5 (3.0)
Decreased appetite	4 (2.3)	4 (2.3)	3 (1.8)	1 (0.6)
Nausea	4 (2.3)	4 (2.3)	3 (1.8)	3 (1.8)
ESOPHAGITIS	4 (2.3)	4 (2.3)	0	0
ANEMIA	0	0	6 (3.6)	6 (3.6)
THROMBOCYTOPENIA	0	0	7 (4.1)	7 (4.1)

Source: Study 1014 CSR Tables 14.3.1.1.3.2, 14.3.1.1.3.2.1, 14.3.1.1.3.4, and 14.3.1.1.3.4.1.
MedDRA Version 16.1 coding dictionary applied.
Events presented in decreasing order of frequency based on all-causality events for crizotinib.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; n/N=number of patients.
a. Only includes data before crossover to crizotinib for those patients who crossed over to receive crizotinib treatment.

Forty-four (40.4%) crossing over patients had all-causality AEs associated with temporary discontinuation. AEs were considered treatment-related for 35 patients. The most frequently reported all-causality AEs were ALT increased (9 patients, 11%), AST increased (6 patients, 8.3%) and Neutropenia (6 patients, 5.5%). All the reported AEs were considered treatment-related.

Patients who experienced AEs associated with permanent treatment discontinuation were 21 (12.3%) and 24 (14.2%) in the crizotinib and in the chemotherapy arm, respectively. These events were considered treatment-related in 8 (4.7%) patients who received crizotinib and 14 (8.3%) patients in the chemotherapy group before cross-over.

The most frequently reported all-causality and treatment-related AEs by treatment arm are listed in the following table:

Table 44: Treatment-Emergent All-Causality and Treatment-Related AEs associated with Permanent Discontinuation from treatment in ≥1% patients by treatment arm in Study 1014-SA Population

MedDRA Preferred Term or CLUSTERED TERM	Crizotinib (N=171)		Chemotherapy (N=169)[a]	
	All-Causality n (%)	Treatment-Related n (%)	All-Causality n (%)	Treatment-Related n (%)
Disease progression	7 (4.1)	0	1 (0.6)	0
ELEVATED TRANSAMINASES	2 (1.2)	2 (1.2)	1 (0.6)	1 (0.6)
HEPATOTOXICITY	2 (1.2)	2 (1.2)	0	0
INTERSTITIAL LUNG DISEASE	2 (1.2)	2 (1.2)	0	0
Blood creatinine increased	0	0	2 (1.2)	2 (1.2)
Fatigue	0	0	2 (1.2)	1 (0.6)
THROMBOCYTOPENIA	0	0	2 (1.2)	2 (1.2)
PULMONARY EMBOLISM	0	0	2 (1.2)	0
All-causality AEs associated with permanent discontinuation of 1 patient (0.6%) in the crizotinib arm (TRAEs in boldface): Acute respiratory failure, Diabetic ketoacidosis, Intestinal obstruction, **Nausea**, Pleural effusion, Pulmonary sepsis, **RENAL CYST**, Septic shock				
All-causality AEs associated with permanent discontinuation of 1 patient (0.6%) in the chemotherapy arm (treatment-related AEs in boldface): **Abdominal pain**, Arthralgia, **Azotaemia**, Bile duct obstruction, Cardiac arrest, **Cardiotoxicity**, Completed suicide, **Depression**, DYSPNOEA, Haemoptysis, **NEUTROPENIA, Renal failure acute**, **Syncope, Vomiting**				

Source: Study 1014 CSR Tables 14.3.1.1.1.2.1, 14.3.1.1.1.2.1.1, 14.3.1.1.1.2.2, and 14.3.1.1.1.2.2.1.
MedDRA Version 16.1 coding dictionary applied.

Permanent discontinuation due to all-causality AEs was necessary in 17 (15.6%) patients who crossed over from chemotherapy to crizotinib. Disease progression (4 patients, 3.7%), Respiratory failure (3 patients, 2.8%) and elevated transaminases (2 patients, 1.8%) were the most commonly reported AEs leading to treatment discontinuation. The following AEs were considered treatment-related for a total of 6 (5.5%) patients: elevated transaminases (2 patients, 1.8%), cerebral ischemia, hepatotoxicity, dysgeusia, dysphagia and interstitial lung disease (each in 1 patient, 0.9%).

Study 1007

Twenty- nine (16.9%) patients in the crizotinib arm and 16 (9.4%) in the chemotherapy group had all-causality SAEs associated with permanent treatment discontinuation. SAEs leading were considered treatment-related in a total of 8 (4.7%) patients in the crizotinib arm and 8 (4.7%) patients in the chemotherapy group; interstitial lung disease (4 patients, 2.3%) and neutropenia (3 patients, 1.8%) were the only treatment-related SAE associated with discontinuation in ≥1 patient respectively in the crizotinib and chemotherapy arm.

Study 1005

SAEs were associated to permanent discontinuation in 175 (16.5%) patients, and in 32 (3%) patients these events were considered treatment-related, having interstitial lung disease (10 patients, 0.9%) and hepatotoxicity (5 patients, 0.5%) as the most commonly reported.

Study 1001

In the ALK-positive NSCLC RP2D cohort, 20 (13%) patients had all-causality SAEs associated with permanent discontinuation of crizotinib. These events were considered treatment-related in 2 patients (1 with dyspnoea and 1 with interstitial lung disease).

In the Other RP2D cohort, SAEs leading to permanent discontinuation were experienced by 24 (11.8%) patients, including treatment-related SAEs Anaemia and Chest pain each in 1 patient (0.5%).

Study 1013

Two (4.5%) patients had treatment- related SAEs associated with permanent discontinuation (Cerebral infarction and interstitial lung disease, each in 1 patient).

Post marketing experience

Xalkori is approved in more than 70 countries worldwide. Based on submitted PSURs, there are cumulatively around 11,659 patients exposed to crizotinib from marketing experience.

2.5.1. Discussion on clinical safety

This variation application includes safety data from the pivotal study 1014, comparing crizotinib versus standard platinum-based doublet in previously untreated ALK-positive NSCLC patients, together with selected safety data from supportive studies. Safety data have been presented by single study and as ad hoc pooled tables including data from the 1669 ALK-positive advanced NSCLC patients treated with crizotinib across clinical studies (1001, 1005, 1007 and 1014). The SmPC has been updated on the basis of the pooled safety data set.

The most common (>30%) Treatment-Related AEs (TRAEs) were vision disorder, diarrhoea, nausea, vomiting, elevated transaminase, constipation and oedema in the crizotinib arm and nausea, fatigue, vomiting and decreased appetite in the chemotherapy group. As expected, elevated transaminase and neutropenia were the most frequently reported crizotinib Grade 3/4 TRAEs, while in patients

randomized to chemotherapy Grade 3/4 events related to bone marrow toxicity were mainly registered.

Among the most common crizotinib TRAEs, the cluster term abdominal pain (19.3% in the crizotinib arm and 6.5% in the chemotherapy group) is the only one newly reported. In the pooled population of 1669 ALK+ NSCLC patients who received crizotinib across clinical studies, the frequency of abdominal pain ADRs was 20.7%.

Considering the longer duration of study treatment in the crizotinib (47.4 weeks) in comparison to chemotherapy (18 weeks), exposure adjusted incidence rates were calculated for treatment-emergent AEs of special interest. The rate of bradycardia, diarrhoea, dysgeusia, oedema, and vision disorder was statistically higher in patients treated with crizotinib, while for the chemotherapy group the rate was higher for all-causality AEs of constipation, dyspnoea, hypokalaemia, leukopenia, nausea, neuropathy, neutropenia, pulmonary embolism, and vomiting.

A similar rate of patients discontinued treatment in both arms for all-causality AEs (12.3% with crizotinib and 14.2% with chemotherapy), while a higher rate of treatment-related permanent discontinuation was needed in the chemotherapy group (8.3% vs 4.7%).

Almost the same number of deaths occurred in the two arms, mainly due to disease under study (39/44 in the crizotinib arm and 43/46 in the chemotherapy group). One treatment-related death (pneumonitis) occurred in a patient who received crizotinib after cross-over.

No major differences are highlighted in terms of AEs frequency and severity when crizotinib is administered as first line or in patients previously treated, also taking into account events reported in the 109 patients enrolled in study 1014 that after randomization to chemotherapy crossed over to crizotinib.

No new crizotinib safety signal was detectable from study 1014 and from supportive studies. Based on the updated safety data, 3 new cases of drug-induced liver injury (including 2 cases in study 1014) and 2 additional de novo ILD cases (including 1 with fatal outcome in study 1014) have been reported.

2.5.2. Conclusions on clinical safety

Crizotinib safety profile is consistent in terms of frequency and type of events in patients with ALK-positive advanced NSCLC in both pretreated and untreated patients, regardless of line of treatment.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP).

The PRAC considered that Xalkori (crizotinib) RMP version 6.0 (dated 06 November 2014) could be acceptable if the Applicant implements the changes to the document, as described in the PRAC Advice and Assessment Overview dated 12 March 2015.

The CHMP endorsed this advice.

The Applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The PRAC considered that Xalkori (crizotinib) RMP version 6.2 (dated 11 August 2015) is acceptable. The PRAC endorsed PRAC Rapporteur Updated AR (dated 30 September 2015) is attached.

The CHMP endorsed the RMP version 6.2 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Summary of Safety Concerns	
Important identified risks	• Hepatotoxicity • Pneumonitis/Interstitial lung disease • QTc Prolongation • Bradycardia • Vision Disorder • Renal Cyst • Oedema • Leukopenia • Neuropathy • Gastrointestinal perforation*
Important potential risks	• Reproductive Toxicity (including pregnant and lactating women) • Photosensitivity • Malignant melanoma
Missing information	• Patients with severe hepatic impairment • Paediatric patients • Drug interaction with strong CYP3A inhibitors, strong • CYP3A4 inducers, CYP3A4 substrates with narrow • therapeutic indices, or P glycoprotein substrates • Patients undergoing long-term treatment

*Considered as an important identified risk in the EU only

Pharmacovigilance plan

Table of Ongoing and Planned Additional PV Studies / Activities in the Pharmacovigilance Plan

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)
Update of the OS status of Study A8081007 and of the final efficacy and safety data. Category 2	To provide mature overall survival data to confirm the benefit/risk of crizotinib.	Updated safety and overall survival data from Study 1007 to support the efficacy and safety results from the originally submitted report.	Started	31 March 2016
Study A8081014 ECG Assessment/Safety Analysis of events of special interest Phase 3, randomized, open-label study of the efficacy and safety of crizotinib versus pemetrexed/cisplatin or pemetrexed/carboplatin in previously untreated patients with non-squamous carcinoma of the lung harbouring a translocation or inversion event involving the anaplastic lymphoma kinase (*ALK)* gene locus Category 3	To evaluate the effect of crizotinib on the QT interval	QTc prolongation	Enrollment closed	30 June 2016

Table of Ongoing and Planned Additional PV Studies / Activities in the Pharmacovigilance Plan

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)
Study A8081038 A multi-national post-approval database surveillance study is planned. It is a non-interventional, active safety surveillance study using existing health care data sources in Europe to evaluate safety outcomes among lung cancer patients. Existing health care data sources in Denmark, Finland, the Netherlands, Sweden and the United States will be used to evaluate safety outcomes among lung cancer patients receiving crizotinib prescriptions over a 3-year period under real-world conditions. To contextualize the findings, the study will also obtain data among lung cancer patients receiving prescriptions of erlotinib or gefitinib in the same data sources during the study period. Category 3	To estimate the incidence rate and incidence proportion over a 3-year period of observation for hepatotoxicity, pneumonitis/ILD, QTc prolongation related events, bradycardia, visual disorders, renal cysts, oedema, leukopenia, neuropathy, GI perforation, photosensitivity, and malignant melanoma among lung cancer patients receiving crizotinib dispensation.	Hepatotoxicity, Pneumonitis/ ILD, QTc prolongation, Bradycardia, Vision disorder, Renal cysts, Oedema, Leukopenia, Neuropathy, GI perforation, Photosensitivity, Malignant melanoma, Patients with hepatic impairment, Patients with renal impairment, Patients undergoing long-term treatment.	Started	30 June 2018
Study A8081012 A Phase 1 study to evaluate the effect of hepatic impairment on the pharmacokinetics and safety of crizotinib in advanced cancer patients. Category 3	To evaluate the effect of hepatic impairment on the steady state pharmacokinetics and safety of crizotinib in advanced cancer patients.	Patients with hepatic impairment.	Started	30 October 2017
Study A8081001 (Amendment #18 Rifampin substudy) Category 3	Evaluate the effect of rifampin (a strong inducer of CYP3A) on multiple-dose PK of crizotinib in advanced cancer patients.	Drug interaction with CYP3A inducers.	Started	31 December 2015
Study A8081001 (Amendment #20 Itraconazole substudy) Category 3	Evaluate the effect of itraconazole (a strong inhibitor of CYP3A) on multiple-dose PK of crizotinib in advanced cancer patients.	Drug interaction with CYP3A inhibitors.	Planned	31 December 2016

Table of Ongoing and Planned Additional PV Studies / Activities in the Pharmacovigilance Plan

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)
Study A8081049 XALKORI Physician Survey Study Category 3	Evaluate the effectiveness of crizotinib educational materials.	Hepatotoxicity, ILD/ Pneumonitis, QTc prolongation, Bradycardia, Vision disorder, Leukopenia	Started	30 March 2017
Study A8081050 XALKORI Patient Survey Study Category 3	Evaluate the effectiveness of crizotinib educational materials.	Hepatotoxicity, ILD/ Pneumonitis, QTc prolongation, Bradycardia, Vision disorder, Leukopenia	Started	30 March 2017
A retrospective study investigating the creatinine levels and eGFR across studies A8081001, A8081005, A8081007 and A8081014 Category 3	Evaluate effect of crizotinib treatment on createnine level, and eGFR. Assess reversibility of effect on eGFR.	Renal function during crizotinib treatment	Started	07 August 2015

Category 1 studies are imposed activities considered key to the benefit risk of the product.

Category 2 studies are specific obligations

Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Table 45. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risk		
Hepatotoxicity	SmPC Section 4.2, 4.3, 4.4, 4.8	**Educational Materials** The risk of hepatotoxicity is described in the therapeutic management guide and patient information brochure.
Pneumonitis/ Interstitial lung disease	SmPC Sections 4.2, 4.4, 4.8.	**Educational Materials** The risk of Pneumonitis/ILD is described in the therapeutic management guide and patient information brochure.

Table 45. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
QTc prolongation	SmPC Sections 4.2, 4.4, 4.8.	**Educational Materials** The risk of QTc prolongation is described in the therapeutic management guide and patient information brochure.
Bradycardia	SmPC Sections 4.2, 4.4, 4.5, 4.8	**Educational Materials** The risk of bradycardia is described in the therapeutic management guide and patient information brochure.
Vision disorder	SmPC Sections 4.4, 4.7, 4.8	**Educational Materials** The risk of vision disorder is described in the therapeutic management guide and patient information brochure.
Renal cyst	SmPC Section 4.8.	**Educational Materials** The risk of renal cyst is described in the therapeutic management guide and patient information brochure.
Oedema	SmPC Section 4.8.	**Educational Materials** The risk of oedema is described in the therapeutic management guide and patient information brochure.
Leukopenia	SmPC Sections 4.2, 4.4, 4.8.	**Educational Materials** The risk of leukopenia is described in the therapeutic management guide and patient information brochure.
Neuropathy	SmPC Section 4.8.	**Educational Materials** The risk of neuropathy is described in the therapeutic management guide and patient information brochure.
Gastrointestinal perforation	SmPC Section 4.8.	**Educational Materials** The risk of gastrointestinal perforation is described in the therapeutic management guide and patient information brochure.
Important Potential Risks		
Reproductive Toxicity (including pregnant and lactating women)	SmPC Section 4.6, 5.3.	**Educational Materials** The risk to pregnant and breastfeeding women is described in the therapeutic management guide and patient information brochure.

Table 45. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Photosensitivity	SmPC Section 5.3.	None
Malignant Melanoma	None proposed	None
Missing Information		
Patients with severe hepatic impairment	SmPC Section 4.3	None
Paediatric patients	Section 4.2.	None
Drug interaction with strong CYP3A inhibitors, strong CYP3A4 inducers, substrates with narrow therapeutic indices, or P glycoprotein substrates.	Section 4.4	Educational Materials The risk of drug-drug interactions is described in the therapeutic management guide and patient information brochure.
Patients undergoing long-term treatment	None proposed	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the MAH took the opportunity to implement minor editorial and QRD-template related changes in the SmPC, Annex II and Package Leaflet.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

Limited sections of the PL were affected, particularly section 4; some differences in the adverse drug reactions came out on the basis of the pooled safety database including both indications. The posology section remained unchanged. Xalkori continues to be subject to medical prescription and treatment to be initiated and supervised by a physician experienced in the use of anticancer medicinal products. Moreover, the extension of indication does not change the requirements for having the combined PL of 200 mg and 250 mg hard capsules, and no changes were made to the labelling. In conclusion, results from user testing assessed during the initial Marketing Authorization application can be considered applicable to the updated PL.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In the full analysis population of study 1014, the median PFS was 10.9 months for crizotinib and 7.0 months for chemotherapy. The HR comparing crizotinib with chemotherapy was 0.454 (95% CI: 0.346, 0.596), with a p-value of <0.0001 (1-sided, based on a stratified log-rank test). There was also a non-statistically significant improvement in OS in the crizotinib arm (HR: 0.821 [95% CI: 0.536, 1.255]; 1-sided p-value=0.1804). However, after adjusting for treatment and other factors in the model, patients with ECOG PS of 0/1 had a statistically significantly better OS than patients with ECOG PS of 2 (2-sided p-value <0.0001). Median OS was not reached in either arm and only a positive trend in overall survival is observed. These results were anticipated in such a first line setting. The primary OS analysis was also impacted by the high degree of cross-over from chemotherapy to crizotinib.

Crizotinib treatment resulted in a clinically and statistically significant improvement in IRR-assessed PFS as compared with platinum-based chemotherapy in patients with ALK-positive advanced non-squamous NSCLC. These results suggest that Xalkori has shown a relevant effect in the first line setting.

Finally, quality of life results, even statistically significant, should be taken with caution with such an open label study.

Uncertainty in the knowledge about the beneficial effects

Based on study design, no information on PFS of treatments received post-progression (PFS2), including crizotinib, can be provided. Therefore, the potential impact of first line crizotinib on next line therapies cannot be evaluated. However, for patients progressing after first-line crizotinib there are at present therapeutic options which were not available at the time the study was conducted. However OS data are reassuring and no overall detrimental effect is expected.

Risks

Unfavourable effects

The crizotinib safety profile observed in Study 1014 was generally consistent with the known AE profile reported for Studies 1007 1005 and 1001. For patients who received crizotinib after cross-over from chemotherapy, the adverse event profile was consistent with that observed for the previously untreated patients in the crizotinib arm and with that previously observed for the crizotinib arm in Study 1007.

The most common (>30%) Treatment-Related AEs (TRAEs) were vision disorder, diarrhoea, nausea, vomiting, elevated transaminase, constipation and oedema. As expected, elevated transaminase and neutropenia were the most frequently reported crizotinib Grade 3/4 TRAEs.

Among the 109 patients who crossed over from chemotherapy to receive crizotinib, 20 (18.3%) patients had Grade 5 all-causality AEs. The most commonly reported Grade 5 all-causality AE for the cross-over patients was disease progression in 14 (12.8%) patients and respiratory failure in 3 (2.8%) patients.

Uncertainty in the knowledge about the unfavourable effects

The safety data provided by study 1014 is consistent with the already known safety profile of crizotinib.

Benefit/risk balance

Importance of favourable and unfavourable effects

Results from the pivotal study are considered clinically meaningful. Patients treated with crizotinib in first line of NSCLC (adenocarcinoma) have a higher probability of remaining stable without tumour progression than those treated with the traditional chemotherapy (gain of 3.9 months). This positive effect on the PFS was supported by all the sensitivity analyses carried out by the MAH. The investigator's analysis also showed the same trend in this regard. In addition, the subgroups analyses on PFS both by the IRRas the investigators give robustness to the main analysis. Secondary variables point out in the same direction. Most adverse reactions were Grade 1 or 2 in severity. The most common any grade adverse reactions (>25%) across both studies were vision disorder, nausea, diarrhoea, vomiting, oedema, constipation, elevated transaminases, decreased appetite, fatigue, dizziness and neuropathy. The most common Grade 3 or 4 adverse reactions across all studies are increased ALT and neutropenia. The safety of crizotinib is overall manageable in the intended patient population. No major differences are highlighted in terms of AEs frequency and severity when crizotinib is administered as first line or in patients previously treated.

Benefit/risk balance

In the first line setting of ALK+ NSCLC, crizotinib showed a statistically significant 3.9 months improvement of PFS compared to chemotherapy. This benefit in a patient population, for which there is currently no targeted treatment approved outweighs the risks related to gastrointestinal AEs, elevated transaminases and neutropenia.

Discussion on the benefit-risk assessment

Crizotinib treatment resulted in a statistically significant, robust, and clinically meaningful improvement in IRR-assessed PFS as compared with platinum-based chemotherapy in patients with ALK-positive advanced non-squamous NSCLC.

Without PFS2 results, the impact of first line crizotinib on next line therapies remains uncertain. Nevertheless, data from other ALK-inhibitor has shown a clinical benefit for patients previously exposed to crizotinib, and this benefit is likely better than that expected from chemotherapy in last line.

No new crizotinib safety signal has been identified from study 1014 and from supportive studies and the risk profile remains unchanged.

Conclusion

The benefit risk of crizotinib in the first line treatment of adult patients with ALK+ advanced NSCLC patients is considered positive. Moreover, the MAH requested to convert Conditional Marketing Authorisation into full Marketing Authorisation cannot be accepted as the updated OS data from study A8081007 which is the remaining specific obligation has not been provided.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to add first-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) based on the results of the pivotal Study A8081014; a multinational, multicenter, randomized, open-label, Phase 3 study comparing the efficacy and safety of crizotinib to first-line chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin) in patients with previously untreated ALK-positive advanced non-squamous NSCLC, as well as updated safety results from Studies A8081001, A8081005 and A8081007. As a result sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial and QRD-template related changes in the SmPC, Annex II and Package Leaflet. A revised RMP version 6.2 was agreed during the procedure.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.