

Clinical Study Protocol				
1. Title and Phase of Study				
Title: Study regarding the clinical efficacy of Synatura® in patients with chronic bronchitis type COPD				
Phase: Interventional, single center, single group, open-label study				
2. Name and Address of Study Site				
Site Name: The Catholic University of Korea Seoul St. Mary's Hospital				
Address: 222, Banpo-daero, Seocho-gu, Seoul, Republic of Korea				
3. Name and Title of Principal Investigator, Subinvestigator and co-investigator				
Role	Name	Affiliation	Title	Contact (Mobile)
Principal Investigator	Chin Kook Rhee	Pulmonology and Allergy	Associate Professor	82-10-2285-9601
4. Name and Title of Clinical Research Pharmacist				
Not applicable: the study drug (Synatura®) is currently approved by Korean Ministry of Food and Drug Safety (MFDS) and prescribed for patients with chronic bronchitis, and this is an open-label study with no placebo.				
5. Name and Address of Sponsor				
Ahngook Pharm(613, Siheung-daero, Yeongdeungpo-gu, Seoul, Republic of Korea)				
6. Background and objectives of Study				
<p>Synatura® is a drug commonly used to suppress cough and sputum in patients with acute upper respiratory tract infection and chronic inflammatory bronchitis. According to the Phase III studies conducted in Korea, the safety and efficacy of Synatura® on antitussive and expectorant effects were confirmed in patients with acute upper respiratory infection and chronic inflammatory bronchitis. However, no studies have been conducted for the effects of Synatura® in patients with COPD. COPD is divided into emphysema type and chronic bronchitis type, while typical clinical symptoms of chronic bronchitis are cough and sputum. Therefore, Synatura®, which is effective for chronic bronchitis, is expected to be effective in patients with chronic bronchitis accompanied by COPD.</p> <p><input type="checkbox"/> Primary Objective: Establish clinical efficacy of Synatura® in patients with chronic bronchitis-type chronic obstructive pulmonary disease</p>				

<p>4) Pregnant women</p> <p>5) Breast-feeding women</p> <p>6) Patients with fructose intolerance</p> <p>Sample size: 30 subjects</p> <p>Rationale:</p> <p>The primary outcome of this study is CAT reduction after taking Synatura®.</p> <p>The margin of error was set at 3 points. Also, the standard deviation of the CAT score is reported to be 7.7 from the previous study (Int J Chron Obstruct Pulmon Dis. 2015;10:1623-1631). Assuming Alpha to be 0.05, beta 0.2, 25.307 subjects will be calculated. Assuming a drop rate of 0.15, 29.773 subjects will be required.</p>
<p>10. Study Period</p>
<p>From approval date of the study to 31 December 2018</p>
<p>11. Clinical Study Methods (including Dose, Treatment Method, Treatment Period and Concomitant Medications)</p>
<p>1) Overview</p> <p>The clinical study on the effect of Synatura® will be conducted in COPD patients with symptoms of chronic bronchitis. The enrolled patients will be prescribed Synatura® following measurement of pre-dose pulmonary functions, quality of life and systemic inflammatory state. Pulmonary functions, quality of life and systemic inflammatory state will be repeatedly measured after taking Synatura® for 3 months, and the changes from pre-dose measurements will be observed.</p> <p>2) Group: Single group</p> <p>3) Study drug: Synatura® 15 mL TID for 3 months</p> <p>Patients will be administered the above drug, and changes from pre-dose measurements will be observed.</p> <p>① Changes from pre-dose measurement in pulmonary functions will be observed (FVC, FEV1, post bronchodilator FVC, FEV1).</p> <p>② Changes from pre-dose scores in quality of life will be observed (COPD assessment test - CAT).</p> <p>③ Changes from pre-dose measurement in systemic inflammatory state will be observed (CRP, fibrinogen, IL-6, TNF-a).</p>

Item	At enrollment	After 3 months
Pulmonary functions	O	O
CAT	O	.O
BSS	O	O
CRP	O	.O
fibrinogen	O	.O
IL-6	O	.O
TNF-a	O	O

4) Prohibited concomitant medications

Xanthine derivatives (aminophylline, theophylline, choline theophyllinate, oxtriphylline), central nervous system stimulants (cocaine, amphetamine, codeine), antitussives and expectorants except for the study drug

5) Cost for procedures

In the case of pulmonary function test performed before and after treatment, it will be prescribed as a non-covered item and the actual cost of the test is paid the subject back.

6) Transportation cost

Patients participating in the study will be paid 50,000 KRW per visit.

7) Cost for study drug

Synatura® will be prescribed for 3 months, and patients will receive the drug at the pharmacy in the study site. The cost for study drug will be paid from the research fund as a non-covered drug.

12. Observation Items/Clinical Test Items, Observation and Test Methods

1) Pulmonary functions - pulmonary function test will be performed before and 3 months after taking Synatura®.

2) Quality of life - CAT score and BSS will be performed before and 3 months after taking Synatura®.

3) Systemic Inflammation - blood samples will be taken before and 3 months after taking Synatura®, then stored and measured by ELISA in the laboratory.

13. Expected Side Effects and Precautions

According to the results of previous phase III studies, nausea, vomiting and dizziness can occur after taking Synatura®. Most of them are mild side effects and severe side effects that require medical interventions are not expected to occur. Currently, Synatura® is approved by the Ministry of Food and Drug Safety in March 2011, and widely used in clinical practice. In the 4-year post-marketing survey conducted in 606 patients for re-examination in Korea, the incidence of adverse events was reported to be 2.64% (16/606 patients, 16 cases) regardless of the causal relationship. No significant adverse events have been reported.

14. Discontinuation/Withdrawal Criteria
If the patient no longer wants to participate in the study
15. Evaluation Criteria, Evaluation Methods and Analysis Methods for Efficacy (Statistical Analysis Method)
The paired t-test will be used to establish the statistical significance of changes pre-dose measurement. 1) Changes from pre-dose measurement in pulmonary functions will be observed (FVC, FEV1, post bronchodilator FVC, FEV1). 2) Changes from pre-dose scores in quality of life will be observed (COPD assessment test - CAT). 3) Changes from pre-dose measurement in systemic inflammatory state will be observed (CRP, fibrinogen, IL-6, TNF-a).
16. Evaluation Criteria, Evaluation Methods and Reporting Methods for Safety (including Side Effects)
Side effects evaluation criteria and evaluation methods - in the investigator's opinion, severity based on CTCAE 4.0, relationship to study drug and actions will be determined. Reporting adverse events Suspected unexpected serious adverse reactions will be reported to IRBs immediately. Suspected unexpected serious adverse reactions will be reported within following timeframe: ① Causes death or be life-threatening: within 7 days ② For other suspected unexpected serious adverse reactions: within 15 days.
17. Agreement on Compensation for Victims
1) For the safe characteristics of Synatura®, which will be administered in this study, it is considered that the risk to a victim is extremely low. 2) Any serious adverse events or unexpected problems should be reported to IRBs immediately (within 24 hours). 3) In case of damage due to participation in the study, study staffs will be notified and patients will be received urgent emergency treatment by staffs from Department of Pulmonology and Allergy. It will also be reimbursed under the responsibility of the principal investigator for all medical problems that arise. 4) Insured for compensation.
18. Care and Treatment Criteria for subjects after the Study
After the end of the study, patients may continue to take Synatura® or discontinue. After the end of the

study, continuation of taking Synatura® will be decided by the investigator based on the patient's symptoms (cough and sputum).

19. Measures to Protect the Safety of Subjects

- 1) Voluntary consent will be obtained from the subject based on sufficient explanation and understanding of the study.
- 2) Personal identification number (resident registration number, case number, name) of the subject will not be collected.
- 3) Extracted information will be safely stored for 5 years to prevent leakage, and discarded completely.
- 4) After extracting the data, the patient ID will be used after substituting with an alternative key. Access to the file will be limited to the person in charge of the study conduct and analysis

20. Other Necessary Details for safe and scientific implementation of Study

In case of damage due to participation in the study, study staffs will be notified and patients will be received urgent emergency treatment by staffs from Department of Pulmonology and Allergy.

Attachments: Informed Consent Form, Case Report Form Two references