NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	A cross-sectional study to evaluate the effectiveness of XALKORI Therapeutic Management Guide among physician prescribing XALKORI in Europe
Protocol number	A8081049
Protocol version identifier	1.0
Date of last version of protocol	25 March 2014
EU Post Authorisation Study (PAS) register number	Study not registered yet
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 Therapeutic Management Guide implemented in Europe.
Countries of study	Belgium, Denmark, France, Germany, Italy, and the Netherlands.
Author	Kui Huang, PhD, MPH Emily Freeman, PhD Pfizer Inc 235 East 42nd Street New York, NY 10017

Marketing Authorisation Holder(s)

Marketing Authorisation Holder(s)	Pfizer Limited Ramsgate Road, Sandwich, Kent CT130NJ United Kingdom
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1. TABLE OF CONTENTS

APPENDICES

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug reaction
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
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
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
ISPE	The International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
NIS	Non-interventional study
NSCLC	Non small cell lung cancer
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

Name, degree(s)	Title	Affiliation	Address
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Country Coordinating Investigators

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4. ABSTRACT

Title and Main Author: A cross-sectional study to evaluate the effectiveness of XALKORI Therapeutic Management Guide among physician prescribing XALKORI in Europe, final, March 25, 2014. 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 (referred to as Prescriber), respectively, about adverse reactions associated with XALKORI. The TMG includes common adverse reactions with XALKORI with a focus on vision disorders and QTc prolongation. The TMG also includes information on other important identified risks including hepatotoxicity, neutropenia and leukopenia, bradycardia, and interstitial lung disease (ILD)/pneumonitis. This study (A8081049) is designed to evaluate the effectiveness of the XALKORI TMG among Prescribers in Europe. This non-interventional study (NIS) 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 TMG implemented to mitigate the risks of visual disorders, QTc prolongation, hepatotoxicity, neutropenia and leukopenia, bradycardia, and (ILD)/pneumonitis in 6 countries in the European Union including Belgium, Denmark, France, Germany, Italy, and the Netherlands. The study will assess whether the Prescribers received, read, understood, and utilized the XALKORI TMG.

Study Design: This is a cross-sectional study.

Population: A non-probability sample (ie, convenience sample) of medical oncologists or pulmonologists that have prescribed XALKORI within 12 months prior to taking the survey from September 2014 to September 2015 at major university hospitals or cancer centers in 6 participating countries including Belgium, Denmark, France, Germany, Italy, and the Netherlands in the European Union are considered the potential study population for the survey.

Variables: Variables to be evaluated in the study include six key risk messages in the XALKORI TMG for vision disorders, QTc prolongation, hepatotoxicity, Neutropenia and Leukopenia, bradycardia, and ILD/pneumonitis.

Data collection: All data for this study will be collected through self-administered internet surveys.

Study Size: The target sample size for the study is 150 Prescribers completing the survey.

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

Milestones: This study is projected to begin in September 2014 and end in September 2015. The final study report is planned to be submitted to the EMA in March 2016.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
None					

6. MILESTONES

Milestone	Planned date
Start of data collection	September 2014
End of data collection	September 2015
Registration in the EU PAS register	By September 2014
Final study report	March 2016

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, 2010a). In Europe, estimates for the year 2008 were 391,000 new cases of lung cancer and 342,000 deaths (Ferlay et al, 2010b). The majority of lung cancers (85%) is NSCLC (Jemal et al, 2011) 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).

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 8081001) 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, pneumonitis/interstitial lung disease (ILD), QT interval prolongation, bradycardia, neutropenia and leukopenia, 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 treatment. Additionally, neutropenia and leukopenia were common among XALKORI-treated patients in both Studies 1007 and 1005. 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 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 (referred to as Prescriber), respectively, about adverse events associated with XALKORI. The TMG includes information on adverse reactions with XALKORI with a focus on vision disorders and QTc prolongation. The TMG also comprises information on hepatotoxicity, neutropenia and leukopenia, bradycardia, and ILD/pneumonitis. This study is designed to evaluate the effectiveness of the XALKORI TMG among Prescribers in Europe. Given that the PIB is distributed to patients through Prescribers, the study will also assess whether Prescribers give out the PIB to their patients. 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 TMG and PIB implemented to mitigate the risks of visual disorders, QTc prolongation, bradycardia hepatotoxicity, neutropenia and leukopenia, and ILD/pneumonitis in 6 countries including Belgium, Denmark, France, Germany, Italy, and the Netherlands in the European Union (EU).

Specifically, the objectives of the study are to:

- Assess the awareness of the XALKORI PIB and TMG by estimating the proportion of Prescribers who acknowledge receiving the tools.
- Evaluate Prescribers' utilization of the XALKORI PIB and TMG by estimating the proportion of Prescribers who acknowledge reading and utilizing the tools.
- Assess Prescribers' knowledge/comprehension of the risks listed on the XALKORI TMG by estimating the proportion of Prescribers who provide correct responses to risk knowledge/comprehension questions.

- Evaluate whether Prescribers' behavior/practices with respect to minimizing the risks of visual disturbances, QTc prolongation, hepatotoxicity, bradycardia, neutropenia and leukopenia, and ILD/pneumonitis are in accordance with the SmPC and the XALKORI TMG. This will be evaluated by estimating the proportion of Prescribers whose responses to the behavior/practice-related vignettes are consistent with the SmPC and the XALKORI TMG.

9. RESEARCH METHODS

9.1. Study Design

This is a cross-sectional study among XALKORI Prescribers that will collect information on the distribution of the XALKORI TMG, the level of awareness of key risk messages and the level of knowledge of key risk messages in the XALKORI TMG. The study will be conducted among physicians who have prescribed XALKORI at least once 12 months prior to taking the survey from September 2014 to September 2015 in 6 countries in the EU including Belgium, Denmark, France, Germany, Italy, and the Netherlands.

9.2. Setting

A random or probability sample is not feasible for this survey given that there is no available database of physicians who prescribe XALKORI in Europe. A non-probability sample (ie, convenience sample) of physicians who prescribe XALKORI in 6 participating countries including Belgium, Denmark, France, Germany, Italy, and the Netherlands will be recruited from September 2014 through September 2015. A database including a mailing list of oncologists in these 6 participating countries is going to be used in this study. According to a survey conducted in Europe by the European Society for Medical Oncology (ESMO) in 2008, the vast majority of patients with lung cancer received chemotherapy treatment from medical oncologists and pulmonologists at university hospitals or cancer centers (ESMO, 2008). Since XALKORI treatment requires ALK testing, it is likely that Prescribers of XALKORI are medical oncologists and pulmonologists at major university hospitals or cancer centers as well. Thus, these physicians in the 6 participating countries are considered the potential survey population for the Prescriber survey.

9.2.1. Inclusion Criteria

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

- Physicians must have prescribed XALKORI per SmPC at least once within 12 months prior to taking the survey.

The 12 month period is used because it is considered to be a reasonable length of time for Prescribers to be expected to recall the key risk messages, provided that they have read the XALKORI TMG.

9.2.2. Exclusion Criteria

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

- Participated in the cognitive pre-testing of the draft 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, screening questions will be included prior to the Prescribers beginning the survey.

9.3. Variables

Variables to be evaluated in the study include the six key risk messages included in the XALKORI TMG for Prescribers below:

- **Vision disorders:** Ophthalmological evaluation (eg, visual acuity, fundoscopy, and slit lamp examinations) should be considered if visual effects persist or worsen. Patients who experience visual effects should be advised to take special care when driving and using machines. Counsel patients about the risk of vision disorders and inform them of what symptoms to be aware of and the actions to take.

- **QTc prolongation:** The benefits and potential risks of XALKORI should be considered before beginning therapy in patients with pre-existing bradycardia, who have a history of or predisposition for QTc prolongation, who are taking antiarrhythmics or other medicinal products that are known to prolong QT interval and in patients with relevant pre existing cardiac disease, and/or electrolyte disturbances. XALKORI should be administered with caution in these patients and periodic monitoring of electrocardiograms (ECG), electrolytes and renal function is required. ECG and electrolytes (eg, calcium, magnesium, potassium) should be obtained as close as possible prior to the first dose of XALKORI and periodic monitoring with ECGs and electrolytes is recommended, especially at the beginning of treatment in case of vomiting, diarrhoea, dehydration or impaired renal function. Correct electrolytes as necessary. If QTc increases by greater than or equal to 60 msec from baseline but QTc is <500 msec, XALKORI should be withheld and cardiologist advice should be sought. If QTc increases to greater than or equal to 500 msec, cardiologist advice must be immediately sought.

- **Hepatotoxicity:** Transaminases (ALT, AST) and total bilirubin should be monitored every two weeks during the first 2 months of treatment, then once a month and as clinically indicated, with more frequent repeat testing for Grades 2, 3 or 4 elevation. Treatment with XALKORI should be used with caution in patients with mild and moderate hepatic impairment. XALKORI should not be used in patients with severe hepatic impairment. It is important to counsel patients about the risk of hepatotoxicity and inform them of what symptoms and signs to be aware of and actions to take.

- Grade 3 or 4 ALT or AST elevation with Grade ≤1 total bilirubin, withhold until recovery to Grade ≤1 or baseline, then resume at 250 mg once daily and escalate to 200 mg twice daily if clinically tolerated.

- Grade 2, 3, or 4 ALT or AST elevation with concurrent Grade 2, 3, or 4 total bilirubin elevation (in the absence of cholestasis or haemolysis), permanently discontinue XALKORI.

- **Neutropenia and leukopenia:** Complete blood counts including differential white blood cell counts should be monitored as clinically indicated, with more frequent repeat testing if Grade 3 or 4 abnormalities are observed, or if fever or infection occurs.

  - For Grade 3, withhold XALKORI until recovery to Grade ≤2, then resume at the same dose schedule.

  - For Grade 4, withhold XALKORI until recovery to Grade ≤2, then resume at 200 mg twice daily.

- **ILD/pneumonitis:** Patients should be monitored for any pulmonary symptoms indicative of ILD/pneumonitis. XALKORI treatment should be withheld if ILD/pneumonitis is suspected. Physicians should permanently discontinue XALKORI if treatment-related ILD/pneumonitis is diagnosed.

- **Bradycardia**: Avoid using XALKORI in combination with other bradycardic agents (eg, betablockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) to the extent possible, due to the increased risk of symptomatic bradycardia. Monitor heart rate and blood pressure regularly. Dose modification is not required in cases of asymptomatic bradycardia. For management of patients who develop symptomatic bradycardia, see below.

  - Grade 2, 3 Bradycardia: Symptomatic, may be severe and medically significant, medical intervention indicated:

    - Withhold until recovery to Grade ≤1 or to heart rate 60 or above;

    - Evaluate concomitant medications known to cause bradycardia, as well as antihypertensive medications;

    - If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤1 or to heart rate 60 or above;

- If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to Grade ≤1 or to heart rate 60 or above.

- Grade 4 Bradycardia: Life-threatening consequences, urgent intervention indicated:

  - Permanently discontinue if no contributing concomitant medication is identified;

  - If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to Grade ≤1 or to heart rate 60 or above, with frequent monitoring.

In addition, the study will also collect information on whether the Prescribers received the XALKORI PIB and TMG, read the XALKORI TMG, and gave out the XALKORI PIB to patients.

9.4. Data Sources

All data for this study will be collected through self-administrated internet surveys. Survey questions consist of yes/no and multiple-choice answers. The majority of questions will evaluate the key risk messages for XALKORI noted above. The detailed questions for the survey are described in Appendix 1.

Prescribers will be recruited through a list of medical oncologists or pulmonologists generated by a commercial partner. Mapi will send oncologists or pulmonologists in the participating countries an invitation via mail inviting them to participate in the survey.

The invitation letter will include a unique code and directions for accessing the survey via the internet. The unique code on the surveys will be used by Mapi to track who has already completed a survey so that reminders are only sent to those who have not yet completed the survey.

Initial invitation letters will be sent out in "batches," beginning with survey launch. The last batch will be sent 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 non-respondents. The last reminder letters will be sent no later than 4 weeks prior to the end of the study. The reminders serve the purpose to increase response rates by reaching out to physicians who have not yet completed the survey. If the target number of completed surveys is met prior to the end of the study, the study will continue to recruit more Prescribers until the end of the study.

Prescribers who complete the survey will be compensated for their time according to the local law and regulations.

9.4.1. Cognitive Pre-testing of Survey Questionnaire

The survey data collection instrument will undergo cognitive pre-testing in a small sample of physicians who meet the 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. Physician pre-testing of the draft survey questionnaire will be completed through 1-on-1 interviews. Six physicians (1 per country) will be recruited and scheduled to participate in qualitative interviews. Eligible physicians will be oncologists or pulmonologists from universities or cancer treatment centers that have prescribed XALKORI within the last 12 month, and will be recruited from targeted lists. Physicians who complete the cognitive pre-test will be compensated for their time 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 solicit feedback. The interviewer will also record information regarding any questions received by physicians or other observations indicating difficulty with any particular question or wording.

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

9.4.2. Screening and Survey Administration

An internet-based survey system will be used for conducting this study. The internet survey will be convenient for participants since they can complete the survey at any time and location during the study period. The survey will begin with screening questions to determine the participant's eligibility (Appendix 1). Depending on the answers to the screening questions, survey participation could either be terminated or continued. If eligible, participants are invited to continue survey participation. All physicians must complete a question indicating their agreement to use their responses in aggregate to report information to applicable regulatory authorities. Once the administrative details are complete, eligible physicians who wish to proceed will automatically be routed to complete the actual survey. It is expected that completion of the whole survey will take approximately 25 minutes.

9.5. Study Size

The size of the sample was determined based on both practical and statistical considerations given the rarity of ALK positive NSCLCs (ie, 2.7% of all NSCLCs) (Varella-Garcia, et al, 2010). A sample of 150 completed Prescriber surveys is targeted for this study. Although all efforts will be made to reach the target, the actual sample size will depend on actual use of XALKORI as well as physicians' willingness to participate in the survey. Table 1 shows Precision and 95% CIs (two-sided) for various combinations of assumed sample size and levels of understanding. For example, assuming 150 Prescribers will complete surveys and the percentage of correct responses to survey questions among these Prescribers is 80%, then the corresponding precision and 95% CI are 6.4% and 73.6%-86.4%, respectively. The

Confidence Interval for One Proportion with simple asymptotic formula from PASS software (version 2008.0.5) was used for the calculations. If the target number of completed surveys is reached prior to the end of the study, the study will continue to recruit more Prescribers until the end of the study.

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

Sample size	Rate of comprehension (%)	Precision (%)	Estimated 95% Confidence Interval (%)
100	50	±9.8	40.2-59.8
100	60	±9.6	50.4-69.6
100	70	±9.0	61.0-79.0
100	80	±7.9	72.2-87.8
150	50	±8.0	42.0-58.0
150	60	±7.9	52.2-67.8
150	70	±7.4	62.7-77.3
150	80	±6.4	73.6-86.4
200	50	±7.0	43.1-56.9
200	60	±6.8	53.2-66.8
200	70	±6.4	63.7-76.4
200	80	±5.6	74.5-85.5
250	50	±6.2	43.8-56.2
250	60	±6.1	53.9-66.1
250	70	±5.7	64.3-75.7
250	80	±5.0	75.0-85.0

9.6. Data Management

Data collected in this study will be stored at secure servers, and will be maintained by trained 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 physicians who are screened and eligible for this study. All statistical analyses in this study will be descriptive. All variables collected are categorical. Frequencies and percentages, with 95% CIs where appropriate, will be presented. Country specific analyses 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 TMG by assessing whether oncologists and pulmonologists received, read, and understood the XALKORI TMG in 6 countries in the EU. This study will provide valuable data on Prescribers' awareness and knowledge of the material. 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 Prescribers to participate in the study, one limitation is potential selection bias. One way to minimize selection bias is to increase the response rate. Therefore, all efforts will be made to recruit oncologists and pulmonologists to participate in this study. Another limitation is that the study relies on self-reporting. It is possible that Prescribers may inaccurately report the information because of recall bias and errors in self-observation.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Physician Information and Consent

Prescribers will be asked to provide electronic acknowledgement of consent prior to completing the survey. All parties will ensure protection of participant personal data and will not include names on any sponsor forms, reports, publications, or in any other disclosures, except where required by the local laws and regulations.

10.2. Participant Withdrawal

Participants may withdraw from the study at any time at their own request. If the participant 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 other relevant documents, (eg, recruitment advertisements), if applicable, from the IEC. All correspondence with the IEC should be retained in Mapi's study specific 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 *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Outcomes Research Practices issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), and European Medicines Agency (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. There is no mechanism by which information on safety events for an individual patient will be captured by a study participant during the course of data collection; thus reporting of adverse events is not feasible in the data collection process. However, any information on a safety event inadvertently volunteered by a study participant during the course of this research must be reported as described below.

The survey for this study will be completed online via a secure website. The survey does not include questions that could potentially identify a safety event, nor does it provide a free text field where study participants could specify information that may constitute a safety event. Further, routine communication with study participants via email or phone with Mapi or Mapi's designated third party associate is not expected during the conduct of the study. However, it is possible that a study participant may provide information that could constitute a safety event to Mapi or Mapi's designated third party associate while in conversation about the survey for any other reason (eg, seeking information about the purpose of the study). In the event that a study participant in the study reports a safety event associated with the use of the Pfizer product, Mapi or Mapi's designated third party associate will complete a 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, as well as the contact information for the applicable primary healthcare provider; complete contact information should be obtained so that, once the NIS AEM Report Form is transferred to Pfizer, the NIS AEM Report Form will be assessed and processed according to Pfizer's standard operating procedures, including requests for follow-up regarding the safety event to the study participant, or as appropriate, the individual patient's primary healthcare provider.

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 survey. 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. Copies of all signed training certificates must be provided to Pfizer.

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

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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.(85% NSCLC).

4. 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.

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14. LIST OF TABLES

None

LIST OF FIGURES

None

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Appendix 1	March 12, 2014	Physician Survey Questionnaire

Appendix 1. Draft Prescriber Survey Questionnaire

The purpose of this study is to evaluate Prescribers' awareness and understanding of XALKORI additional risk minimization measures .You have been identified as a potential participant for this study because you are a physician who treats ALK positive NSCLC patients. This survey is being administered to approximately 150 physicians across several countries within the European Union (EU). The questionnaire will take approximately 20 minutes to complete.

[BEGIN INCLUSION/EXCLUSION QUESTIONS]

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

2. Have you previously participated in a pre-test of this survey about XALKORI®?
   - ○ Yes **[TERMINATE]**
   - ○ No
   - ○ I don't remember **[TERMINATE]**

3. Have you prescribed XALKORI® at least once within the last 12 months?
   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't remember **[TERMINATE]**

4. Have you or any immediate family member worked for Pfizer Inc., Mapi Group (the study vendor) or the European Medicines Agency (EMA) within the past 10 years?

   ○ Yes **[TERMINATE]**

   ○ No

   ○ I don't know **[TERMINATE]**

[END ELIGIBILITY QUESTIONS]

[PREAMBLE 1]

The next set of questions is about the physician educational materials (ie, the Therapeutic Management Guide and the Patient Informational Brochure) **for XALKORI®.**

5. Prior to today, were you aware of the XALKORI® Therapeutic Management Guide?

   ○ Yes

   ○ No (Go to question 10)

   ○ Not sure

6. Have you received the XALKORI therapeutic management guide?

   ○ Yes

   ○ No (Go to question 10)

   ○ I don't know

7. Have you read the XALKORI Therapeutic Management Guide?

   ○ Yes

   ○ No (go to question 9)

   ○ I don't know (go to question 9)

8. How much of the XALKORI Therapeutic Management Guide did you read?

○ All of it

○ Some of it

○ None of it

○ Not sure

9. How did you receive the XALKORI Therapeutic Management Guide? Please select Yes, No or I don't know for each response option.

	Yes	No	I don't know
Mail	○	○	○
E-mail	○	○	○
Pharmaceutical Representative	○	○	○
Conference	○	○	○

Other, please specify: **[MULTILINE INPUT]**

10. Prior to today, were you aware of the XALKORI® Patient Information Brochure?

○ Yes

○ No (Go to Question 15)

○ Not sure

11. Have you received the XALKORI Patient Information Brochure?

- ○ Yes
- ○ No (Go to question 15)
- ○ I don't know (Go to question 15)

12. Have you given the XALKORI Patient Information Brochure to your patients who receive XALKORI treatment?

- ○ Yes
- ○ No (Go to question 15)
- ○ I don't know (Go to question 15)

13. How often do you give the XALKORI Patient Information Brochure to your patients who receive XALKORI treatment?

- ○ Always
- ○ Sometimes
- ○ Not at all
- ○ Not sure

14. How did you receive the XALKORI Patient Information Brochure? Please select Yes, No or I don't know for each response option.

	Yes	No	I don't know
Mail	○	○	○
E-mail	○	○	○
Pharmaceutical Representative	○	○	○
Conference	○	○	○

Other, please specify: **[MULTILINE INPUT]**

15. Which of the following are known risks associated with treatment with XALKORI®? Please select Yes, No, or I don't know for each of the following response options.

		Yes	No	I don't know
A	Hepatotoxicity	○	○	○
B	ILD/pneumonitis	○	○	○
C	Intestinal perforation	○	○	○
D	QT interval prolongation	○	○	○
E	Visual disorders	○	○	○
F	Cardiomyopathy	○	○	○
F	Neutropenia and leukopenia	○	○	○
G	Bradycardia	○	○	○
H	Asthma	○	○	○

Please select the single best answer for the following questions

16. According to the XALKORI® SmPC or the XALKORI® Therapeutic Management Guide, transaminase elevations among patients treated with XALKORI® can be expect occur predominantly within the first _____ months of treatment:

    a. 6

    b. 4

    c. 3

    d. 2

    e. I don't know

17. According to the XALKORI® SmPC or the XALKORI® Therapeutic Management Guide, patients treated with XALKORI® should be monitored for liver function tests (ALT, AST, and total bilirubin) at least _____ during the first 2 months of treatment.

    a. Once a month

    b. Every 2 weeks

    c. Every week

    d. I don't know

18. A patient has received XALKORI® treatment for 6 weeks and has developed transaminase elevations (Grade 3 ALT with Grade ≤1 total bilirubin). What is the most appropriate management of this reaction according to the XALKORI® SmPC or the XALKORI® Therapeutic Management Guide?

    a. Permanently discontinue XALKORI®

    b. Withhold XALKORI® until recovery to Grade ≤1 or baseline, then resume at 250 mg once daily and escalate to 200 mg twice daily if clinically tolerated

    c. I don't know

19. A patient has been diagnosed with treatment-related pneumonitis after receiving XALKORI® treatment for 5 weeks. What is the most appropriate dose modification of XALKORI® according to the XALKORI® SmPC or the XALKORI® Therapeutic Management Guide?

    a. Permanently discontinue XALKORI®

    b. Continue with regular dosing of XALKORI®

    c. Withhold until symptoms are resolved

    d. I don't know

20. According to the XALKORI® SmPC or the XALKORI® Therapeutic Management Guide, XALKORI® should be administered with caution to patients with all following conditions except:

    a. who have a history of QTc prolongation

    b. who have brain metastasis

    c. who are taking antiarrhythmics

    d. who have a history of bradycardia

    e. I don't know

21. The most appropriate dose modification of XALKORI® for suspected QTc prolongation (Grade 3) according to the XALKORI® SmPC or the XALKORI® Therapeutic Management Guide is:

    a. Permanently discontinue

    b. Withhold until recovery to grade ≤1, check and if necessary correct electrolytes, then resume at 200 mg twice daily

    c. Withhold for 1 weeks then resume regular dosing

    d. I don't know

22. A patient who has received XALKORI® for 3 months has been complaining about blurred vision and photopsia for four weeks and symptoms getting worse, How should the physician proceed with dosing of XALKORI® according to the XALKORI® SmPC or the XALKORI® Therapeutic Management Guide?

    a. Counsel the patient about the risk and actions to take with visual disorders and there is no change in dose of XALKORI®

    b. Send the patient for Ophthalmological evaluation

    c. Permanently discontinue XALKORI®

    d. I don't know

23. According to the XALKORI® SmPC or the XALKORI® XALKORI® Therapeutic Management Guide, a patient's complete blood count including differential white blood cell counts should be monitored how frequently?

    a. Monthly

    b. Weekly

    c. As clinically indicated

    d. I don't know

24. A patient who has received XALKORI® for 4 months has developed Grade 4 bradycardia. How should the physician proceed with dosing of XALKORI® according to the XALKORI® SmPC or the XALKORI® Therapeutic Management Guide?

    a. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to Grade ≤1 or to heart rate 60 or above, with frequent monitoring

    b. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg twice daily upon recovery to Grade ≤1 or to heart rate 60 or above, with frequent monitoring

    c. Permanently discontinue XALKORI®

    d. 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.

25. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

26. Please indicate your practice type (select one response):
    - ○ General community hospital
    - ○ Cancer center
    - ○ Academic teaching hospital
    - ○ Other (please specify): **[MULTILINE INPUT]**

27. Please indicate your specialty (select one response):
    - ○ Medical oncologist
    - ○ Pulmonologist
    - ○ General practitioner
    - ○ Other (please specify): **[MULTILINE INPUT]**

28. In total, how many years have you been a practicing physician?
    - ○ Less than 3 years
    - ○ 3 – 5 years
    - ○ 6 – 10 years
    - ○ 11 – 15 years
    - ○ More than 15 years
    - ○ Prefer not to answer

29. Approximately how many times per month have you prescribe XALKORI® within the last 12 months?
    - ○ 1-2 times
    - ○ 3 – 5 times
    - ○ 5 – 7 times
    - ○ More than 7 times
    - ○ I don't remember

30. When was the last time you prescribed XALKORI®?
    - ○ 0 – <3 months ago
    - ○ 3 – <6 months ago
    - ○ 6 – <8 months ago
    - ○ 8 – <10 months ago
    - ○ 10 – 12 months ago
    - ○ I don't remember

31. Are you currently an investigator for one of XALKORI clinical trials?

- ○ Yes
- ○ No
- ○ I don't know

[CLOSING] (ONLY FOR PHYSICIANS FROM A COUNTRY WHERE COMPENSATION IS ALLOWED BY THE LOCAL LAW AND REGULATIONS).

We would like to send you a gift card within the next few weeks to thank you for your time, but we need your name and address to do so. If you do not provide your name and address, you will not receive the gift card for your time and participation in the survey.

32. Do you agree to give us your name and mailing address so we can send you the gift card?

- ○ Yes
- ○ No

FIRST NAME: _____

LAST NAME: _____

ADDRESS: **[MULTILINE INPUT]**

CITY: _____

STATE/PROVINCE: **[DROP-DOWN LIST INPUT WITH STATES/PROVINCE TABLE]**

COUNTRY: **[DROP-DOWN LIST INPUT WITH COUNTRIES TABLE]**

Post code: _____

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:
A Cross-Sectional Study to Evaluate the Effectiveness of XALKORI Physician Therapuetic Guide among Physcians Perscribing XALKORI Treatment In Europe

Study reference number:
Protocol #: A8081049

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]	☒	☐	☐	8,11
1.1.2 End of data collection[2]	☒	☐	☐	8,11
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	1
1.1.6 Final report of study results.	☒	☐	☐	8,11

Comments:

None

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)	☒	☐	☐	8, 12
2.1.2 The objective(s) of the study?	☒	☐	☐	8, 13
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8, 13
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:

None

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

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

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)	☒	☐	☐	8, 14
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:

None

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	8, 14
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?				
4.2.2 Age and sex?	☒	☐	☐	8, 14
4.2.3 Country of origin?	☐	☐	☒	8, 14
4.2.4 Disease/indication?	☒	☐	☐	8, 14
4.2.5 Co-morbidity?	☒☐	☐	☐	8, 14
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)	☒	☐	☐	8, 14

Comments:

None

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:

This protocol is a physician survey to evaluate the effectiveness of risk minimisation measures.

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?	☒	☐	☐	14, 15
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:

This protocol is a physician survey to evaluate the effectiveness of risk minimisation measures.

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:

None

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.)	☒	☐	☐	17, 18
8.1.2 Endpoints? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	17, 18
8.1.3 Covariates?	☒	☐	☐	17, 18
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.)	☒	☐	☐	18
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)	☒	☐	☐	18

Comments:

None

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	18

Comments:

None

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?	☒	☐	☐	19
10.3 Are descriptive analyses included?	☒	☐	☐	19
10.4 Are stratified analyses included?	☒	☐	☐	19
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

None

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)	☒	☐	☐	20
11.3 Are methods of quality assurance described?	☒	☐	☐	20
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	20
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

For point 11.1, the design of the EDC system is such that respondents must complete each answer before advancing so there should not be missing data.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	20
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)	☐	☐	☒	
12.3 Does the protocol address other limitations?	☒	☐	☐	20

Comments:

None

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	20
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	20

Comments:

None

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?	☒	☐	☐	10

Comments:

None

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)?	☒	☐	☐	21
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	21

Comments:

None

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

Date: 3/25/2014

Signature:_____  _____

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

Document Approval Record

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Mo, Jingping	27-Mar-2014 12:39:07	Manager Approval
Zurlo, Maria Grazia	27-Mar-2014 13:30:53	Final Approval
Reynolds, Robert F	27-Mar-2014 14:34:03	Final Approval