RETROSPECTIVE NON-INTERVENTIONAL, NON-PFIZER PRODUCT STUDY PROTOCOL (NINPP Study)

RETROSPECTIVE EPIDEMIOLOGY STUDY OF ALK REARRANGEMENT IN NON-SMALL CELL LUNG CANCER PATIENTS IN THE MIDDLE EAST & NORTH AFRICA

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1.INTRODUCTION

1.1. Background & Rationale

Lung cancer is the most common cancer worldwide [1]. In 2008, an estimated 1.61 million people worldwide were diagnosed with pulmonary carcinoma, accounting for 13% of total cancer diagnoses [1]. Pulmonary carcinoma can be divided into two major histopathological groups: small-cell lung cancer (SCLC) and non-small-cell lung cancers (NSCLC) [2]. The latter group, NSCLC, comprises around 85% of lung cancers and represents a heterogeneous group of malignancies including adenocarcinoma, squamous cell carcinoma and large-cell carcinoma. In small tissue sample when diagnostic features are not clear, cases may be classified as NSCLC, not otherwise specified (NOS) [2].

Recently, a number of oncogenic drivers of NSCLC have been identified, such as activating mutations in the epidermal growth factor receptor (*EGFR*) gene, and translocations in the anaplastic lymphoma kinase (*ALK*) gene discovered in 2007 [3-5].

The echinoderm microtubule-associated protein-like 4 anaplastic lymphoma kinase (EML4-ALK) fusion gene has been identified as a potent oncogenic driver in non–small-cell lung cancer, in particular adenocarcinoma (ADC), & it represents a novel, promising molecular target for NSCLC treatments. [8] ALK alterations play a significant role in the pathogenesis of NSCLC, where it has been demonstrated to be a potent oncogenic driver, and accordingly, the *ALK* pathway represents a therapeutic target for novel NSCLC treatment [5, 6, 7] This fusion gene results from an inversion within the short arm of chromosome 2 (involving 2p21 and 2p23), which leads to a fusion of the echinoderm microtubule-associated protein-like (*EML4*) gene with the anaplastic lymphoma kinase (*ALK*) gene[8] . This gene translocation activates *ALK* oncogene expression that induces cell transformation *in vitro* and *in vivo* [9].

Treatment decisions by using biomarkers including ALK rearrangements and mutations in the EGFR gene have brought dramatic improvements in response and clinical benefit for NSCLC patients.

In clinical studies, Crizotinib, an oral small-molecule tyrosine kinase inhibitor targeting ALK MET, and ROS1 tyrosine kinases [5,10,11], showed marked antitumor activity in patients with advanced *ALK*-positive NSCLC, with objective response rates of approximately 60% and a median progression-free survival of 8.1 months and 9.7 months, respectively [12, 13]. In a recent comparative open label phase 3 study crizotinib proved superior to standard chemotherapy in patients with previously treated advanced NSCLC with *ALK* rearrangement, with median progression-free survival of 7.7 months in the Crizotinib group versus 3.0 months in the chemotherapy group (P<0.001), & the response rates were 65% with crizotinib, as compared with 20% with chemotherapy (P<0.001). [14]

Therefore, acquiring relevant biomarker information is essential in order to provide targeted and personalized treatment aimed at tumors harboring specific genetic abnormalities. In the era of personalized medicine, diagnostic strategies should be carefully considered in order to provide the necessary information to implement targeted therapy. Biopsy techniques, sample processing, histological diagnosis and biomarker testing should all be optimized. To achieve this goal requires adoption of a multidisciplinary approach in which interactions between the oncologist, molecular biologist, pathologist, pulmonologist, radiologist and/or other specialists are paramount.

Development of robust and reliable laboratory tests for predictive biomarkers is essential to select appropriate patients for targeted therapy. A variety of methods have been adopted for the detection of ALK rearrangement, including fluorescent in situ hybridization (FISH), immunohistochemistry (IHC) and reverse transcriptase polymerase chain reaction (RT-PCR). [8] Currently, FISH analysis is the only FDA approved companion diagnostic test to detect ALK gene rearrangements.. However, the equipment required for FISH analysis is not always readily available in routine diagnostic laboratories. ALK rearrangement frequently involves short intrachromosomal inversion. [8] The resulting subtle changes may be difficult to interpret by FISH analysis, and have led to false-negative results. [15, 16] IHC has been considered an alternative to FISH, which also can detect ALK rearrangements independent of the fusion partners. [8]

In 2008, the highest incidence rates for lung cancer were seen in Central and Eastern Europe [1]. However, developing countries are now experiencing an increasing lung cancer burden [17]. Of note, lung cancer has the highest incidence rate of all cancers in 7 of 14 Arab countries and is the third most common cancer in Africa [1, 18].

Several studies confirmed the presence of EML4-ALK fusion in 2% to 7% of NSCLC patients. [19 - 24] In a meta-analysis of 14 publications, the ALK rearrangement has been observed in 4.84% of cases of NSCLC (1). ALK rearrangements in NSCLC are mainly associated with adenocarcinomas. Patients affected are on average 10–15 years younger than patients lacking an ALK rearrangement and mostly have a history of never having smoked or of former light smoking (≤10 pack-years). ALK rearrangement, EGFR mutation, and KRAS mutation are generally (but not always) found to occur independently of one another and represent distinct molecular subsets [2,4,6]. However, little is known about the prevalence of *EML4-ALK* gene fusion in NSCLC patients in Africa Middle East countries and on their clinic-pathological parameters related to *ALK* fusion.

Immunohistochemical (IHC) analysis of FFPE tissue specimens remains a mainstay of routine pathology practice. The major advantage of this approach is an ability to assay for tumor-specific antigen expression without loss of the cytologic and architectural features that distinguish normal from pathologic tissue (5). Cell Signaling Technologies and Ventana have developed the *"VENTANA anti-ALK (D5F3) Rabbit Monoclonal Primary Antibody" which is intended for laboratory use in the detection of the anaplastic lymphoma kinase (ALK) protein in*

formalin-fixed, paraffin-embedded NSCLC tissue stained with Ventana BenchMark XT, or BenchMark Gx immunohistochemical automated slide stainers. The VENTANA ALK IHC assay is the only CE-marked IVD IHC test indicated as an aid in identifying patients eligible for treatment with XALKORI® (crizotinib).(25)

There is almost complete lack of any epidemiologic data regarding the prevalence of ALK rearrangement in Middle East & North Africa NSCLC patients. Also the clinico-pathologic characteristics for patients with *ALK*-positive NSCLC in this region need to be investigated.

Therefore the current study aims to estimate the prevalence of ALK rearrangement in the Middle East North Africa (MENA) population by using the Ventana ALK-IHC method for *ALK* protein detection in retrospective NSCLC clinical samples, & to evaluate the association of *ALK* rearrangement with clinical and pathological parameters of NSCLC patients in MENA.

2.STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of this retrospective epidemiology study is to conduct a large-scale study to estimate the prevalence of *ALK* rearrangement in a large cohort of approximately 700 retained tissue samples of MENA NSCLC patients. The diagnostic testing of retained clinical tissue samples (tissue block) will be tested by using the Ventana IHC test for *ALK* protein detection.

The secondary objectives are:

- To evaluate the association of *ALK* rearrangement with demographic, clinical and pathological parameters in NSCLC patients with or without ALK rearrangement, if this data is available.

- To assess the concordance between Vysis FISH and Ventana IHC methods for *ALK* rearrangement detection in a subset of tissue samples included.

The study results will provide valuable information to understand the epidemiologic and clinical characteristics of ALK alterations in Africa Middle East NSCLC patients.

2.2. Study Endpoints

2.2.1. Primary Endpoint

To estimate the prevalence of *ALK* rearrangement in the Middle East & North Africa NSCLC patients

2.2.2. Secondary Endpoints

Medical charts will be reviewed to gather data on the secondary endpoints described below if available.

1- To evaluate the association of *ALK* rearrangement with demographic, clinical and pathological parameters in NSCLC patients

2- To assess the concordance between Vysis FISH and Ventana IHC methods for *ALK* rearrangement detection in a subset of tissue samples (200-250) included in 2-3 centers.

A Case Report Form (CRF) will be developed for the study with the above variables defined carefully to standardize data collection.

3. STUDY DESIGN

This is a retrospective, cross-sectional non-interventional epidemiology study to investigate the prevalence of ALK rearrangement in NSCLC patients in Middle East & North Africa. Approximately 700 retained tumor tissue specimens (tissue block) of patients previously diagnosed with NSCLC will be selected & subjected to ALK immune-staining using Ventana anti-ALK (D5F3) Rabbit Monocolonal Primary Antibody combined with OptiView Benchmark System in 6-8 centers in 5-7 countries in the MENA region.

The tissue samples of NSCLC cases will be retrieved from tissue banks of the molecular diagnostic units & pathology departments in these study centers. The histological diagnosis will be confirmed by the pathologists. The retained samples will then be tested by performing the Ventana ALK-IHC to assess the absence or presence of the ALK rearrangement by the *detection of the ALK protein in formalin-fixed, paraffin-embedded NSCLC stored tissue samples* using Ventana anti-ALK (D5F3) Rabbit Monoclonal Primary Antibody (Roche Diagnostics GmbH) *in the selected study centers.*

The results of ALK testing within this study population will then be used to establish the prevalence of ALK rearrangement in MENA NSCLC patients.

The patients' characteristics, demographic, clinical and pathologic parameters will be obtained from their medical records & analyzed to determine any association with the presence of the *EML4-ALK* fusion gene in MENA NSCLC patients.

The samples & data collected will be coded by 'Study Subject ID' to protect patient confidentiality. No identifiable personal data will be stored.

The medical records of included NSCLC patients' tissue samples will be reviewed to obtain the following information if available:

- Age
- Gender (male / female)
- Race
- Nationality
- Occupation
- Medical history of prior lung disease, e.g. TB, COPD, etc.
- Smoking history (never, current, or ex-smoker / Age at starting smoking / Number of cigarettes/day, years of cigarette smoking / If ex-smoker, years since quitting smoking)
- Specimen types (Surgically resected, Biopsy, Unknown)
- Primary cancer diagnosis (Date of cancer diagnosis, duration since diagnosis, & age at diagnosis)
- Date when the first sign/symptom of lung cancer appeared
- Source of tissue sample
- Tumor histologic types (Adenocarcinoma, SCC, LCC, NOS)
- Tumor stages
- Treatment type (Surgery with or without chemotherapy, Chemotherapy and other, Unknown)
- Line of therapy (First-line, ≥ Second-line, Unknown)
- Response to treatment.
- Presence of other biomarkers like EGFR & KRAS (Wild type, Mutant, Unknown)
- Date of disease relapse/recurrence
- Date of death
- Last date of follow-up and vital status
- Cause of death

The assessment of concordance of the results between FISH & IHC will be done in 2-3 centers. Results of FISH testing will be collected & recorded, if the retained tissue samples had been previously tested. If not, the Vysis FISH test will be performed, to assess the concordance between the results obtained using Vysis Break-apart FISH & Ventana IHC testing methods for ALK rearrangement detection.

4. SUBJECT SELECTION

4.1. Inclusion Criteria

Since this is a retrospective epidemiology study, no patients will be enrolled. Tissue samples of non-squamous NSCLC cases less than 5 years old from each of the centers will be selected. Cases will be eligible for inclusion in this study if all of the following criteria are met:

1. Histological confirmation of nonsquamous NSCLC, with any TNM stage.
2. Available and sufficient tissue sample for ALK testing
3. Tissue samples are less than 5 years old
4. Routinely processed formalin-fixed, paraffin-embedded tissue samples only (see exclusion criteria pertaining to tissue samples).
5. Histological sections mounted on glass slides must not be older than 3 months
6. Age > 18 years
7. Any ECOG Performance status
8. Still alive, or death confirmed before inclusion, or is unknown
9. Disease diagnosis and/or treatment in one of the centers, in the last 5 years, assigned to participate in the study;
10. Written informed consent for general investigational testing was previously obtained, or specifically obtained for this retrospective epidemiology study, or having a documented waiver for the Informed consent document use, as required by local regulatory authorities, &/or Research Ethics committee/Institutional Review Board.

4.2. Exclusion Criteria

Cases with any of the following exclusion criteria are not eligible:

1- Tumor tissue samples older than 5 year period or samples not properly stored.
2- Tumor tissue samples fixed by using AFA, B5, Bouin's, 95% ETOH, & alcohol fixatives.
3- Under-fixed tissue samples (i.e. < 6 hrs)
4- Tumor tissue samples that have been subject to any decalcification processes.
5- Recycled paraffin-embedded tissue samples.
6- Cut slides stored longer than 3 months.
7- Insufficient tissue samples with less tumor cells & high amount of necrosis.

5. STUDY TREATMENT AND DURATION (Not Applicable)

This is a study that does not required administration of study drug, placebo, or any study specific therapeutic intervention.

6. STUDY PROCEDURES

No patients will be enrolled or be directly involved. This study involves laboratory testing of retained tissue specimens, of retrospectively diagnosed cases with NSCLC, & reviewing of their medical records and therefore will not require enrollment of subjects for prospective surveillance. Prior to initiation of the study, Pfizer and the study team will be responsible for identifying and selecting sites (hospitals/institutes) suitable for performing the study tests & data collection. Sites will be selected so that they are as representative as possible of the general population within a country. Site selection also will be based on practical factors such as the availability of tissue banks, availability of Benchmark GX or XT system, & on its qualification to perform the Ventana ALK-IHC test.

Retrospectively collected NSCLC formalin-fixed, paraffin-embedded tissue (FFPET) tumor tissue specimens will be identified & retrieved from the tissue banks of the study centers.

Cases which will meet the inclusion/exclusion criteria will be selected for analysis for ALK rearrangements using Ventana ALK-IHC testing method.

Local research ethical approvals will be in place or will be applied for, & appropriate consenting or waiver documentation will be obtained.

Implementation of the ALK IHC procedure and validation on ALK positive slide (known ALK-positive NSCLC case; human appendix tissue; Ventana 2 in 1 control cell lines slide).

Online ALK IHC procedure and interpretation training through Webinar

Ventana ALK-IHC testing method will be performed on the eligible NSCLC formalin-fixed, paraffin-embedded tissue (FFPET) tumor tissue specimens.

The medical records of included NSCLC patients' tissue samples will be reviewed to obtain data on their demographic, clinical and pathologic parameters.

In 2-3 of the study centers, ALK break apart FISH results are either already available or will be done after IHC has been performed, in order to assess the concordance between Vysis FISH and Ventana IHC in this subset of tissue samples.

Clinical & histopathological characteristics of ALK positive cases will be compared to the clinical characteristics of al ALK negative cases.

The CRFs will be used to record all information required by the study for collection of primary endpoint data & for collection of the secondary endpoints. Upon receipt and compilation of the analytic datasets collected from each site, the data analyses described in the analysis plan will be performed. To complete the study, a final study report will be developed.

- **Immunohistochemistry (IHC):**

Routinely processed, formalin-fixed, paraffin-embedded tissues are suitable for IHC testing with VENTANA anti-ALK (D5F3) primary antibody.

VENTANA anti-ALK (D5F3) primary antibody has been developed for use on VENTANA BenchMark XT and BenchMark GX automated slide stainers in combination with Rabbit Monoclonal Negative Control Ig, OptiView DAB IHC Detection Kit, and OptiView Amplification Kit and accessories.

Sections should be cut approximately 4 µm thick and mounted on positively-charged glass slides. Slides should be stained promptly, as antigenicity of cut tissue sections diminishes over time and is compromised within 3 months after cutting. For reading of the slides, the Ventana kit guidance of the manufacturer should be followed. (Please refer to VENTANA anti-ALK (D5F3) Scoring Interpretation Guide and Performance Characteristics using the package insert as a reference).

Scoring Criteria for Determination of ALK status in NSCLC:

Clinical Interpretation	Staining Description
Positive for ALK	Presence of strong granular cytoplasmic staining in tumor cells (any percentage of positive tumor cells). Known staining elements should be excluded, including: • light cytoplasmic stippling in alveolar macrophages, • cells of neural origin (nerve and ganglion cells), • glandular epithelial staining, and • cells within lymphocytic infiltrate.
Negative for ALK	Absence of strong granular cytoplasmic staining in tumor cells.

- **Fluorescent In Situ Hybridization:**

FISH analysis may also be performed on the FFPE tumor tissues using a break apart probe specific to the ALK locus (Vysis LSI ALK Dual Color, break apart rearrangement probe; Abbott Molecular) according to the manufacturer's instruction. In brief, 4-µm-thick sections are deparaffinized, dehydrated, immersed with Vysis pretreatment Solution (Abbott Molecular) at 80°C for 15 minutes, and treated with Protease Solution (Abbott Molecular) at 37°C for 20 minutes. Dual probe hybridization will be performed using the LSI ALK dual-color probe, which hybridizes to the 2p23 locus with Spectrum Orange and Spectrum Green on either side of the ALK gene breakpoint.

ALK FISH will be considered positive when more than 15% of 50 or more analyzed cells showed splitting of the fluorescent probes flanking the ALK locus.

For assay procedure, interpretation & result reporting, & other information, please refer for **Vysis ALK Break Apart FISH Probe Kit document.**

7. DATA ANALYSIS/STATISTICAL METHODS

This study involves the analysis of the test results performed on retrospectively collected NSCLC FFPE tissue specimens stored in tissue banks. The required study data will be collected via retrospective review of subject charts and/or hospital records for subjects' clinical & histo-pathological characteristics. The data analyzed in this study will be documented in a non-interventional statistical analysis plan, which will be developed by the study team and maintained by Pfizer. This document may modify the plans outlined in the protocol; however, any major modifications will be reflected in a protocol amendment.

7.1 Sample Size Considerations

In the event that no sites can provide access to an electronic database of hospital discharge records, a quasi-random sample of records from the combined discharge populations at the selected sites will be selected (as described in Section 2.2.1) and conducted initially as a pilot, no minimum sample will be determined prior to this manual review, but as many charts as possible will be reviewed to maximize precision for the incidence estimates.

Approximately 700 patients will be recruited for the proposed study. Assuming that the expected prevalence is no greater than 10%, a sample size of 700 patients previously

diagnosed with NSCLC permits the estimation of the percent of patients with EML4-ALK fusion to within + or – 2.1% with 95% confidence; ie, the half-width of the 95% confidence interval will be < 2.2%. For example, if the prevalence is 5%, the half-width of the 95% confidence interval is + or – 1.6%.

7.2 Analysis Populations

For the analysis of ALK incidence, the number of incident cases will be collected directly from centers participating in the study

Epidemiology data will be extracted by testing of retained clinical samples by using the Ventana ALK-IHC diagnostic method to assess the absence or presence of the ALK rearrangement by the detection of the ALK protein in formalin-fixed, paraffin-embedded NSCLC stored tissue samples. The results of ALK rearrangement within this study population will then be used to establish the prevalence of ALK rearrangement in MENA NSCLC patients.

The Full Analysis Set (FAS) is defined as all included cases which meet the selection criteria in Section 4.

7.3 Statistical Methods

Analyses will be primarily descriptive in nature. Binary data will be summarized using the percent of subjects with the event and a 95% confidence interval. Continuous data will be reported using n, mean, standard deviation, median, and range; a 95% confidence interval for the mean will also be computed. No interim analyses are planned.

7.4 Primary Analysis

The prevalence of ALK rearrangement is the primary endpoint of the study, and it will be calculated as the 100 x number of cases with ALK rearrangement divided by the total number of cases which met the inclusion & exclusion criteria, and 95% confidence interval will be presented along with the estimated prevalence.

7.5 Secondary Analysis

Univariate comparison between the proportion of subjects with ALK rearrangement within categories of demographic, clinical and pathological parameters, will be summarized using p-values of chi-square tests, odds ratios and 95% confidence intervals (CIs) for the odds-ratios. A multiple regression analysis will be performed using the presence of ALK rearrangement as the dependent variable. Independent variables to be included in the model are the ones above mentioned. A stepwise method will be used for the selection of independent variables. Odds ratios and 95% confidence intervals (CIs) for the odds-ratios will be presented for the variables

selected for the final model.

The concordance between Vysis ALK-FISH and Ventana ALK IHC tests results will be evaluated by assessment of positive, negative and overall percent agreement between tests and associated 95% CIs.

Full details of the planned statistical analyses will be given in a statistical analysis plan.

8. DATA COLLECTION

8.1. Primary Endpoint:

This study involves laboratory testing of retained tissue specimens, of retrospectively diagnosed cases with NSCLC, which meet the inclusion criteria of study. Epidemiology data will be collected by performing the testing on retained clinical samples by using the Ventana ALK-IHC diagnostic method to assess the absence or presence of the ALK rearrangement. The result of each test will be recorded as positive or negative for ALK rearrangement.

The data obtained within this study population will then be used to establish the prevalence of ALK rearrangement in MENA NSCLC patients.

8.2. Secondary Endpoints

The manner in which data will be collected to evaluate the clinic-pathological characteristics associated with of ALK rearrangement will depend on the data availability and technical capabilities of each participating hospital/center. Ideally, the selected hospitals /centers will have an electronic database of the patients and the corresponding stored tissue samples. In this case medical records can be retrospectively analyzed locally to obtain the required information. For centers without electronic database, a manual review of their medical records will be necessary to collect data.

In these 2-3 centers, if Vysis ALK-FISH was previously performed on this tissue sample & its result was reported in the patient's medical record, so this result will be obtained, recorded, & be compared with ALK-IHC test result.

Vysis ALK-FISH test will be performed if not previously done, & its result will be recorded.

8.3. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the principal investigator from the study team will keep records, including any electronic extracts of administrative hospital data, original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator for a period according to local regulations, or as specified in the clinical study agreement, whichever is longer.

9. ADVERSE EVENT REPORTING

Should evidence emerge from study documentation of the occurrence of an adverse reaction due to a Pfizer product, such information must be reported within 24 hours to the local Pfizer Drug Safety Unit.

10. ETHICS

10.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Because this study is a retrospective analysis of preexisting, anonymous, and de- identified data, an informed consent waiver will be sought by an Independent Ethics Committee or Institutional Review Board (IEC/IRB).

Depending on the level of risk and nature of the research, a study may be ruled as exempt from IRB review by an IRB chair or designated IRB member. Studies that are not exempt must be approved either by an IRB chair or designated IRB member (if the study qualifies for expedited review) or by a full IRB committee. Since de-identified, non- interventional patient data will be collected retrospectively for the proposed study, an exemption from the participating IRB committee will be sought. It is the responsibility of the investigator to obtain the study protocol & other relevant documentations, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

10.2. Ethical Conduct of the Study

This 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 such as *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidances, Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines and similar.

10.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In the case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data. Because all data will be de- identified, non-interventional, and retrospective in nature, no personal information on subjects will be collected or transmitted to either the study investigator or to Pfizer.

11. PUBLICATION OF STUDY RESULTS

11.1. Communication of results by Pfizer

This study is a non interventional epidemiology study and as such does not require disclosure as per Pfizer SOP CT28.

11.2. Publications by Investigators

The selected study investigator or contracted research team will provide manuscripts, abstracts, or the full text of any other intended disclosure (e.g., poster presentation invited speaker or guest lecturer presentation) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days. The investigator will, on request, remove any previously undisclosed confidential information (other than the study results themselves) before disclosure. For all publications relating to this study, the investigators will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

11.3. Communication of Issues:

The investigator will inform Pfizer Immediately of any serious breached of this NI study protocol that the investigator becomes aware of.

12. REFERENCES

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