NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	A cross-sectional study to evaluate the effectiveness of XALKORI Patient Information Brochure among non-small cell lung cancer (NSCLC) patients receiving XALKORI treatment in Europe
Protocol number	A8081050
Protocol version identifier	1.2
Date of last version of protocol	30 March 2015
EU Post Authorisation Study (PAS) register number	ENCEPP/SDPP/7393
Active substance	L01XE16/Crizotinib
Medicinal product	XALKORI®
Product reference	EU/1/12/793/001-004
Procedure number	EMEA/H/C/002489
Marketing Authorisation Holder (MAH)	Pfizer Limited
Joint PASS	No
Research question and objectives	The objective of this study is to evaluate the effectiveness of XALKORI Patient Information Brochure implemented in Europe.
Countries of study	Belgium, Denmark, France, Germany, Italy, the Netherlands, Sweden, Austria, Ireland, and the United Kingdom

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALK	Anaplastic lymphoma kinase
CIOM	the Council for International Organizations of Medical Sciences
CI	Confidence Interval
EMA	European Medicines Agency
EML4	Echinoderm microtubule-associated protein-like 4
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
ISPE	The International Society for Pharmacoepidemiology
NSCLC	Non-small cell lung cancer
NIS	Non-interventional study
PASS	Post-authorization safety study
PIB	Patient information brochure
RMM	Risk minimization measure
SAE	Serious adverse event
SEER	Surveillance, Epidemiology, and End-Results
SmPC	Summary of Product Characteristics
SOP	Standard operating procedures
TMG	Therapeutic management guide

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title and Main Author: A cross-sectional study to evaluate the effectiveness of XALKORI Patient Information Brochure among non-small cell lung cancer (NSCLC) patients receiving XALKORI treatment in Europe, Final Protocol Amendment 2, March 30, 2015. Kui Huang, PhD, MPH, Pfizer Inc.

Rationale and Background: XALKORI® (crizotinib), an orally administered small molecule inhibitor of the anaplastic lymphoma kinase (ALK), has been approved in Europe and other countries outside Europe, for the treatment of patients with previously treated locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC). Pfizer has developed educational materials in Europe, which include a patient information brochure (PIB) and a therapeutic management guide (TMG) to further inform ALK positive NSCLC patients receiving XALKORI treatment and physicians prescribing XALKORI respectively about adverse reactions associated with XALKORI. The PIB includes information on common adverse reactions associated with XALKORI with a focus on vision disorders and QTc prolongation. The PIB also includes information on other important identified risks including hepatotoxicity, bradycardia, and interstitial lung disease (ILD)/pneumonitis. This study (A8081050) is designed to evaluate the effectiveness of the XALKORI PIB among patients receiving XALKORI treatment in Europe. This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the European Medicines Agency (EMA).

Research Question and Objectives: The objective of this study is to evaluate the effectiveness of the XALKORI PIB implemented to mitigate the risks of visual disorders, QTc prolongation, hepatotoxicity, bradycardia, and ILD/pneumonitis in 10 countries in the European Union including Belgium, Denmark, France, Germany, Italy, the Netherlands, Sweden, Austria, Ireland, and the United Kingdom.. The study will assess whether the patients treated with XALKORI received, read, understood, and utilized the XALKORI *PIB*.

Study Design: This is a cross-sectional study.

Population: A non-probability sample (ie, a convenience sample) of patients who have received XALKORI treatment within 90 days prior to taking the survey from September 2014 to September 2016 at major university hospitals or cancer centers in the 10 participating countries including Belgium, Denmark, France, Germany, Italy, the Netherlands, Sweden, Austria, Ireland, and the United Kingdom are considered the survey population for the study.

Variables: Variables to be evaluated in the study consist of the five key risk messages in the XALKORI PIB including vision disorders, QTc prolongation, hepatotoxicity, bradycardia, and ILD/pneumonitis.

Data collection: All data for this study will be collected through self-administered internet or paper surveys that are identically worded.

Study Size: The estimated sample size for the study is 50 patients completing the survey.

Data Analysis: All statistical summaries in this study will be descriptive. The study population will include all patients who are screened and eligible for this study. All variables collected in this study are categorical. Frequencies and percentages, with 95% confidence intervals (CIs) where appropriate, will be presented. Additional exploratory analyses and sensitivity analyses may be conducted.

Milestones: This study began in September 2014 and will end in September 2016. The finial study report is planned to be submitted to the EMA in March 2017.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1.1	4 December 2014	Administrative	1. PASS information page 2. Section 10.1 3. Appendix 1	1. Added EU PAS registration number 2. Changed the wording on the second bullet point 3. Replaced the draft patient survey questionnaire with the final patient survey questionnaire	1. The study is now registered at EU PAS register 2. The new wording reflects on informed consent practice in participating European countries for a patient survey when an informed consent is needed. 3. The draft survey questionnaire was pretested and the final survey questionnaire incorporated comments from patients who did the pretesting.
1.2	30 March 2015	Substantial amendment	1. PASS information page 2-3. List of abbreviation, Abstraction, Milestone, and Sections 8 and 9.	1. Added 5 more countries to the survey 2. Extended the recruitment period from one year (ie, September 2014-September 2015) to two years (ie, September 2014-September 2016) 3. Changed the date for the final study report from March 2016 to March 2017	1. The survey was initiated in September 2014. The response rate has been low. Adding more countries will add a pool of patients for the survey. 2. The extension of recruitment is necessary to achieve the target number of patients completing the survey because of the low response rate. 3. It is necessary to change the date of the final study report because the recruitment period is extended from one year to two years.

6. MILESTONES

Milestone	Date
Start of data collection	September 30 2014
End of data collection	September 30 2016
Registration in the EU PAS register	September 2 2014
Final study report	March 30, 2017

7. RATIONALE AND BACKGROUND

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 2008, the number of new lung cancer cases worldwide was estimated at 1.61 million, or 12.7% of all new cancers, and the number of lung cancer deaths at 1.38 million, or 18.2% of the total cancer deaths (Ferlay et al, 2010b).[2] In Europe, estimates for the year 2008 were 391,000 new cases of lung cancer and 342,000 deaths (Ferlay et al, 2010a).[1] The majority of lung cancers (85%) is NSCLC (Jamel et al, 2011)[3] and is mainly inoperable locally advanced (Stage IIIB) or metastatic (Stage IV) disease for which no curative treatment is available.

With the evolving understanding of the molecular basis of the disease, agents that target specific pathways, particularly in genetically defined subsets of patients, have become an increasing focus of cancer drug development. One of the newer molecular targets identified in NSCLC is the echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) fusion oncogene. ALK-positive NSCLC constitutes a molecularly defined subgroup with an estimated prevalence of 2.7% of NSCLC (Varella-Garcia, et al, 2010).[5]

XALKORI is a selective small-molecule inhibitor of the ALK receptor tyrosine kinase (RTK) and its oncogenic variants (ie, ALK fusion events and selected ALK mutations). Results from 2 ongoing single-arm clinical studies (Study A8081005 and Study A8081001) showing objective response rates (ORRs) of 51% to 61% with a favorable safety profile supported accelerated marketing approval of XALKORI in the US for the treatment of patients with locally advanced or metastatic NSCLC. XALKORI also received conditional approval in the European Union (EU) in 2012, for the treatment of adults with previously treated ALK-positive advanced NSCLC.

The results of a Phase 3, randomized open-label trial (Study A8081007) comparing XALKORI to standard of care second-line chemotherapy (pemetrexed or docetaxel) among patients with previously treated ALK-positive advanced NSCLC showed that median progression-free survival was 7.7 months for patients randomized to XALKORI, statistically significantly greater than the 3.0 months for patients randomized to chemotherapy: the hazard ratio of XALKORI compared to chemotherapy was 0.487 (95% CI: 0.371, 0.638; $p < 0.0001$). The ORR for 173 XALKORI-treated patients was 65%, which was statistically significantly greater than the ORR of 20% for 174 patients treated with chemotherapy, p-value <0.0001.

A number of safety risks have been associated with XALKORI in Studies A8081001 and A8081005 including hepatotoxicity, ILD/pneumonitis, QT interval prolongation, bradycardia, and vision disorder; each of these risks is listed as an adverse reaction in the XALKORI label or Summary of Product Characteristics (SmPC). XALKORI-related hepatotoxicity has been reported in <1% of patients in XALKORI clinical studies. Across Studies 1007, 1005, and 1001 (N=1259), there have been 7 (0.6%) cases of severe, potentially drug-induced liver injury, 3 of which had a fatal outcome. Severe, life-threatening, or fatal treatment-related ILD/pneumonitis has occurred in <3% of patients

in XALKORI clinical studies. Treatment-related Grade 3 QTc prolongation has occurred in <2% of patients in XALKORI clinical studies without any associated deaths reported. Symptomatic and asymptomatic bradycardia can occur in patients receiving XALKORI. XALKORI has been associated with a consistently mild and generally asymptomatic slowing of the heart rate. In Study 1007 and Study 1005, 11.2% and 10.1% of patients, respectively, had pulse rates of <50 bpm while on XALKORI treatment. Finally, vision disorder was the most common XALKORI-related adverse event (AE) and was reported in 58.7% of patients in the XALKORI arm of Study 1007. The frequency of vision disorder in Study 1005 (53.1%) was similar to that among patients receiving XALKORI treatment in Study 1007. Almost all events were Grade 1 or 2 in severity and had no or minimal impact on daily activities.

Pfizer has developed educational materials in Europe that include a patient information brochure (PIB) and a therapeutic management guide (TMG) to further inform ALK positive NSCLC patients receiving XALKORI treatment and physicians prescribing XALKORI about known risks associated with XALKORI. The PIB includes information on adverse reactions with a focus on vision disorders and QTc prolongation. The PIB also comprises the information on hepatotoxicity, ILD/pneumonitis, and bradycardia. In addition, a patient identification (ID) card is included in the PIB, which instructs patients to fill out the card with their name, their oncologist's name, and start date of XALKORI treatment and to present the card to their other healthcare providers. This study is designed to evaluate the effectiveness of the XALKORI PIB in Europe. This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the European Medicines Agency (EMA).

8. RESEARCH QUESTION AND OBJECTIVES

The overall objective of this study is to evaluate the effectiveness of the XALKORI PIB implemented to mitigate the risks of visual disorders, QTc prolongation, hepatotoxicity, ILD/pneumonitis, and bradycardia in 10 countries in the EU including Belgium, Denmark, France, Germany, Italy, the Netherlands, Sweden, Austria, Ireland, and the United Kingdom.

Specifically, the objectives of the study are to:

- Assess the patients' awareness of the PIB and the patient ID card included in the PIB by estimating the proportion of patients who acknowledge receiving the PIB.
- Evaluate the patient's utilization of the PIB by estimating the proportion of patients who acknowledge reading the PIB and using the patient ID card.
- Assess the patient's knowledge/comprehension of the risks of vision disorders, QTc prolongation, hepatotoxicity, ILD/pneumonitis, and bradycardia by estimating the proportion of patients with correct responses to risk knowledge/comprehension questions.

9. RESEARCH METHODS

9.1. Study Design

This is a cross-sectional study for patients that will collect information on the distribution of the XALKORI PIB, the level of awareness of the key risk messages and the level of knowledge of the key risk messages included in the XALKORI PIB. The study will be conducted in NSCLC patients who receive XALKORI treatment within 90 days prior to taking the survey from September 2014 to September 2016 in 10 countries including Belgium, Denmark, France, Germany, Italy, the Netherlands, Sweden, Austria, Ireland, and the United Kingdom.

9.2. Setting

A random or probability sample is not feasible for this survey given that there is no available database of NSCLC patients who receive XALKORI treatment in Europe. A non-probability sample (ie, a convenience sample) of NSCLC patients who receive XALKORI treatment in participating countries including Belgium, Denmark, France, Germany, Italy, the Netherlands, Sweden, Austria, Ireland, and the United Kingdom will be recruited through their treating oncologists or pulmonologists from September 2014 through September 2016. According to a survey conducted in Europe by European Society for Medical Oncology (ESMO) in 2008,[4] the majority of patients with lung cancer received chemotherapy treatment from medical oncologists and pulmonologists at university hospitals or cancer centers (ESMO, 2008). Given that XALKORI treatment requires ALK testing, it is likely that the vast majority of patients treated with XALKORI receive their care at major university hospitals or cancer centers. Thus, NSCLC patients who receive XALKORI at major university hospitals or cancer centers in 10 countries of Europe are considered the potential survey population for this patient survey. Recruiting oncologists or pulmonologists may or may not be prescribers who participate in XALKORI physician survey.

9.2.1. Inclusion Criteria

Participants of this study must meet all of the following inclusion criteria to be eligible for inclusion in the study:

- Patients must be treated with XALKORI per SmPC at least one dose within 90 days prior to taking the survey.
- Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study if the informed consent is required by local laws and regulations.

The 90-day period is used because it is a reasonable length of time for a patient to be expected to recall the key risk messages, provided that s/he has read the XALKORI PIB.

9.2.2. Exclusion Criteria

Participants meeting any of the following criteria will not be included in the study:

- Participated in the pre-testing of the survey for the study.
- Have immediate family members who have worked for Pfizer, Mapi (the study vendor), or the EMA within the past 10 years.

To determine a participant's eligibility, separate screening questions will be included prior to patients beginning the survey.

9.3. Variables

Variables to be evaluated in the study include the five key risk messages of the XALKORI PIB below:

- **Visual effects (ie, Vision disorders):** You may experience some visual effects. In most cases, these arise within one week after starting treatment and could include: flashes of light, blurred vision, and double vision. Please be especially careful when driving or operating machinery. You may need to stop these activities if you feel that the changes to your vision prevent you from doing these activities safely. Sometimes these changes get better over time. However, if you experience changes that persist, or that seem to get worse over time, you should inform your doctor, who may refer you to an eye doctor for an examination.
- **Light-headedness, fainting, chest discomfort, irregular heartbeat (ie, QTc prolongation)**: Tell your doctor right away if you experience these symptoms which could be signs of changes in the electrical activity (seen on electrocardiogram) or rhythm of the heart. If you have a pre-existing heart condition, your healthcare professional will closely monitor your heart function and may adjust your XALKORI dosage. Your doctor may perform electrocardiograms to check that there are no problems with your heart during treatment with XALKORI.
- **Liver damage (ie, Hepatotoxicity):** Regular blood tests are conducted during therapy with XALKORI. This allows monitoring the function of various organs including the liver. Please inform your doctor immediately: if you feel more tired than usual, your skin and whites of your eyes turn yellow, your urine turns dark or brown (tea colour), you have nausea, vomiting, or decreased appetite, you have pain on the right side of your stomach, you have itching, or if you bruise more easily than usual. These may be signs that your liver is affected by the treatment, and your doctor may perform blood tests to check your liver function. If the results are abnormal, your doctor may decide to reduce the dose of XALKORI or stop your treatment. If you experience any of the above symptoms, contact your doctor immediately, and do not wait for your next clinic visit.

- **Breathing problems (ie, ILD/pneumonitis):** One potential side-effect is a non-infectious inflammation of the lungs. After starting your XALKORI treatment, if you experience any new complaints such as difficulties with breathing, cough, fever, or if any existing conditions get worse, inform your doctor immediately.

- **Reduced heart rate (ie, Bradycardia):** XALKORI may cause reduced heart rate. Your doctor will monitor your heart function and may adjust your XALKORI dosage.

In addition, the study will also collect the information on whether the patients received and read the XALKORI PIB.

9.4. Data Sources

All data for this study will be collected through self-administered internet or paper surveys on local languages. The wording of questions on both modalities is identical. Survey questions primarily consist of yes/no and true/false answers. All questions will evaluate the key risk messages for XALKORI noted above. The detailed questions of the English master version for the survey are described in Appendix 1. The survey is written to follow principles of health literacy and readability. For questions where there is a list of response options, the list of options is randomized for the self-administered internet surveys. The translations will be performed in accordance with current good practice in translation of international survey questions. The English master version is subject to parallel translation into the language of choice by independent translators familiar with survey research. 'Back translation' will be conducted to check validity of the terminology and the translated version will be pretested in the participating country.

Patients will be recruited through their treating oncologists or pulmonologists at university hospitals or cancer centers in 10 participating countries in Europe. Potential treating oncologists or pulmonologists will receive local language recruitment packets from Mapi. The package includes invitation letters for patients, paper copies of surveys, and pre-stamped envelopes. The invitation letter will include a unique code and directions for accessing the survey via the internet. Initial recruitment packages will be sent out to potential treating oncologists or pulmonologists in "batches," beginning with survey launch. The last batch will be sent to treating physicians no later than 8 weeks prior to the end of the study in an attempt to avoid volunteer bias by providing each potential respondent at least 4 weeks to participate. Up to two reminder letters will be sent to oncologists or pulmonologists. The last reminder letters will be sent no later than 4 weeks prior to the end of the study. If the estimated number of 50 completed surveys is met before the end of the study, the study will continue to recruit patients until the end of study.

Treating oncologists or pulmonologists who recruit patients for the study will be compensated for their time according to local laws and regulations. Additionally, patients who complete the survey will be compensated for their time according to local laws and regulations.

9.4.1. Cognitive Pre-testing of the Survey Questionnaire

The survey questionnaire will undergo cognitive pre-testing in a small sample of individuals who meet each study's eligibility criteria. The objective of the pre-test is to identify any survey questions that require clarification or revision based on areas of confusion or miscomprehension revealed by participants in the cognitive pre-test interviews.

Given the low frequency of ALK positive NSCLC, and the need to pre-test the patient survey in multiple languages, it is infeasible to efficiently conduct a live patient focus group to pre-test the patient survey questionnaire. Therefore, patient cognitive pre-testing will be conducted using 1-on-1 interviews. Eight patients (1 in each language) will be recruited and scheduled to participate in qualitative interviews. Eligible patients will be recruited through their treating physicians. Patients who complete the cognitive pre-test will receive a gift card if allowed per the local law and regulations.

During the conduct of the pre-test, the survey questionnaire will be presented item by item, and feedback will be obtained for each question using a pre-developed interviewer guide designed to specifically feedback. The interviewer will also record information regarding any questions received by patients or other observations indicating difficulty with any particular question or wording.

Based on results of the cognitive pre-test, the survey questionnaire will undergo additional revision if necessary.

9.4.2. Screening and Survey Administration

This survey will be administered using two modalities: self-administered using a paper questionnaire or via a secure web-site depending on patient preference for the survey modality. Screening questions will be used to determine patients' eligibility (Appendix 1). Depending on the answers to the screening questions, study participation could either be terminated or continued. If eligible, participants are invited to continue survey participation. It is expected to take approximately 15 minutes to complete the survey. To minimize the likelihood of ineligible patients receiving surveys, their recruiting physicians will be instructed to ascertain eligibility in advance, to the degree possible and in compliance with the local law and regulations.

Patients who agree to participate may elect to complete the survey either on-line or on paper; for those who prefer to complete the survey on-line, the initial invitation will include a url link to the survey and a telephone number to call if additional information is desired. All patient surveys will contain a unique code so that treating physicians can be provided with information on how many of their patients have completed the survey and to facilitate gift card payment processing.

The unique patient identifier that is pre-assigned to each patient survey will be comprised of a part that links to their treating physician, and a part that links to the patient. Treating physicians will be provided with a patient survey recruitment pack that includes these unique identifiers on each survey invitation they distribute. Treating physicians will have to record

the unique identifier for each patient they distribute materials to in the patient medical record (or other mechanism).

When the reminders are sent to treating physicians for their patients, Mapi will not know how many patients each physician invited. Mapi will only be able to provide a list of all patient unique identifiers assigned in each physician's patient survey recruitment pack along with information on which unique identifiers have already completed the survey. The physician will have to refer to their distribution list to see who has not yet returned the survey in order to issue reminders. This will be done to preserve the anonymity of the study respondents from both Mapi and Pfizer.

9.4.3. Paper

The paper survey will be self-administered at a patient's oncologist's office or at home. Patients who complete paper-based surveys will record their eligibility screening questions on paper, and if ineligible, the survey will thank them for their time and direct them to not proceed further. While there are advantages to using an internet based system, it is anticipated a paper format may be preferred for some patients given that study populations are usually older compared to the general population. Patients will place their completed surveys in a pre-stamped envelope, and send it to Mapi and/or give the sealed envelope to their treating oncologists or pulmonologists or their designees who will send it to Mapi. Treating oncologists or pulmonologists will be advised that the ultimate goal of the study is to evaluate the XALKORI PIB. They will be counseled not to alter patient education to influence the study results.

9.4.4. Internet

An internet-based survey system will also be used for conducting this survey. The internet survey will be convenient for participants since they can complete the survey at any time and location during the study period. The online survey will include a secure survey administration module where patients can complete eligibility screening questions, and if eligible, will automatically be routed to complete the actual survey.

9.5. Study Size

The size of the sample is determined based on both practical and statistical considerations taking into account the rarity of ALK positive NSCLCs (2.7% of all NSCLCs) (Varella-Garcia, et al, 2010),[5] life expectancy of the condition (one-year survival of lung cancer is about 45.5%) (SEER, 2009),[6] and the low response rate in cross sectional studies (a typical response rate for a survey ranges from 1% to 15%). It is estimated that the sample size of 50 patients completing the survey is reasonable in 10 participating countries during the two-year study period. Although all efforts will be made to reach the estimate, the actual sample size will also depend on actual use of XALKORI as well as patients' willingness to participate in the survey. Table 1 shows precision and 95% CIs (two-sided) for various combinations of sample size and levels of understanding. For example, assuming 50 patients will complete surveys and a percentage of correct responses to survey questions among these patients is 80%, then the corresponding precision and 95% CI are 11.9% and 66.3%-90.0.1%.

The Confidence Interval for One Proportion with exact (Clopper-Pearson) formula from PASS software (version 2008.0.5) was used for the calculations. If the estimated number of completed surveys is met before the end of the study, the study will continue to recruit patients until the end of study.

Table 1. Precision and 95% Confidence Intervals (Two sided) for Various Combinations of Sample Sizes and Rates of Comprehension

Sample size	Rate of comprehension (%)	Precision (%)	Estimated Confidence Interval (%)
30	50	±18.7	31.3-68.7
30	60	±18.4	40.6-77.3
30	70	±17.4	50.6-85.3
30	80	±15.5	61.4-92.3
50	50	±14.5	35.5-64.5
50	60	±14.2	45.2-73.6
50	70	±13.4	55.4-82.1
50	80	±11.9	66.3-90.0
80	50	±11.4	38.6-61.4
80	60	±11.2	48.4-70.8
80	70	±10.5	58.7-79.7
80	80	±9.3	69.6-88.1
100	50	±10.2	39.8-60.2
100	60	±10.0	49.7-69.7
100	70	±9.4	60.0-78.8
100	80	±8.3	70.8-87.3

9.6. Data Management

Data collected in this study will be stored on a secure server, and will be maintained by a trained cadre of statisticians and data managers ensuring compliance with local or national regulations. SAS software will be used for statistical analyses.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan, which will be dated, filed and maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of key risk messages or their analyses would be reflected in a protocol amendment.

The survey population will include all patients who are screened and eligible for this study. All statistical analyses in this study will be descriptive. Frequencies and percentages, 95% CIs where appropriate, will be presented for categorical variables. Country specific analysis will be presented. Additional exploratory analyses and sensitivity analyses may be conducted.

9.8. Quality Control

Mapi is responsible for following their standard operating procedures (SOPs) as well as Pfizer's SOPs whenever appropriate to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, and description of available data.

9.9. Limitations of the Research Methods

This cross-sectional study is useful in evaluating the effectiveness of the XALKORI PIB by assessing whether patients treated with XALKORI received, read, and understood the material in 10 European countries. This study will provide valuable data on Patients' awareness and knowledge of the XALKORI PIB in the real world setting. Results of the multi-country survey are likely to be more generalizable than those obtained from single or fewer country studies. Given that it is not feasible to have a random sample of patients to participate the study, one limitation is selection bias. One way to minimize bias is to increase the response rate. Therefore, all efforts will be made to recruit patients to participate in this study. Another source of selection bias may be introduced by recruiting physicians. In theory, physicians who are more interested in drug safety in general or learning more information about a product are likely to spend more time educating their patients, give XALKORI PIB to their patients, and invite their patients to complete the survey. Thus, their patients may not be representative of overall patients receiving XALKORI treatment with respect to their knowledge about XALKORI. Another limitation is that the study relies on self-reported data. It is possible that patients may inaccurately report the information because of recall bias and errors in self-observation. To minimize recall bias, a time frame between last dose of XALKORI treatment and completion of the survey (ie, less or equal to 90 days) is used as one of the inclusion criterion.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form, if required, must be in compliance with local regulatory requirements and legal requirements.

If a patient informed consent form is required in the study,

- The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by the IEC and Pfizer.

- Mapi will work with treating physicians to ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. Treating physicians will obtain written informed consent from each patient before any study-specific activity is performed. Treating physicians will retain the original copy of each patient's signed consent form.

10.2. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the sponsor for safety, behavioral, or administrative reasons.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected.

10.3. Independent Ethics Committee (IEC)

It is the responsibility of Mapi to have prospective approval of the study protocol, protocol amendments, and informed consent forms if required, and other relevant documents, (eg, recruitment advertisements), if applicable, from the IEC. All correspondence with the IEC should be retained in Mapi's file. Copies of IEC approvals should be forwarded to Pfizer.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the module VIII (Post-Authorisation Safety Studies) and the module XVI (Risk Minimisation Measures) of the EMA guideline on Good Pharmacovigilance Practices (GVP), *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study does not involve data collection on clinical endpoints on individual patients. However, safety information may be identified during the course of data collection. Any safety information for an individual patient that is volunteered by a study participant (eg, health care professional, lay person) during the course of this research must be reported as described below.

The following safety events must be reported on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form: serious and non-serious AEs when associated with the use of the Pfizer product, and scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure **(all reportable, regardless of whether associated with an AE)**, when associated with the use of a Pfizer product.

Mapi or Mapi's designated third party associate will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training will be provided to Mapi or Mapi's designated third party associate prior to commencement of the study. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Mapi will also provide copies of all signed training certificates to Pfizer.

Study participants will complete the survey on paper or online. The survey questionnaire does not include questions that could potentially identify a safety event, and does provide an opportunity (eg, free text field, blank margins on a paper survey) where study participants could provide information that may constitute a safety event. Further, routine communication with participants via email or phone with Mapi or Mapi's designated third party associate may not be expected during the conduct of the survey. However, it is possible that a study participant may provide information that could constitute a safety event (eg, serious and non-serious AEs and/or scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure) to Mapi or Mapi's designated third party associate while in conversation about the survey for any reason (eg, seeking information about the purpose of the survey). Mapi or Mapi's designated third party associate will be trained to identify safety event information. In the event that a study participant reports a safety event associated with a Pfizer product, Mapi or Mapi's designated third party associate will complete the NIS AEM Report Form and submit to Pfizer within 24 hours of becoming aware of the safety event. Included in the completion of the NIS AEM Report Form is the study participant's contact information as the reporter; complete contact information should be obtained so that, once the NIS AEM Report Form is transferred to Pfizer, the NIS AEM Report Form can be assessed and processed according to Pfizer's standard operating procedures, including requests for follow-up to the study participant.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The final study report will be submitted to the EMA and posted on EU PAS register.

13. REFERENCES

1. Ferlay J, Shin HR, Bray F, et al (Ferlay et al, 2010a). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 20120; 127(12):2893-917.

2. Ferlay J, Parkin DM, Steliarova-Foucher E (Ferlay et al, 2010b) . Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer. 2010; 46(4):765-81.

3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: a cancer journal for clinicians 2011;61(2):69-90.

4. ESMO 2008. http://www.esmo.org/content/download/8358/170037/file/2008-ESMO-MOSES-PhaseIII.pdf

5. Varella-Garcia M, Cho Y, Lu X, et al. ALK gene rearrangements in unselected caucasians with non-small cell lung carcinoma (NSCLC). J Clin Oncol (Meeting Abstracts) 2010; 28 (15 suppl (May 20 Supplement)):10533. .

6. SEER, 2009. http://seer.cancer.gov/csr/1975_2010/results_merged/sect_15_lung_bronchus.pdf

14. LIST OF TABLES

Table 1. Precision and 95% Confidence Intervals (Two sided) for Various Combinations of Sample Sizes and Rates of Comprehension 18

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Appendix 1	December 4 , 2014	Final Patient Survey Questionnaire

Appendix 1. Final Patient Survey Questionnaire

The purpose of the study is to assess patients' awareness and understanding of risks associated with XALKORI treatment. The entire survey should take approximately 15 minutes to complete. Your responses will be kept completely confidential and will not be shared with your doctor or other health care professionals. Please answer the following questions to confirm that you are eligible for this study.

[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1. Do you agree to take part in this survey about XALKORI®?
   - ○ Yes
   - ○ No **[TERMINATE]**

Please complete the remainder of the questionnaire and answer all questions related to your experience as a patient with XALKORI®.

2. Have you been treated with XALKORI® within the past 90 days?
   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

3. Have you ever taken part in a pre-testing survey about XALKORI® before?
   - ○ Yes **[TERMINATE]**
   - ○ No
   - ○ I don't know **[TERMINATE]**

4. Have you or any immediate family member worked for Pfizer Inc., Mapi, or the European Medicines Agency (EMA) within the past 10 years?
   - ○ Yes **[TERMINATE]**
   - ○ No
   - ○ I don't know **[TERMINATE]**

[END INCLUSION/EXCLUSION QUESTIONS]

[PREAMBLE 1]

Please answer the following questions based on information you know about XALKORI®. Please think of the information that you read or that was provided to you by an oncologist, pulmonologist, nurse, or other healthcare professional. If you don't know the answer to any of the following questions please respond "I don't know" instead of guessing the correct response.

1. XALKORI® may cause which of the following side effects? Please answer True, False, or I don't know for each response option.

		True	False	I don't know
A	Breathing problems	○	○	○
B	Abnormalities in liver blood tests	○	○	○
C	Headaches	○	○	○
D	Dizziness, light-headedness, fainting, tiredness	○	○	○
E	Muscle pain	○	○	○
F	Chest discomfort or irregular heartbeat	○	○	○
G	Changes to vision	○	○	○
H	Slow in heart rate	○	○	○
I	Depression	○	○	○

2. Please answer True, False, or I don't know for each of the following statements about XALKORI®.

		True	False	I don't know
A	You may need to stop driving or operating machinery if you feel that the changes to your vision prevent you from doing these activities safely	○	○	○
B	You experience vision changes that persist, or that seem to get worse over time; there is no need to inform your doctor.	○	○	○
C	Your doctor will monitor your heart function and may adjust your XALKORI dosage.	○	○	○

3. For which of the following should you call your doctor right away while taking XALKORI®? Please answer Yes, No, or I don't know for each response option.

		Yes	No	I don't know
A	Light-headedness, chest discomfort, fainting	○	○	○
B	Skin and whites of your eyes turn yellow	○	○	○
C	Urine turns dark or brown (tea color)	○	○	○
D	Nausea, vomiting	○	○	○
E	Difficulties with breathing, cough, fever	○	○	○
F	Itching, or bruised more easily than usual	○	○	○
G	Tingling in fingers and feet	○	○	○

The next set of questions is about the XALKORI® patient educational material (ie, Patient Information Brochure)

- The Patient Information Brochure is a paper handout that contains important information about the risks associated with the use of XALKORI® and how to use it safely.
- The Patient Information Brochure should have provided to you by the doctor or other healthcare provider.

4. Prior to today, were you aware of the XALKORI® Patient Information Brochure?
   - ○ Yes
   - ○ No
   - ○ I don't know
5. Have you ever received a Patient Information Brochure for XALKORI®?
   - ○ Yes
   - ○ No (Go to question 13)
   - ○ I don't know (Go to question 13)
6. Where did you get the Patient Information Brochure? Please select Yes, No, or I don't know for each option.

	Yes	**No**	**I don't know**
The doctor or another healthcare professional in the doctor's office gave me the PIB	○	○	○
Somewhere else; please specify: **[MULTILINE INPUT]**			

7. How much of the Patient Information Brochure did you read?
   - ○ All of it
   - ○ Some of it
   - ○ None of it
   - ○ I don't know
8. How much of Patient Information Brochure did you understand?
   - ○ All of it
   - ○ Some of it
   - ○ None of it
   - ○ I don't know
9. Did someone offer to explain the Patient Information Brochure to you?
   - ○ Yes
   - ○ No (Go to question 13)
   - ○ I don't know (Go to question 13)

10. Who offered to explain Patient Information Brochure to you? Please select Yes, No, or I don't know for each option.

	Yes	No	I don't know
The doctor or another healthcare professional in the doctor's office	○	○	○

Someone else; please specify: **[MULTILINE INPUT]**

11. Did you accept the offer to have the Patient Information Brochure explained to you?
    - ○ Yes
    - ○ No (Go to question 13)
    - ○ I don't know

12. How much of the explanation did you understand?
    - ○ All of it
    - ○ Some of it
    - ○ None of it
    - ○ I don't know

13. Do you know whether there is a card (ie, a patient ID card) in the Patient Information Brochure for XALKORI®?
    - ○ Yes
    - ○ No (Go to question 15)
    - ○ I don't know (Go to question 15)

14. Have you ever used the card by telling your other doctors you are on XALKORI® treatment?
    - ○ Yes
    - ○ No
    - ○ I don't know

[DEMOGRAPHICS AND OTHER INFORMATION PREAMBLE]

There are just a few more questions to help us combine your answers with other answers we have received.

15. When was the last time you were treated with XALKORI®?
    - ○ Within the last month
    - ○ 1 month ago
    - ○ 2 months ago
    - ○ 3 months ago
    - ○ I don't know

16. Are you currently participating in a XALKORI® clinical trial?
    - ○ Yes

- ○ No
- ○ I don't know

17. What is your gender?
    - ○ Male
    - ○ Female
    - ○ Prefer not to answer
18. Which of the following group best describes your age?
    - ○ 18 – 44
    - ○ 45 – 54
    - ○ 55 – 64
    - ○ 65 – 74
    - ○ 75 -84
    - ○ 85 or older
19. What is the highest level of education you have completed?
    - ○ Less than high school
    - ○ Some high school
    - ○ High school graduate
    - ○ Some college/Associate's degree
    - ○ Bachelor's degree
    - ○ Master's degree
    - ○ Professional or Doctoral degree
    - ○ Prefer not to answer

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for 1.1.1 Start of data collection[1]	☒	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (eg, cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☒	☐	
3.3 Does the protocol describe the measure(s) of effect? (eg, relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

[2] Date from which the analytical dataset is completely available.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	
4.2.4 Disease/indication?	☒☐	☐	☒	
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?		☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (eg, operational details for defining and categorising exposure)	☐	☐	☒	
5.2 Does the protocol discuss the validity of exposure measurement? (eg, precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (eg, current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	
6.2 Does the protocol discuss the validity of endpoint measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (eg, collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (eg, collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	
8.1.2 Endpoints? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	
8.1.3 Covariates?	☒	☐	☐	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
8.2.2 Endpoints? (eg, date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
8.2.3 Covariates? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
8.3 Is a coding system described for:				
8.3.1 Diseases? (eg, International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (eg, Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (eg, based on a unique identifier or other)	☒	☐	☐	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	
10.4 Are stratified analyses included?	☒	☐	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	
11.2 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	
11.3 Are methods of quality assurance described?	☒	☐	☐	
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	
12.1.2 Information biases? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (eg, sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.3 Does the protocol address other limitations?	☒	☐	☐	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	

Comments:

Name of the main author of the protocol: Kui Huang, PhD, MPH

Date: / /

Signature:_____

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

Document Approval Record

Document Name:	A8081050_PROTOCOL AMENDMENT 2_Crizotinib Patient Survey_30 March 2015 Clean (with Approval Page)
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Mo, Jingping	07-Apr-2015 15:45:47	Manager Approval
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