Mesothelioma Early Detection by VOCs

ID: 1432436

NCT04106973

Study Protocol v2.0 of 04/08/2020

Research Application:

A. Type of Study: Human

B. Brief Summary of Proposal:

(1) Project Background: Mesothelioma is a rare, aggressive and treatment-resistant disease and, in the United States, is caused almost exclusively by exposure to asbestos fibers. Although predominantly associated with the pleura of the lung and peritoneum, mesothelioma may also develop in a variety of other locations in which mesothelial tissue exists including pericardium and tunica vaginalis testis. There is often a lengthy latency period of 40-50 years between exposure and disease onset. The median age of diagnosis is 65 years while the median survival time after diagnosis without treatment is 9 months. Symptoms, where present, may be non-specific, which further contributes to delayed diagnosis. Because patients with mesothelioma may be asymptomatic until very late in the course of their disease, they may have very limited therapeutic options available because advanced disease is less amenable to treatment. With interventions, survival is extended only to 12 months. As a result, patient prognosis is poor, and mesothelioma carries with it a high mortality rate. Further compounding this issue is the fact that the incidence of mesothelioma is low (approximately 2 per 100,000 capita) in comparison with other types of cancer and as a result, little research has been conducted on either the early identification or early treatment of disease. The ability to identify the presence of disease at an early stage or increase clinical suspicion for the presence of disease among asbestos exposed individuals, would enable earlier detection and earlier treatment, thus reducing morbidity and mortality. In this study, the volatile organic compound (VOC) profile from subjects with histologically confirmed mesothelioma will be compared against case-matched control subjects with bilateral pleural plaques or bilateral pleural thickening. Putative markers will then be tested against a blinded cohort to test predictive value of the markers.

(2) Project Rationale: This study seeks to identify markers for mesothelioma using a non-invasive technique which samples volatile organic compounds (VOC) in the breath of test subjects (Owlstone Medical Ltd, Cambridge, England). A comparison will be made with an FDA-approved, serum-based assay (Lumipulse Mesomark, Fujirebio Diagnostics Inc., Malvern, PA). Identifying patients who are either predisposed to developing mesothelioma by pleural findings as an indication of asbestos exposure or who may be at an early disease stage, is expected to improve prognosis by limiting disease progression through more effective medical and surgical therapeutics.

(3) Purpose of Study and/or Hypothesis: Individuals with pleural mesothelioma are anticipated to have a different volatile organic compound (VOC) profile in comparison with appropriately matched controls. These specific compounds may have a diagnostic potential which enables the early detection of patients with disease before overt clinical symptoms become manifest. Following the identification of putative

biomarkers, the predictive capability of these markers alone and in concert with a serum-based assay, will be tested.

(4) Anticipated Outcome: We anticipate that one or more VOC markers in breath samples from affected subjects will be identified using the Owlstone Breath Biopsy sampling methodology which will show an association with the presence of pleural mesothelioma in patients. Furthermore, we will evaluate participant's Lumipulse Mesomark serum assay, comparing those results with the VOC profile to discern parameters of efficacy.

(5) Importance/Relevance: Identifying patients who are either likely to develop mesothelioma or who are at an early disease stage, is expected to improve prognosis by limiting disease progression through more effective medical and surgical therapeutics.

C. References and Supporting Data: See accompanying Owlstone's Breath Biopsy® The Complete Guide Second Edition as part of this IRB submission and the two 2004 American Radiology Letters to the Editor consisting of a response to a peer-reviewed article on chest radiograph B-readers and the author's reply.

D. Detailed Plan of Proposed Research: As submitted in the IRB A-1 Research Application document.

E. Specific Objectives or Aims: Specific Aim 1: Identify putative VOC biomarkers in the breath samples of subjects with mesothelioma in comparison with case-matched controls.

Specific Aim 2: Test the predictive capability of VOC biomarkers and serum-based mesothelioma biomarkers both individually and collectively.

F. Experimental Design: This will be a prospective, non-randomized, case-controlled study. In Specific Aim 1, the disease status of the study population will not be blinded to the investigators in order to select disease-specific biomarkers. In Specific Aim 2, the Investigators and the analytics team will be blinded to the presence of disease to determine the predictive value of the markers. Predictive capability will be defined by determining the sensitivity, specificity and positive and negative predictive capability of the selected VOC biomarkers in identifying subjects with mesothelioma. In addition, study subjects will also be tested with an FDA approved, serum-based ELISA assay (Lumipulse, Mesomark, Fujirebio). The predictive capabilities of both tests will be evaluated both individually and collectively.

Phase 1 - Discovery of VOCs associated with the presence of mesothelioma: A total of 200 volunteers - 100 with objective evidence of exposure to asbestos and no evidence of mesothelioma, and 100 with histologically confirmed evidence of mesothelioma - will be recruited into this phase of the study with an expected study duration of up to 24 months. Objective evidence of asbestos exposure for purposes of this study include, but may not be limited to, a history of exposure to asbestos and bilateral pleural plaques or bilateral pleural thickening. Radiographic evidence of exposure will be rendered by an A reading, B reading, or an interpretation of a radiologist board certified by the American College of Radiology.

Phase 2 **-** Validation study to assess the predictive capability, sensitivity and specificity of selected VOCs in identifying subjects with mesothelioma: A total of 100 volunteers - 65 with objective evidence of

asbestos exposure and no evidence of mesothelioma, and 35 with objective evidence of mesothelioma - will be recruited into this phase of the study with an expected duration of up to 12 months. The investigators and testing laboratories will be blinded as to the presence of mesothelioma among the participants.

Phase 2 is contingent on the successful identification of VOCs during the Phase 1 discovery study. If no putative biomarkers are identified in Phase 1 of this study or if the predictive capability proves to be too low, the study will be discontinued.

The following inclusion and exclusion criteria will apply to both Specific Aim 1 and 2 of this study.

Inclusion Criteria

- Male or Female subjects over the age of 18
- Reported prior exposure to asbestos
- Radiologically confirmed bilateral pleural plaques or bilateral pleural thickening, or histologically confirmed mesothelioma

Exclusion Criteria

- Presence of any other malignancies within the past 6 months
- Treatment of any malignancies within the past 6 months
- Unwilling or unable to provide past clinical data
- Unwilling or unable to participate in the breath collection aspect of the study
- Unwilling or unable to provide a blood sample
- Eating, smoking, inhalation of nebulized medication or consuming alcohol within the 2 hours prior to breath and serum collection

The following demographic and clinical information will be collected for both Phase 1 and Phase 2 of this study:

Cardinal Demographic and Clinical Features

- Gender
- Age
- Race/Ethnicity
- Occupations
- Date of first asbestos exposure
- Highest education completed. One year of apprenticeship equals one year of college
- Height
- Weight
- Co-morbidities
- Social Hx (smoking, drinking, recreational drug use)
- Current list of medications, including OTC and “natural” remedies

Case-Matched Controls

Age
- Gender
- Ethnicity
- Co-morbidities
- Presence of benign responses to asbestos exposure (Plaques, pleural thickening, etc.)
- Smoking status

Disease type and severity stratification

- Presence of mesothelioma
- Disease stage classification (IMIG)
- Date of initial mesothelioma diagnosis
- Histologic data
- Radiographic data
- Nature of exposure Acute/chronic exposure
- Presence of benign disease indicators (asbestosis, pleural plaques, thickening of the pleura)

Potential Test confounders

- When did you last smoke
- When did you last drink and what was it
- When did you last eat and what was it
- Time since brushing teeth, or rinsing with anything other than distilled water
- Nebulized inhaled medication less than 2 hours prior to breath collection

G. Data Analysis: Phase 1, which is designed to identify putative VOC markers, will be non-randomized and non-blinded. Statistical analysis will be performed by both the Owlstone and Fujirebio laboratories using their trained biostatisticians. Selected biomarkers will then be used in Phase 2. Study subjects in Phase 2 will be anonymized and the Owlstone and Fujirebio laboratory staff will be blinded with regards to disease presence.

H. Materials and Methods:

(1) Breath sampling masks, collection tubes and the collection apparatus will be provided by Owlstone Medical Ltd (OML) ($300/breath sampling kit for 300 subjects). OML has developed a breath sampling system for the collection of human breath samples that is comprised of two main parts:

1. ReCIVA® Breath Sampler: the breath sample collection unit, and
2. CASPER: the air supply unit.

The intended use of ReCIVA is to collect samples of Volatile Organic Compounds (VOCs) present in exhaled breath for subsequent laboratory analysis. CASPER is used to provide a filtered ambient air supply to the ReCIVA breath sampler.

The Insulators Union considers that use of the OML breath sampling system as part of the study constitutes use of a diagnostic test system in the laboratory research phase of development. The Insulators Union also considers that the OML breath sampling test system meets the requirements for exemption of diagnostic devices from part 812 IDE regulations as set out in part 812.2(c)(3). The OML devices will therefore be deployed as "Research Use Only" (RUO) products for the purposes of the study. A detailed description of the OML breath sampling system, including a risk assessment, can be found in reference OW-019034-RE attached as part of this IRB submission package.

(2) The serum-based assays will be provided free of charge by Fujirebio.

(3) Statistical Analysis: Descriptive statistics from the study population and statistics intended to determine the predictive capability, sensitivity and specificity of the Owlstone Breath Biopsy, will be conducted by Owlstone biostatisticians. Predictive capability, sensitivity and specificity of the Fujirebio Lumipulse Mesomark assay will be conducted by the Fujirebio biostatisticians.

I. Time/Task Summary for study procedures

TIME TASK SUMMARY

STUDY DESIGN/APPROVAL

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PHASE 1 – Determination of VOC markers

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PHASE 2

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26

Months

PHASE 2 – Predictive capability of VOC markers

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27 28 29 30 31 32 33 34 35 36

Months