Division: Development & Medical Affairs Div., GlaxoSmithKline K.K.
Information Type: Clinical Study Protocol

Title: Survey of chronic obstructive pulmonary disease (COPD) morbidity in Japanese people with smoking history who are aged 40 years or older and not diagnosed with COPD

Compound Number: None
Development Phase: Not applicable
Effective Date: January 5 2012
Version: 1.0

Description:
This study has been planned to survey the morbidity of COPD or chronic bronchitis in Japanese people with smoking history who are aged 40 years or older, based on the pulmonary functions on not using a bronchodilator and the past sputum-related symptoms. In this study, it will also be investigated whether the CAT developed as a tool to evaluate the health status in COPD patients can be used as a COPD screening tool.

Subject:
COPD, chronic bronchitis, spirometry, CAT, screening

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## Abbreviation and Definition of Term

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<tr>
<td>CAT</td>
<td>COPD Assessment Test (COPD アセスメントテスト)</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval (信頼区間)</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease (chronic obstructive pulmonary disease)</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form (eCRF)</td>
</tr>
<tr>
<td>FAS</td>
<td>Full Analysis Set (全症例から成る解析対象集団)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced Expiratory Flow in one second (努力性呼気時の 1 秒間の呼出量)</td>
</tr>
<tr>
<td>%FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Percentage of predicted Forced Expiratory Flow in one second (努力性呼気時の 1 秒間の呼出量の予測値に対する割合)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;6&lt;/sub&gt;</td>
<td>Forced Expiratory Flow in 6 seconds (努力性呼気時の 6 秒間の呼出量)</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced Vital Capacity (努力肺活量)</td>
</tr>
<tr>
<td>PPS</td>
<td>Per Protocol Set (プロトコル遵守例から成る解析対象集団)</td>
</tr>
<tr>
<td>UMIN</td>
<td>University hospital Medical Information Network Center (大学病院医療情報ネットワーク)</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization (世界保健機関)</td>
</tr>
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PROTOCOL SUMMARY

Positioning of This Study
In this study, the morbidity of COPD or chronic bronchitis will be surveyed in Japanese people with smoking history who are aged 40 years or older, based on the pulmonary functions on not using a bronchodilator and the past sputum-related symptoms. In addition, it will also be investigated whether the CAT developed as a tool to evaluate the health status in COPD patients can be used as a COPD screening tool.

Objectives

Primary Objective
To survey the morbidity of COPD or chronic bronchitis in the primary care, based on the results of pulmonary function tests and the past sputum-related symptoms.

Secondary Objective
To investigate the usefulness of CAT in screening of COPD by evaluating the “correlation between CAT score and morbidity of COPD” and “correlation between CAT score and morbidity of chronic bronchitis”

Other
To confirm the usefulness of the simple spirometer in COPD screening by comparing the pulmonary function test values between the simple spirometer and the regular spirometer.

Study Design
A multi-center collaborative, non-drug-intervention, pulmonary function survey study.

Endpoints
- \( FEV_1 \)
- \%FEV_1 \)
- \( FEV_6 \)
- \( FEV_1/FEV_6 \)
- COPD Assessment Test (hereinafter referred to as CAT)
- FVC (only in some subjects)
1. Introduction

1.1. Background / History

Chronic obstructive pulmonary disease (COPD) is a pulmonary inflammatory disease caused by long-term inhalation exposure to hazardous substances mainly including cigarette smoke. Airflow obstruction is induced by complex actions of peripheral airway lesion and emphysematous lesion combined at various ratios, and it is progressive. Clinically, COPD is characterized by difficulty in breathing on moving the body and chronic cough and sputum. COPD is classified into chronic bronchitis and emphysema, based on the symptoms and pathomorphological characteristics, but many of the patients have both chronic bronchitis and emphysema concurrently.

According to the epidemiological survey of COPD performed in Japan [Aizawa, 2007], the number of Japanese COPD patients is estimated to exceed 5.3 million. According to the recent demographic statistics, the number of deaths due to COPD in Japan reached 16,293 in 2010, and COPD was the ninth leading cause of death [MHLW, 2010]. The WHO is warning that COPD will be the fifth leading cause of death in the world in 2020 [Lopez, 1998]. It is estimated that the number of deaths will increase also in Japan where the population is aging rapidly. On the other hand, according to the Ministry of Health, Labour and Welfare, the number of patients treated for COPD in 2008 was reported to be 173,000 [MHLW, 2008], suggesting that many of COPD patients are not treated. The discrepancy between the estimated number of patients and the number of treated patients suggests that an extremely large number of COPD patients do not consult a specialist physician.

COPD proceeds along with year-course decreases of pulmonary functions, but the progression can be delayed by cessation of smoking or drug therapy. It is therefore possible to prevent the marked deterioration of pulmonary functions or QOL due to COPD and improve the prognosis of COPD by early and appropriate treatments. It is also pointed out that repetition of acute exacerbation causes progression, and early diagnosis may lead to prevention of COPD exacerbation, especially in the case of chronic bronchitis tending to exacerbate easily [Burgel, 2009; Kim, 2011].

From the above, early discovery of COPD (especially, chronic bronchitis) is considered important. For early discovery of COPD, it is considered useful to perform screening in the primary care estimated to involve many latent patients. It is therefore desired to establish a COPD-screening method which can be easily introduced into the primary care.
1.2. Positioning of This Study

This study has been planned to survey the morbidity of COPD or chronic bronchitis in Japanese people with smoking history who are aged 40 years or older, based on the pulmonary functions on not using a bronchodilator and the past sputum-related symptoms.

This study will be conducted mainly at medium- or small-sized medical institutions not upholding “department of respiratory disease” to clarify the actual status of latent COPD patients in the primary care. In this study, also CAT data will be collected. CAT was developed as a tool to evaluate the health status in COPD patients, but there is a possibility that it can be used for preliminary diagnosis of COPD. Therefore, the usefulness of CAT as a COPD screening tool will be investigated.

2. Objectives

Primary Objective

To survey the morbidity of COPD or chronic bronchitis in the primary care, based on the results of pulmonary function tests and the past sputum-related symptoms

- Definition of COPD: 
  FEV₁/FEV₆ < 73%[Vandevoorde, 2006], %FEV₁ < 80%
- Definition of chronic bronchitis: 
  FEV₁/FEV₆ < 73%, %FEV₁ < 80%, and sputum-related symptoms are noted for at least 3 months in one year. This state continues for at least two consecutive years.

Secondary Objective

To investigate the usefulness of CAT in screening of COPD

Other

To confirm the usefulness of the simple spirometer in COPD screening by comparing the pulmonary function test values between the simple spirometer and the regular spirometer

3. Study Plan

3.1. Study Design

A multi-center collaborative, non-drug-intervention, pulmonary function survey study
4. Subject Selection and Discontinuation Criteria

4.1. Number of Subjects

At least 1,000 subjects who have completed the pulmonary function tests using the simple spirometer (maximum 2,000 subjects)

The subjects will be stratified into the following 4 age layers and enrolled with a composition ratio of 1: 1: 1: 1.

- 40-49 years
- 50-59 years
- 60-69 years
- 70 years or older

In some subjects (subjects at some medical institutions), the pulmonary function tests will be performed using also the regular spirometer. The number of such subjects will be at least 100 (maximum 200) as the number of subjects who have completed the pulmonary function tests. Also in the pulmonary function tests using the regular spirometer, the subjects will be stratified into the above 4 age layers and enrolled with a composition ratio of 1: 1: 1: 1.

4.2. Inclusion Criteria

It is most important to comply with the inclusion criteria specified in the protocol, and any deviation from the inclusion criteria is not allowed from the scientific viewpoint. Only the subjects meeting all of the following conditions will be enrolled in this study.

1) Japanese males and females who are aged 40 years or older at the time of enrolment
2) A smoking history of at least 10 pack-years\(^1\) (regardless of present or former smoker)
3) Experienced respiratory tract infection at least twice in the past two years
   [Note: Cannot be enrolled when applicable to Exclusion Criterion 1) or 2)]
4) Judged as capable of complying with the protocol by the investigator or subinvestigator
5) Capable of giving written consent

\(^1\) 10 pack-years: a state of smoking 20 cigarettes (one pack) a day for 10 years, corresponding to smoking 10 cigarettes (0.5 pack) a day for 20 years and smoking 40 cigarettes (2 packs) a day for 5 years.
4.3. Exclusion Criteria

It is most important to comply with the exclusion criteria specified in the protocol, and any deviation from the exclusion criteria is not allowed from the scientific viewpoint and is not allowed also from the viewpoint of securing the subject safety.

When applicable to any of the following conditions, the subjects concerned will not be enrolled in this study.

1) Having a chronic respiratory disease other than bronchial asthma
   (Example: COPD, bronchiectasia, pulmonary fibrosis, tuberculosis, lung cancer, etc. diagnosed by spirometry, X-ray photography or CT scanning)

2) Experienced an acute respiratory disease within 4 weeks before enrolment into the study

3) Used a bronchodilator within 24 hours before enrolment into the study

4) Judged as inappropriate to participate in this study by the investigator or subinvestigator
4.4. Discontinuation Criteria

1) A case where the subject or his/her proxy consent giver wishes discontinuation
In the cases applicable to 2) to 3) below, the study can be discontinued in the subject concerned at the discretion of the investigator or subinvestigator.

2) A deviation from the protocol has been found.

3) The investigator or subinvestigator has judged it necessary to discontinue the study for any other reason.

5. Subject Registration Method

When a subject is considered to fulfil the study enrolment conditions, the subject concerned will be registered according to the following procedures.

<table>
<thead>
<tr>
<th>1. Subject registration status checking</th>
<th>Confirm that the number of registered subjects has not reached the upper limit on the web site of eCRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Consent obtaining</td>
<td>The investigator or subinvestigator explains the contents of the study to a subject considered to fulfil the study enrolment conditions and obtains written consent from the subject concerned.</td>
</tr>
<tr>
<td></td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>3. Subject registration</td>
<td>Input the birth date and eligibility of the subject into eCRF.</td>
</tr>
<tr>
<td>4. Conduct of survey and tests</td>
<td>Perform the survey and tests specified in the protocol.</td>
</tr>
</tbody>
</table>

6. Evaluations and Procedures in the Study

6.1. Subject Backgrounds

In this study, the following subject backgrounds will be surveyed.

- Age (birth date)
- Gender
- Body height
- Body weight
- Smoking history (present smoker or former smoker)
- Past sputum-related symptoms (whether sputum-related symptoms were noted for at least 3 months in one year and this state continued for at least two consecutive years)
- Present use status of antitussive drug, expectorant drug or bronchodilator
- Presence/absence of complication, diagnosed name thereof
6.2. Symptom Scores

Subject symptoms will be surveyed using CAT (Figure 1). Perform the CAT evaluation before the pulmonary function tests.

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.
6.3. Pulmonary Function Tests

6.3.1. Tests Performed in Entire Subjects

After the completion of CAT, the pulmonary functions will be determined with the simple spirometer “High Checker” after confirming that no bronchodilator has been used within 24 hours before determination of pulmonary functions. For the method to use “High Checker”, see the instruction manual.

Determination items
- FEV<sub>1</sub>
- FEV<sub>6</sub>

Determination procedures
1. Keep the subject at rest before determination.
2. Perform the determination in the sitting position. At the time of determination, perform forced expiration for 6 seconds or more as far as possible.
3. Perform the determination twice or more until reproducible high FEV<sub>6</sub> values (when two high FEV<sub>6</sub> values are compared, the difference is not more than 0.10 L) are obtained. But, when reproducible high values cannot be obtained by the 5<sup>th</sup> determination, the determination can be discontinued in consideration of the subject’s fatigue. When the determination is continued, the maximum determination frequency should be 8 times.
4. When 2 or more reproducible high values are obtained in Procedure 3, adopt the value accompanied by a higher FEV<sub>1</sub> value. When FEV<sub>1</sub> is equal, adopt a higher FEV<sub>6</sub> value.
   When no reproducible high values are obtained in Procedure 3, compare two high FEV<sub>6</sub> values, and adopt the value accompanied by a higher FEV<sub>1</sub> value.

6.3.2. Tests Performed in Some Subjects (Performed at Some Medical Institutions)

After the completion of “6.3.1. Test Performed in Entire Subjects”, the pulmonary function tests using the regular spirometer will be performed in some subjects (at some medical institutions).

This test will be performed from the subject enrolled first at the medical institution concerned in the order of enrollment until reaching the contract number related to these tests. But, when the subject does not give consent to conduct of these tests, these tests can be omitted.
Determination Items
- FEV<sub>1</sub>
- FVC

Determination procedures
5. After the completion of Procedure 3, keep the subject at rest for 15 minutes.
6. Perform the determination in the sitting position. At the time of determination, perform forced expiration for 6 seconds or more as far as possible.
7. Perform the determination twice or more until reproducible high FVC values (when two high FVC values are compared, the difference is not more than 0.10 L) are obtained. But, when reproducible high values cannot be obtained by the 5<sup>th</sup> determination, the determination can be discontinued in consideration of the subject’s fatigue. When the determination is continued, the maximum determination frequency should be 8 times.
8. **When 2 or more reproducible high values are obtained in Procedure 7, adopt the value accompanied by a higher FEV<sub>1</sub> value. When FEV<sub>1</sub> is equal, adopt a higher FVC value.**
   **When no reproducible high values are obtained in Procedure 7, compare two high FVC values, and adopt the value accompanied by a higher FEV<sub>1</sub> value.**

7. Data Management
The subject data will be inputted into the eCRF designated by the sponsor, transmitted electronically to the sponsor and combined with other data in the validated data system. In any cases, initials of subjects will not be collected. The eCRF will be stored by the sponsor.

Data management will be performed according to the data cleaning procedures specified separately for the purpose of securing the data integrity by excluding erroneous data or inconsistent data.

8. Data Analysis and Statistical Discussion
8.1. Data Analysis
8.1.1. Analysis Set
The PPS will be handled as the primary data set.
When the rate of subjects non-compliant with the protocol is more than 5%, the analysis will be performed also in the FAS.
8.1.2. Interim Analysis

No interim analysis will be performed.

8.1.3. Important Factors in Analysis Plan

8.1.3.1. Demographic Characteristics

Summary statistics will be calculated for demographic characteristics. All the items will be analyzed also in each age layer.

8.1.3.2. Pulmonary Function Tests

Predicted FEV\textsubscript{1} value

For calculation of predicted FEV\textsubscript{1} value, the following formula [Lung Physiology Committee, Japanese Respiratory Society, 2001] will be used.

Male: FEV\textsubscript{1} (L) = 0.036 x body height (m) - 0.028 x age - 1.178
Female: FEV\textsubscript{1} (L) = 0.022 x body height (m) - 0.022 x age - 0.005

Simple Spirometer

The mean value and 95%CI thereof will be calculated for FEV\textsubscript{1}, FEV\textsubscript{6}, %FEV\textsubscript{1} and FEV\textsubscript{1}/FEV\textsubscript{6} values in the entire subjects and in each age layer.

Regular Spirometer (date obtained from some subjects)

The mean value and 95%CI thereof will be calculated for FEV\textsubscript{1}, FVC, %FEV\textsubscript{1} and FEV\textsubscript{1}/FVC values in the entire subjects and in each age layer. In addition, the correlation will be evaluated between determination results of the simple spirometer and those of the regular spirometer.

8.1.3.3. Sputum-related Symptoms

For the past symptoms, the rate of subjects with each symptom will be calculated in the entire subjects and in each age layer.

8.1.3.4. Presence of COPD

Summary statistics will be calculated for presence of COPD or chronic bronchitis. COPD and chronic bronchitis will be diagnosed according to the following diagnosis criteria.
8.1.3.5. CAT Score
The mean value and 95%CI thereof will be calculated for CAT scores in the entire subjects and in each age layer. In addition, the similar analysis will be performed for score of each inquiry item.

8.1.3.6. Usefulness of CAT as COPD Screening Tool
The correlation between CAT score and COPD morbidity will be evaluated.

9. Study Management

9.1. Information Disclosure to UMIN
The study information related to the protocol will be disclosed to UMIN before starting the subject enrolment.

9.2. Regulatory and Ethical Considerations Including Consent Obtaining Procedures
Prior to participation in this study, written consent will be obtained from each subject. This study will be conducted in compliance with all the ethical requirements and privacy protection requirements for clinical research, including the following items (not limited to these).

- Review and approval of the protocol and its amendments by the Institutional Review Board or Ethical Committee
- Consent of subject
- Reporting requirements of investigator

9.3. Consent Obtaining

Prior to participation in the study, the investigator or subinvestigator will make sufficient explanations to a person considered appropriate as a subject using the explanation form. At that time, opportunities to ask questions and plenty of time will be given, and written consent signed and dated by the subject will be obtained. The subject may bring home the explanation/consent form and sign at home. The investigator or subinvestigator who has made the explanations and the study collaborator who has made the supplementary explanations will sign and date the consent form. The investigator or subinvestigator will store the signed and dated consent form (and explanation form) by attaching the original to the source records such as the case card (according to storage
method specified at each medical institution, if any) and hand over a copy to the subject or his/her proxy consent giver.

9.4. **Study Conduct Period**
   - February 2012 to August 2012
10. References


