

## **Clinical Trial Protocol (brief version)**

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A Multicenter, Randomized, Double-Blind, Parallel,  
Active-controlled, Superiority, Phase III Clinical Trial  
to Evaluate the Efficacy and Safety of  
DW1601 Compared to DW16011 and DW16012  
for Acute Bronchitis

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**Clinical Trial Protocol No. DW1601-301**

**Version 2.4 (11/SEP/2019)**

***CONFIDENTIAL***

**Confidentiality:** All the information contained in this clinical trial protocol are provided for principal investigator, subinvestigators, Institutional Review Board(IRB) and health authorities, and thus cannot be disclosed to the third party without the written consent of the sponsor.

**[Synopsis of clinical trial protocol]**

<b>Title of clinical trial</b>	A multicenter, randomized, double-blind, parallel, active-controlled, superiority, phase III clinical trial to evaluate the efficacy and safety of DW1601 compared to DW16011 and DW16012 for acute bronchitis
<b>Sponsor</b>	Daewon Pharmaceutical Co., Ltd.
<b>Clinical trial duration</b>	About 24 months from the date of IRB's approval
<b>Indication</b>	Cough and sputum caused by acute bronchitis
<b>Investigational product</b>	1) Test drug: DW1601 20 mL 2) Comparator1: DW16011 20 mL 3) Comparator2: DW16012 9 mL 4) Placebo <ul style="list-style-type: none"> <li>- Placebo of DW1601 20 mL</li> <li>- Placebo of DW16011 20 mL</li> <li>- Placebo of DW16012 9 mL</li> </ul>
<b>Number of subjects</b>	204 subjects (aiming for at least 68 subjects per group, including 20% of drop-out rate)
<b>Objective</b>	<u>Primary objective</u> It aims to prove the superiority of DW1601 to DW16011 and DW16012 by evaluating the efficacy through the changes in Bronchitis severity score (BSS) on Day 4 after administration in patients with acute bronchitis.  <u>Secondary objective</u> 1) It aims to comparatively evaluate DW16011(Control group1) and DW16012(Control group2) with respect to the primary efficacy endpoint (changes in BSS on Day 4 after administration) (including statistical significance). 2) It aims to evaluate the safety and efficacy of DW1601 compared to DW16011 and DW16012 in patients with acute bronchitis.
<b>Design</b>	A multicenter, randomized, double-blind, parallel, active-controlled, superiority, phase III clinical trial

	<p>[Figure. Clinical trial diagram]</p>
<b>Method</b>	<p>Subjects judged to meet inclusion/exclusion criteria are randomized either to the testing group (DW1601), control group1(DW16011), or control group2(DW16012) in a 1:1:1 ratio.</p> <p>After the randomization, the investigational product is administered for 7 days. After administration(treatment), subjects visit institutions on Day <math>4 \pm 1</math> (V3) and Day <math>7 \pm 1</math> (V4) to evaluate efficacy and safety. However, if it is confirmed that subject's symptoms completely disappear on Day 4 (V3) after the administration (Total BSS=0)*, the treatment can be discontinued at the discretion of investigator. In the case of discontinuation, safety/efficacy evaluation on the End of Treatment (EOT) visit is conducted.</p> <p>Follow-up visit(V5, F/U) is made via phone call on Day <math>5 (\pm 1)</math> after the EOT to check adverse events.</p> <p>*In this clinical trial, '0(zero)' of Total BSS on V3 is defined as 'complete disappearance of symptoms'.</p>
<b>Inclusion criteria</b>	<p>Subjects should meet all the following criteria:</p> <ol style="list-style-type: none"> <li>1) Men and women aged between 19 and 80</li> <li>2) Acute bronchitis* patients with cough accompanied with sputum within 2 days (48 hours) after the onset of symptom based on randomization visit (Investigators diagnose the disease by referring to the chest X-ray test result and patient's clinical symptoms. And if necessary, bacterial and viral tests may</li> </ol>

	<p>be additionally performed.)</p> <p>3) Subjects who have total bronchitis severity score (BSS) of 5 or higher and sputum score of 1 or higher based on randomization visit)</p> <p>4) Patients who voluntarily consent to the participation in the clinical trial and sign the informed consent</p>
<b>Exclusion criteria</b>	<p>Patients who meet any one of the following conditions cannot participate in the trial:</p> <ol style="list-style-type: none"> <li>1) Severe lung diseases determined by an investigator (e.g.: bronchiectasis, bronchial cancer, interstitial lung disease, pneumonia, active tuberculosis, cystic fibrosis, chronic obstructive pulmonary disease, asthma, chronic bronchitis, pulmonary emphysema, etc.) or clinically significant abnormal findings shown in the chest X-ray examination</li> <li>2) Patients with active infection requiring the administration of systemic antibiotics</li> <li>3) Subjects who have the following diseases: <ul style="list-style-type: none"> <li>- Obstructive sleep apnea syndrome</li> <li>- Hepatic dysfunction (ALT or AST &gt; 3 times the upper limit of normal)</li> <li>- Renal dysfunction (glomerular filtration rate &lt; 30 mL/min)</li> <li>- Uncontrolled diabetes (random plasma glucose <math>\geq</math> 250 mg/dL)</li> <li>- Uncontrolled hypertension (systolic or diastolic blood pressure <math>\geq</math> 160/100 mmHg)</li> <li>- Active peptic ulcer, gastrointestinal bleeding</li> <li>- Significant cardiovascular diseases (NYHA class III/IV heart failure, arteriosclerosis, pulmonary artery hypertension, peripheral artery disease, etc.) according to the judgment of investigator, or QTc interval &gt;450 msec or clinically significant abnormal findings shown in the ECG results</li> <li>- Malignant tumor: However, patients who meet the following conditions can participate in the trial <ol style="list-style-type: none"> <li>(1) At least 5 years have passed since the completion of tumor treatment, or disease-free status</li> <li>(2) At least 1 year has passed since the complete resection of basal cell carcinoma/squamous cell carcinoma, radical resection of papillary thyroid carcinoma or successful treatment of cervical carcinoma in situ</li> </ol> </li> </ul> </li> </ol>

	<ul style="list-style-type: none"> <li>- Blood coagulation disorder</li> <li>- Glaucoma</li> <li>- Lower urinary tract diseases including benign prostatic hyperplasia</li> </ul> <p>4) Subjects who are expected to receive the following drugs during the clinical trial</p> <ul style="list-style-type: none"> <li>- Antibiotics, antiviral agents, systemic/inhaled corticosteroids</li> <li>- ACE inhibitor, ARB (However, patients who are on long-term treatment with ACEI and ARB and who plan to continue administration with the same dosage and regimen during the clinical trial can participate in this trial.)</li> <li>- Mucolytics, expectorants, antitussives, herbal medicines with expectorant and antitussive effects</li> <li>- Antihistamines, <math>\beta_2</math> agonist, anticholinergic agents including bronchodilators, central nervous system stimulants</li> <li>- Coumarin anticoagulants (e.g.: Warfarin etc.)</li> <li>- Symptomatic treatment for other acute bronchitis, analgesics (However, acetaminophen used for antipyretic purposes, at 1.5 g/day and taken 24 hours before the efficacy evaluation visit is allowed)</li> <li>- Sedatives</li> <li>- Phenytoin</li> </ul> <p>5) Subjects who have received MAO inhibitors (antidepressants, antipsychotics, mood stabilizers, antiparkinsonian drugs, etc.) within 2 weeks before the administration of the investigational product or are expected to receive them during the trial</p> <p>6) Heavy smokers(<math>\geq 15</math> cigar/day)</p> <p>7) Subjects with the history of hypersensitivity to the components of investigational products and similar class</p> <p>8) Patients with fructose intolerance</p> <p>9) Pregnant/lactating women and women of childbearing potential who do not intend to use appropriate contraceptive methods* or plan to become pregnant during the clinical trial</p> <p>*Hormonal contraceptives, intrauterine device, spouse's sterilization procedure (vasectomy, tubal ligation, etc.), dual barrier methods (concomitant use of spermicide and condom/diaphragm, vaginal sponge, or cervical cap)</p> <p>10) Subjects who have received other investigational drugs or have been treated</p>
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	<p>with investigational devices within 4 weeks after the participation in the trial</p> <p>11) Patients judged ineligible to participate in the clinical trial by other investigators</p>
<b>Dosage regimen of investigational product</b>	<p>Orally administer the investigational products assigned to each group 3 times a day for a total of 7 days.</p> <ul style="list-style-type: none"> <li>• <b>Test group:</b> DW1601 20 mL + Placebo of DW16011 20 mL + Placebo of DW16012 9 mL</li> <li>• <b>Control group1:</b> DW16011 20 mL + Placebo of DW1601 20 mL + Placebo of DW16012 9 mL</li> <li>• <b>Control group2:</b> DW16012 9 mL + Placebo of DW1601 20 mL + 의 위약 DW16011 20 mL</li> </ul>
<b>Efficacy endpoints</b>	<p><b><u>Primary efficacy endpoints</u></b></p> <p>Each control group is evaluated compared to the test group. If the superiority of the test group to each control group is demonstrated, the effect of the test group is also demonstrated.</p> <ul style="list-style-type: none"> <li>- Changes in total BSS on Day 4 after administration compared to before administration</li> </ul> <p><b><u>Secondary efficacy endpoints</u></b></p> <p>With respect to the following efficacy endpoints, each control group is comparatively evaluated with the test group.</p> <ol style="list-style-type: none"> <li>1) Changes in total BSS at Day 7 after administration compared to before administration</li> <li>2) Changes in BSS by symptom on Day 4 and Day 7 after administration compared to before administration</li> <li>3) Response rate on Day 4 and Day 7 after administration<sup>⌈</sup> <p><sup>⌈</sup>Response: <math>\leq 3</math> points of Total BSS, or reduction of <math>\geq 7</math> points compared to before administration</p> </li> <li>4) Overall improvement evaluated by an investigator and a subject on Day 4 and Day 7 after administration</li> <li>5) Therapeutic efficacy rate according to the overall improvement evaluated by an investigator and a subject<sup>⌈⌋</sup> <p><sup>⌈⌋</sup>Effective: Cure or Significant improvement</p> </li> <li>6) Overall satisfaction evaluated by a subject on Day 4 and Day 7 after</li> </ol>

	<p>administration</p> <p>With respect to the following efficacy endpoints, the control group 1 and control group 2 are comparatively evaluated.</p> <p>7) Changes in total BSS on Day 4 after administration compared to before administration</p>
<b>Safety endpoints</b>	<ul style="list-style-type: none"> <li>- Adverse events</li> <li>- Laboratory test</li> <li>- Vital signs</li> </ul>
<b>Efficacy evaluation analysis method</b>	<p><b><u>Primary efficacy endpoints</u></b></p> <p>Descriptive statistics(number of observed subjects, mean±standard deviation, median(range)) of total BSS before administration and on Day 4 after administration in each group and of Changes in total BSS on Day 4 after administration (total BSS on Day 4 after administration – total BSS before administration) are presented, and the comparison of changes between the experimental and each control group is analyzed by the analysis of covariance(ANCOVA) in which baseline score is adjusted with covariate.</p> <p>A 95% two-sided confidence interval and p-value of the difference in the least squares means (LS means) between the groups are presented. If the upper limit of the confidence interval is less than 0, it is judged that the superiority of the test group to the control group has been demonstrated, the effect of the test group is also demonstrated (If the superiority of the test group to each control group has been demonstrated, it represents the effect of the test group is also demonstrated).</p> <p><b><u>Secondary efficacy endpoints</u></b></p> <p>For the following continuous variables, descriptive statistics(number of observed subjects, mean±SD, median(range)) are presented, and the comparison of changes between the experimental and each control group is analyzed by the analysis of covariance(ANCOVA) in which baseline score is adjusted with covariate.</p> <ul style="list-style-type: none"> <li>- Changes in total BSS at Day 7 after administration compared to before administration</li> <li>- Changes in BSS by symptom on Day 4 and Day 7 after administration compared to before administration</li> </ul>

	<p>For the following categorical variables, the frequency and percentage are presented for each group, and whether there are differences between the test group and each control group is tested using Pearson's chi-square test or Fisher's exact test.</p> <ul style="list-style-type: none"> <li>- Response rate on Day 4 and Day 7 after administration</li> <li>- Overall improvement evaluated by an investigator and a subject on Day 4 and Day 7 after administration</li> <li>- Therapeutic efficacy rate according to the overall improvement evaluated by an investigator and a subject</li> <li>- Overall satisfaction evaluated by a subject on Day 4 and Day 7 after administration</li> </ul> <p>For the following continuous variables, descriptive statistics(number of observed subjects, mean<math>\pm</math>SD, median(range)) are presented, and the comparison of changes between the control group 1 and control group 2 is analyzed by the analysis of covariance(ANCOVA) in which baseline score is adjusted with covariate.</p> <ul style="list-style-type: none"> <li>- Changes in total BSS on Day 4 after administration compared to before administration</li> </ul>
<b>Safety evaluation analysis method</b>	<p><b><u>Adverse events</u></b></p> <p>For adverse events(AEs), treatment-emergent adverse events(TEAEs), adverse drug reactions(ADRs) and serious adverse events(SAEs), descriptive statistics are presented for each group, and whether there are differences in the incidences of AEs, ADRs and SAEs between the test group and each control group is tested using Pearson's chi-square test or Fisher's exact test.</p> <p>AEs, TEAEs, ADRs and SAEs are coded using MedDRA in accordance with system organ class (SOC) and preferred term (PT), and the number of subjects with the coded Aes, incidence and number of occurrence are presented for each group.</p> <p><b><u>Results of laboratory tests and vital signs</u></b></p> <p>In order to check intra-group changes, the continuous variables are analyzed by paired <i>t</i>-test or Wilcoxon's signed rank test depending on whether the normality assumption is satisfied, and the categorical variables by McNemar's test. In order to check inter-group changes, the continuous variables are analyzed by two sample <i>t</i>-test or Wilcoxon's rank sum test, and the categorical variables by Pearson's chi-square test or Fisher's exact test.</p>



**[STUDY FLOW]**

	Screening	Treatment			F/U
		Baseline	Efficacy Evaluation(EOT)		
Visit	Visit 1 <sup>10</sup>	Visit 2 <sup>10</sup>	Visit 3 <sup>11</sup>	Visit 4	Visit 5 <sup>12</sup>
Schedule (window)	Day-2~	Day 1	Day 4(±1)	Day 7(±1)	Day 5(±1) from EOT
Obtainment of informed consent	√				
Subject's basic information <sup>1</sup>	√				
Disease basic information <sup>2</sup>	√				
Medical history <sup>3</sup>	√				
Previous/concomitant drugs and therapies	√ <sup>4</sup>	√	√	√	
Physical examination	√	√	√	√	
Vital signs <sup>5</sup>	√	√	√	√	
Pregnancy test <sup>6</sup>	√			√	
Laboratory test <sup>7</sup>	√			√	
Eelectrocardiography(ECG) <sup>8</sup>	√			√	
Chest X-ray	√				
Bacterial or viral test <sup>9</sup>	√(If necessary)				
BSS evaluation	√	√	√	√	
Inclusion/exclusion criteria evaluation	√	√			
Randomization		√			
Overall improvement evaluation (by investigator & subject)			√	√	
Overall satisfaction evaluation (by subject)			√	√	
Distribution of investigational products		√	√		
Return of investigational products			√	√	
Adverse events			√	√	√

BSS: Bronchitis severity score, EOT: End of treatment, F/U: Follow up

- 1 Subject's demographic information (date of birth, sex) and item of personal preference use history are investigated, and height & weight are measured.
- 2 Date and time of onset of cough · sputum are investigated.
- 3 Medical history (including operation history) within 6 months before screening is investigated. However, medical history within 5 years is recorded for malignant tumor.
- 4 Drugs and treatments given within 30 days before screening are investigated.
- 5 Systolic/diastolic blood pressure, pulse rate and body temperature are measured.
- 6 It is conducted only in women of childbearing potential, and serum or urine hCG tests are performed.

- 7 The following items are performed. If test results obtained within 7 days from the screening visit (V1) are available, this test may be substituted with the screening visit test results.
  - Hematologic examination: RBC, hemoglobin, hematocrit, platelet, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils
  - Blood chemistry examination: Ca, Na, K, Cl, creatinine, BUN, uric acid, ALT, AST, ALP, total bilirubin, albumin, total protein, total cholesterol, triglycerides, glucose (random)
  - Urine test: Specific gravity, pH, protein, glucose, bilirubin, urobilinogen, ketone, blood, WBC, RBC
  - Blood coagulation test (performed only on the screening visit): PT (or INR), aPTT
- 8 ECG: The results of test performed within 30 days of screening can be used.
- 9 It is performed when an investigator deems it necessary to differentiate acute bronchitis.
- 10 Screening visit(V1) and baseline visit (V2) may be made concurrently on the same day.
- 11 If it is confirmed that a subject's symptoms completely disappeared (Total BSS=0), the medication can be discontinued at the discretion of investigator. In the case of discontinuation, safety/efficacy evaluation corresponding to the end-of-treatment (EOT) visit should be performed.
- 12 Follow-up visit(V5, F/U) is made via phone call on Day 5( $\pm$ 1) after the EOT.

**[Abbreviation and definition of terms]**

<b>Abbreviation</b>	<b>Definition</b>
ACEI	Angiotensin-Converting Enzyme Inhibitor
AE	Adverse Event
ADR	Adverse Drug Reaction
ALP	Alkaline Phosphatase
ALT	ALanine Aminotransferase
ANCOVA	Analysis of Covariance
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
BSS	Bronchitis Severity Score
BUN	Blood Urea Nitrogen
Ca	Calcium
Cl	Chloride
CQLQ	Cough Quality of Life Questionnaire
ECG	Electrocardiography
FAS	Full Analysis Set
ICH-GCP	International Conference on Harmonization-Good Clinical Practice
INR	International Normalized Ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
K	Potassium
KCGP	Korea Good Clinical Practice
LOCF	Last-Observation Carried Forward
MAO	MonoAmine Oxidase
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
Na	Sodium
PPS	Per Protocol Set
PT	Preferred Term
RBC	Red Blood Cell
SAE	Serious Adverse Event
SD	Source Document

<b>Abbreviation</b>	<b>Definition</b>
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WBC	White Blood Cell

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## 1. Number of target subjects and its ground

This trial aims to confirm the superiority of test drug(DW1601) to DW16011 and DW16012 in relieving cough and sputum symptoms by evaluating the efficacy of the test drug in patients with acute bronchitis. The hypotheses to test this are as follows:

Hypothesis 1.  $H_{01} : \mu_T = \mu_{C1}$  vs  $H_{11} : \mu_T \neq \mu_{C1}$

Hypothesis 2.  $H_{02} : \mu_T = \mu_{C2}$  vs  $H_{12} : \mu_T \neq \mu_{C2}$

- $\mu_T$  : Mean Change in BSS in the test drug(DW1601) group ( $\mu_T < 0$ )
- $\mu_{C1}$  : Mean Change in BSS in the DW16011 group ( $\mu_C < 0$ )
- $\mu_{C2}$  : Mean Change in BSS in the DW16012 group ( $\mu_C < 0$ )

The formula for calculating the number of subjects for each of the above hypotheses is as follows:

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2 (1 + 1/k)}{\epsilon^2}$$

- $\epsilon$  = Difference between the test group( $\mu_T$ ) and each control group( $\mu_{C1}$  or  $\mu_{C2}$ )
- $k = 1$  (Allocation ratio between test group and each control group=1:1)
- $\alpha$ : Type 1 error,  $\beta$ : Type 2 error

The difference in BSS changes between the test group and each control group is assumed to be -1.5, and the standard deviation of each group was assumed to be 2.4, which is the pooled standard deviation of the BSS changes.

With respect to each hypothesis, the minimum number of subjects for a two-sided significance level(Type 1 error) of 0.05, power of 90% ( $\geq 80\%$  of the total power) and 1:1 randomization to the two treatment groups is calculated together with the above set points as follows:

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2 (1 + 1/k)}{\epsilon^2} = \frac{(1.96 + 1.28)^2 \cdot 2.4^2 \cdot 2}{(-1.5)^2} \approx 54$$



Therefore, this study required at least 54 subjects in each group to satisfy the hypothesis of the test group compared to each control group, and considering 20% of dropout rate, 68 subjects per group (a total of 204 subjects) will be enrolled.

### **Difference in BSS changes between the two groups and basis for setting standard deviation**

Table 1 summarizes and presents the study results which confirm the effect size compared to placebo on the BSS changes 7 days after the administration of EPs 7630 in the treatment of acute bronchitis.<sup>13-18</sup>

There were no evidence literatures which can confirm the expected BSS changes in the combination drug(DW1601) which is the test drug for this clinical trial, or the same ingredient as the combination drug. However, when referring to the results of the same indications and the same endpoints, BSS changes in the test group compared to the control group are expected to decrease by 1.5 or more which is the smallest value among the results presented in Table 1.<sup>18</sup>

In the end, the difference in the effect shown in each control group compared to the test group was assumed to be 1.5, and the SD of each group was assumed to be 2.4 which was the weighted SD of Eps 7630 result values.

Table 1 BSS changes after the administration of Eps 7630 – Summary of references for estimating number of subjects

Ref	Group	N	Mean	SD	Difference from Placebo
13	Active (EPs 7630)	233	-5.9	2.9	-2.7
14	Active (EPs 7630)	64	-7.2	3.1	-2.3
15	Active (EPs 7630)	108	-7.6	2.2	-2.3
16	Active (Eps 7630)	103	-3.4	1.8	-2.2
17	Active (EPs 7630)	99	-5.0	1.9	-1.7
18	Active (Eps 7630)	111	-4.4	1.6	-1.5

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## **2. Clinical trial method**

### **2.1. Clinical trial design**

Subjects judged to meet the inclusion/exclusion criteria are randomized to the test group(DW1601), control group 1(DW16011) and control group 2(DW16012) in a 1:1:1 ratio.

After administration(treatment), subjects visit institutions on Day 4 $\pm$ 1(V3) and Day 7 $\pm$ 1(V4) to evaluate efficacy and safety. However, if it is confirmed that subject's symptoms completely disappear on Day 4(V3) after the administration(Total BSS=0)\*, the treatment can be discontinued at the discretion of investigator. In the case of discontinuation, safety/efficacy evaluation on the End of Treatment(EOT) visit is conducted.

Follow-up visit(V5, F/U) is made via phone call on Day 5( $\pm$ 1) after the EOT to check adverse events.

\*In this clinical trial, '0(zero)' of Total BSS on V3 is defined as 'complete disappearance of symptoms'.

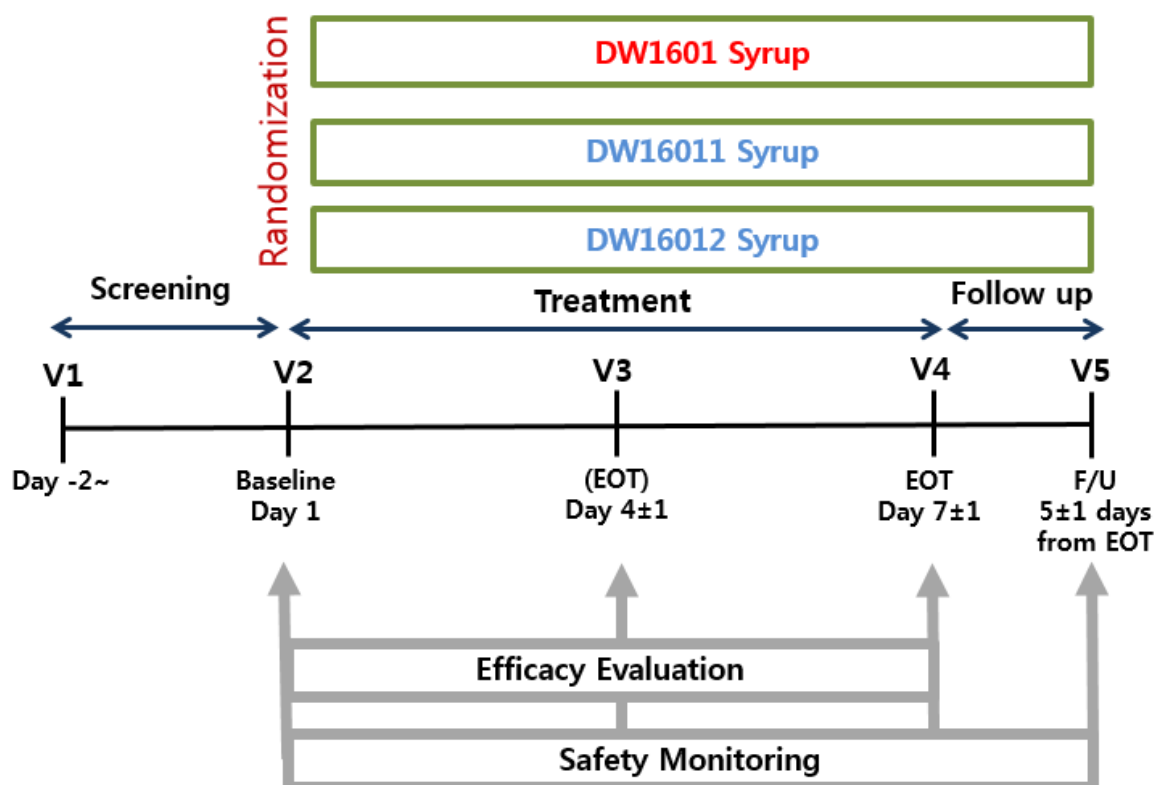


Figure 1 Clinical trial diagram

## 2.2. Basis for clinical trial design

### 2.2.1. Basis for the selection of subjects

#### Diagnosis of acute bronchitis

Acute bronchitis is an acute respiratory infection whose main symptom is cough due to the inflammation of bronchus, and is a lower respiratory tract infection. Symptoms similar to upper respiratory tract diseases are mainly seen in the early stage of acute bronchitis. It is typical that symptoms similar to common cold, along with a fever of 37°C to 39°C, continue for 3~4 days, cough gradually becomes the main symptom, and then systemic symptoms begin. The viscosity and properties of sputum change according to the course of the disease, and patients may complain of chest pain accompanied by severe coughing. The main symptoms of bronchitis usually last 4 to 6 days and then enter the recovery phase, but cough and sputum may persist for more than 1 to 2 weeks.

The common cause of acute cough is acute bronchitis and the other causes are asthma or pneumonia. Especially, pneumonia must be differentiated with caution as it can have serious consequences if not treated with antibacterial agents. The causes include viruses that invade the

lower respiratory tract in more than 90% of cases, such as influenza virus, parainfluenza virus, RSV, corona virus, adenovirus and rhinovirus. *M. pneumoniae*, *Chlamydophila pneumoniae* and *Bordetella pertussis* are isolated from a minority of patients. Sputum may accompany during the course, and bacterial infection cannot be diagnosed based on the presence of purulent sputum alone. If there are no abnormalities in vital signs or auscultation in healthy adults, the incidence of pneumonia is low, so chest radiography is not necessarily required.<sup>21</sup>

Therefore, subjects to be included in this clinical trial are patients with acute bronchitis whose symptoms are expected to improve with symptomatic treatment, and patient group requiring more aggressive treatment who meet the exclusion criteria according to the clinical diagnosis of a specialist will be excluded.

### **2.2.2. Basis for the selection of control group**

In order to verify the efficacy of the test drug, Codaewon Forte Syrup (DW16011) and Umckamin Plus Syrup (DW16012) were decided as active control drugs. Umckamin Syrup was approved by the Ministry of Food and Drug Safety in 2008, and has proven superiority to placebo in many clinical papers, so it is a recommended drug in the treatment guidelines for acute bronchitis. In addition, since there are many papers that have researched on BSS which is an efficacy endpoint, its efficacy can be predicted. Each component of Codaewon Forte Syrup was developed a long time ago and is widely used as a drug.

This clinical trial is conducted to evaluate the efficacy of the test drug (combination drug of each comparator). Based on the guidelines for clinical trials of combination drugs, it is judged that it will be possible to present a valid basis for the development of investigational products by proving the superiority of the test drug to each control drug.

### **2.2.3. Basis for the establishment of efficacy endpoints**

The primary objective of the clinical trial is to prove the efficacy of DW1601 for alleviating cough and sputum symptoms caused by acute bronchitis. The relief of cough and sputum symptoms by antitussive expectorants is a part of symptomatic treatment, not a direct treatment for the disease. Since there is no appropriate biomarker for diagnosis and severity evaluation, it is necessary to establish an index that can objectively evaluate a patient's symptoms.

Bronchitis severity score (BSS) is a scoring system that can quantitatively evaluate each symptom

and all symptoms before and after administration by scoring the severity of symptoms such as cough, sputum, chest pain during coughing and dyspnea. Therefore, in order to alleviate all symptoms including cough, sputum, chest pain during coughing and dyspnea, changes in the total BSS was established as the primary endpoint to evaluate the effect.

#### **2.2.4. Basis for the establishment of observation period**

Antitussive expectorants are not intended to treat the underlying disease, but to relieve various symptoms such as sputum and cough, so it is important to have rapid onset of action regardless of the type of disease.

Acute bronchitis is mostly caused by viruses, and the consequent cough and sputum symptoms usually last for 4-6 days, then enter the recovery phase and disappear naturally after 7-10 days. Therefore, in consideration of the general course in which cough and sputum symptoms mostly disappear according to the treatment of causative disease, the maximum administration period for acute bronchitis patients was set to 7 days, which is the general natural healing period. Kemmerich et al<sup>20</sup> have evaluated BSS on Day 4 & 7 at Thyme-Ivy etc. in patients with acute bronchitis, and reported that the BSS gradually decreased after administration of drug, indicating that a significant decrease compared to the placebo group on Day 4 can be confirmed. Therefore, according to the natural course of the disease, Day 4 after the start of administration was established as the time of evaluating primary endpoint, instead of Day 7 when symptoms disappear in most patients and it is highly likely to be difficult to judge the usefulness of investigational products.

The establishment of time of efficacy evaluation was planned by referring to the results that the superiority of the test drug to placebo was demonstrated by efficacy evaluation already from Day 3~5 in the studies of Matthys et al. (2003) and Chuchalin et al. (2005), and to the fact that the differences in BSS changes between the test group and placebo group on Day 3~5 and Day 7 were 2.2 and 2.3, respectively, indicating no significant difference in the study of Matthys et al. (2007).<sup>13-15</sup>

The follow-up period in this clinical trial was set to 5(±1) days after the end of administration, considering the half-life of the investigational products. According to previously reported data, the half-lives ( $t_{1/2}$ ) of chlorpheniramine and dihydrocodeine which are the components of the test drug were 14.6 to 17.3 hours and 4.3 hours, respectively. Although the information on the

pharmacokinetic parameters evaluated in the human body is not clear for DI-methylephedrine, the half-life ( $t_{1/2}$ ) of ephedrine has been reported to be about 5.2 hours. Considering the half-life ( $t_{1/2}$ ) of the components of the investigational products, the follow-up period for this trial was set to 5( $\pm$ 1) days considering about 5 times the longest half-life.

### [References]

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### 2.2.5. Basis for the establishment of contraindicated drugs

In clinical trials, drugs that affect efficacy or safety may be restricted to minimize confounding factors. In this trial, drugs used for cough and sputum symptoms, drugs that can cause cough and sputum, and representative drugs that interact with the investigational products were established as contraindicated drugs.<sup>1,5,8,9</sup>

Details of related drugs and therapies are presented in '2.4.2 Drug and treatment contraindications'.

### 2.3. Dosage regimen and administration period

Subjects are orally given the investigational products assigned by randomization 3 times a day for a total of 7 days.

- Test group: DW1601
- Control group 1: DW16011(Codaewon Forte Syrup)
- Control group 2: DW16012(Umckamin Plus Syrup)

Table 2 Dosage of investigational products

Group	Single dose of DW1601 (or placebo)	Single dose of DW16011 (or placebo)	Single dose of DW16012 (or placebo)
Test group	20 mL	(20 mL)	(9 mL)
Control group1	(20 mL)	20 mL	(9 mL)
Control group2	(20 mL)	(20 mL)	9 mL

In addition, according to the time of subject's visit, the investigational products are administered as follows:

- Day of first administration/prescription (Visit 2): If prescription is made before 2 pm, they are taken from lunch time, and if prescription is made after 2 pm, they are taken from dinner time
- Subsequent visits to institutions(Visit 3, 4): If visit is made before 12 pm, they are taken until morning, and if visit is made after 12 pm, they are taken until afternoon

## 2.4. Combination therapy and contraindications

### 2.4.1. Allowance of combination therapy

- 1) Combination therapy (drugs and treatment) can be performed at the discretion of the investigator if medically required. For concomitant drugs administered during the clinical trial, the name of ingredients, dosage regimen, administration period and purpose of administration should be recorded in the case report form(CRF).
- 2) Drugs that have been taken due to subject's underlying diseases(ex. hypertension, hyperlipidemia, diabetes, etc.) and drugs judged not to affect the efficacy even after being taken for more than 3 months are allowed.
- 3) Statins and low-dose aspirin (325 mg or less) administered for antithrombotic (preventive) purposes are allowed.

### 2.4.2. Drug and treatment contraindications

The administration of the following drugs is prohibited during the screening and treatment periods(Visit 1~Visit 4). Temporary use of topical preparations except for inhalants and nasal preparations is acceptable at the discretion of investigator, the details of the investigator's judgment should be recorded in the source document.

- 1) Antibiotics and antibacterial agents: Amoxicillin, azithromycin, cefodoxime, cefdinir,

- erythromycin, levofloxacin, moxifloxacin, kanamycin etc.
- 2) Antiviral agents for respiratory diseases: Oseltamivir, pleconaril etc.
  - 3) Systemic/inhaled corticosteroids
  - 4) Angiotensin-converting enzyme inhibitor\*(ACEI)
  - 5) Angiotensin Receptor Blocker\*(ARB)
  - 6) Mucolytics · expectorants · antitussives: Acetylcysteine, ambroxol, carboxymethylcystein, dextran, erdosteine, guaifenesin etc.
  - 7) Antitussives: Benproperine, codeine, dextromethorphan, hydrocodone, hydromorphone, levocloperastine, levodropropizine, morphine, noscapine, theobromine, zipeprol etc.
  - 8) Other drugs with antitussive effect: Amitriptyline, baclofen
  - 9) Herbal medicines with expectorant and antitussive effects: *Coptis japonica Makino*, *Pelargonium sidoides*, Ivy leaf etc.
  - 10) Leukotriene antagonist: Montelukast, zafirlukast etc.
  - 11) Antihistamines: Bromopheniramine, chlorpheniramine, clemastine, cetirizine (levocetirizine), diphenhydramine, fexofenadine, loratadine (desloratadine) etc.
  - 12)  $\beta_2$  agonists: Formoterol, salbutamol, salmeterol etc.(However, indacaterol should be contraindicated from 7 days before the administration of the investigational products.)
  - 13) Bronchodilators: Ipratropium, oxitropium, theophylline etc.
  - 14) Monoamine Oxidase(MAO) Inhibitors: phenelzine, tranylcypromine, moclobemide
  - 15) Coumarin anticoagulants: Warfarin etc.
  - 16) Symptomatic treatment for other acute bronchitis and analgesics(However, acetaminophen used for antipyretic purposes, at 1.5 g/day and taken 24 hours before the efficacy evaluation visit is allowed)
  - 17) Sedatives
  - 18) Phenytoin

\*However, if subjects are on long-term treatment with ACEI and ARB, the combination therapy is allowed for the same dosage regimen during the trial.

### 2.4.3. Others

Because adverse events such as drowsiness may occur depending on the administration of the investigational products, an investigator should instruct subjects to be careful of the following behaviors during the treatment period (Visit 2~Visit 4).

- Driving a car or machine operation



- Drinking

## 2.5. Randomization method

Randomization codes will be generated prior to the start of the trial by an independent statistician not related with the trial. A statistician in charge of randomization will make randomization table for each group in a 1:1:1 ratio using SAS® (Version 9.3 or higher, SAS institute, Cary, NC, USA) and stratified block randomization method). The statistician in charge of randomization should ensure that test group and each control group can be assigned in a 1:1:1 ratio in each institution.

The statistician delivers the prepared randomization code list to a person in charge of drug packaging. The sponsor manufactures and packages the investigational products so that the test drug and the comparator cannot be distinguished, and drugs are produced and distributed to institutions so that an investigator cannot confirm the treatment groups before the enrollment of subjects. Subjects enrolled in the clinical trial who meet the inclusion/exclusion criteria will be assigned to each group sequentially through a web-based interactive web response system (IWRS) according to a randomization number.

## 2.6. Blinding and unblinding

For scientific results of clinical trial, double blindness with the double dummy method is performed. Dosing groups will be disclosed upon completion of data locking and statistical analysis.

If it is required to confirm the investigational products given to the relevant subject due to an emergency during the clinical trial, an investigator can use the unblinding envelope to unblind the subject in discussion with the sponsor. If unblinding is done, the reason and date of unblinding should be recorded and kept. A subject whose randomization code is unblinded cannot continue the clinical trial.

In order to maintain the double-blindness, it is planned to manufacture the same properties and scents of the test drug and the comparator placebo. Considering that the investigational products are liquid, they will be manufactured in an opaque stick-type pouch so that they cannot be distinguished with the naked eye. In addition, it should be instructed to directly discard the pouch taken by a subject among the investigational products issued to subjects and to return only unused ones to avoid unblinding.

## 2.7. Compliance

An investigator manages to maintain compliance of  $\geq 75\%$  and  $< 130\%$  during the clinical trial period. If a subject takes the prescribed drug out of the acceptable compliance with the drug on the scheduled visit day, an investigator should explain the importance of compliance to subjects and instruct them to properly take the investigational products thereafter.

The investigational products should be administered under the guidance of the investigator/pharmacist as specified in the protocol.

When the investigational products are issued, sufficient quantity will be provided, and subjects will be instructed to return any remaining drugs on the next visit. An investigator checks the number of prescribed drugs and the number of drugs which were actually taken to check the compliance with the investigational products.

The compliance during the entire treatment period is evaluated as follows:

$$\text{Compliance(\%)} = \frac{\text{Number of drugs which were actually taken}}{\text{Number of drugs that should be taken in principle}} \times 100$$

## 3. Observation items • clinical laboratory test items and observational study method

### 3.1. Observation by the time of visit and clinical laboratory test items

#### 3.1.1. Visit 1 (Screening: Day -2 ~)

- 1) Obtainment of written informed consent
- 2) Subject's basic information: Demographic information(age, sex), body measurements(height, weight)
- 3) Disease basic information: Date and time of occurrence of cough and sputum
- 4) Medical history
- 5) Check of previous/concomitant drugs and therapies
- 6) Physical examination
- 7) Vital signs

- 8) Pregnancy test
- 9) Laboratory test
- 10) ECG
- 11) Chest X-ray
- 12) Bacterial or viral test(if necessary)
- 13) Bronchitis severity score (BSS)
- 14) Check of inclusion/exclusion criteria

### **3.1.2. Visit 2 (Baseline: Day 1)**

- 1) Check of previous/concomitant drugs and therapies
- 2) Physical examination
- 3) Vital signs
- 4) BSS
- 5) Check of inclusion/exclusion criteria
- 6) Randomization
- 7) Distribution of investigational products

### **3.1.3. Visit 3 (4±1 days)/Efficacy evaluation visit**

- 1) Check of previous/concomitant drugs and therapies
- 2) Physical examination
- 3) Vital signs
- 4) BSS
- 5) Evaluation of overall improvement(by investigator & subject)
- 6) Evaluation of overall satisfaction(by subject)
- 7) Collection of investigational products
- 8) Distribution of investigational products
- 9) Check of adverse events

### **3.1.4. Visit 4 (7±1 days)/ End of Treatment(EOT) visit**

- 1) Check of previous/concomitant drugs and therapies
- 2) Physical examination
- 3) Vital signs

- 4) Pregnancy test
- 5) Laboratory test
- 6) ECG
- 7) BSS
- 8) Evaluation of overall improvement(by investigator & subject)
- 9) Evaluation of overall satisfaction(by subject)
- 10) Collection of investigational products
- 11) Check of adverse events

### **3.1.5. Visit 5 (5±1 days after EOT visit)/ Follow up(/U) visit**

Follow-up visit(V5, F/U) is made via phone call on Day 5(±1) after the EOT.

- 1) Check of adverse events

### **3.1.6. Unscheduled visit**

If necessary during the clinical trial, a subject may make additional visits separately from the visits planned in the protocol. For example, if the occurrence of an adverse reaction(AE) is suspected, or for follow-up after the occurrence of AE, a necessary examination may be performed by visiting the institution. All visits related to this should be recorded in the CRF and source documents.

## **3.2. Observation and clinical laboratory test items**

### **3.2.1. Written informed consent**

A written informed consent is obtained from a subject before the conduct of clinical trial procedures. A subject's screening number is assigned in the order in which subjects agree in written format within institutions.

When obtaining the written informed consent, a total of five-digit screening number, which is a subject identification code, is assigned, and the first two digits represent the institution's unique number, and the last three digits represent the subject number according to the screening order at each institution. For example, S01001 subject means the first screened patient in institution 01.

Screening number: SOO### (OO; institution number, ###; serial number, example; S01001)
--

### **3.2.2. Subject's basic information**

On the screening visit (V1), a subject's demographic information(date of birth and sex) and item

of personal preference(smoking) use history are investigated, and body measurements(height & weight) is performed preference for use are investigated, and physical measurements (height, weight) are performed.

### **3.2.3. Disease basic information**

On the screening visit (V1), the symptoms(cough, sputum) of acute bronchitis and the date and time of occurrence of each symptom are investigated.

### **3.2.4. Medical history**

As a medical history, history of surgical operation performed within 6 months before screening, past history, present illness, presence of hypersensitivity reactions, time of occurrence(year or year & month of occurrence) and investigator's opinion are stated. However, for malignant tumors, a history of less than 5 years should be recorded.

### **3.2.5. Previous/concomitant drugs and therapies**

They should be checked every visit. Previous/concomitant drugs and therapies are investigated only at screening, and data on drugs and/or therapies administered within 30 days prior to screening are collected.

### **3.2.6. Physical examination**

It is performed every visit. Overall appearance, head, ears, eyes, nose and throat, chest, abdomen, spine and extremities, nervous system, skin, lymph nodes, genitourinary system and musculoskeletal system are comprehensively evaluated. Clinically significant abnormal results before the administration of investigational products are recorded in 'Medical history', and clinically significant abnormal results after the administration are recorded in 'Adverse Events'.

### **3.2.7. Vital signs**

On every visit, after a subject rests for 5 minutes, systolic/diastolic blood pressure, pulse rate and body temperature are measured in a sitting position. Clinically significant abnormal results before the administration of investigational products are recorded in 'Medical history', and clinically significant abnormal results after the administration are recorded in 'Adverse Events'.

### **3.2.8. Pregnancy test**

On the screening visit(V1) and EOT visit, serum or urine hCG test are performed only in women of childbearing potential. Post-menopausal woman is defined as follows:

- Menopause: Artificial menopause due to hysterectomy, or amenorrhea for more than 1 year without any other medical cause after the last menstruation

### **3.2.9. ECG**

On the screening visit(V1) and EOT visit, 12-lead ECG is performed. Clinically significant abnormal results before the administration of investigational products are recorded in 'Medical history', and clinically significant abnormal results after the administration are recorded in 'Adverse Events'. However, if test results obtained within 30 days from the screening visit(V1) are available, they can be substituted.

### **3.2.10. Chest X-ray**

Chest X-ray is performed on the screening visit(V1) to check the severe lung diseases.

### **3.2.11. Bacterial or viral test**

If an investigator determines that it is necessary to differentiate acute bronchitis, a bacterial or viral test is performed on the screening visit(V1).

### **3.2.12. Laboratory test**

It is performed on the screening visit(V1) and EOT visit, and the test items are as follows. If test results obtained within 7 days from the screening visit are available, this test may be substituted with the screening visit test results.

- Hematologic examination: RBC, hemoglobin, hematocrit, platelet, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils
- Blood chemistry examination: Ca, Na, K, Cl, creatinine, BUN, uric acid, ALT, AST, ALP, total bilirubin, albumin, total protein, total cholesterol, triglycerides, glucose (random)
- Urine test: Specific gravity, pH, protein, glucose, bilirubin, urobilinogen, ketone, blood, WBC, RBC
- Blood coagulation test(performed only on the screening visit): PT (or INR), aPTT

**3.2.13. BSS evaluation**

BSS is evaluated on every visit. However, if the screening visit(V1) and the baseline visit(V2) are made on the same day, only one evaluation is performed. For the details of evaluation criteria, please refer to '5.3.1 Bronchitis Severity Score'.

**3.2.14. Evaluation of overall improvement(by investigator & subject)**

An investigator and a subject evaluate the overall improvement on the efficacy evaluation visit(V3) and the EOT visit, respectively. The results of an investigator's evaluation are recorded in the source document, and a subject is instructed to evaluate verbally. An investigator should write the results in the source document. For the details of evaluation criteria, please refer to '5.3.2 Overall improvement and therapeutic efficacy rate according to overall improvement'.

**3.2.15. Evaluation of overall satisfaction**

A subject evaluates overall satisfaction at the efficacy evaluation visit(V3) and the EOT visit. The subject evaluates verbally and an investigator writes the results in the source document. For the details of evaluation criteria, please refer to '오류! 참조 원본을 찾을 수 없습니다. 오류! 참조 원본을 찾을 수 없습니다.'.

**3.2.16. Distribution and collection of investigational products**

On the baseline visit(V2) and the efficacy evaluation visit(V3), the investigational products are prescribed and distributed to subjects. However, if it is confirmed that subject's symptoms completely disappear on the efficacy evaluation visit(V3) (Total BSS=0), the treatment can be discontinued at the discretion of investigator and the additional prescription and distribution of the investigational products are not made. (Where applicable, the EOT visit is made.)

On the efficacy evaluation visit(V3) and EOT visit(V4), a subjects should complete the administration and return all unused investigational products.

**3.2.17. Check of adverse events**

Adverse events are checked on every visit after the administration of the investigational products. The reported AEs are collected and recorded in the CRFs according to items of Section 6.2.

### **3.3. Dropout**

Subjects who drop out of the trial should implement the items that should be implemented on the EOT visit (V4).

### **3.4. Unscheduled visit**

If a subject makes visits on a date other than the scheduled dates, adverse events, changes in concomitant drugs, clinical measurement results and medical treatments should be recorded. The unscheduled visits should not change the schedule of clinical trial.

If necessary during the clinical trial, for example, when the occurrence of an adverse event is suspected or follow-up is required after the occurrence of AE, a subject may make an additional visit separately from the visit planned in the clinical trial protocol. An investigator should have a subject understand the need for a separate additional visit during the regular visit, and explain that if AEs occur, an investigator should be contacted immediately. Data on additional visits should be recorded in both the CRF and source document, and the unscheduled visits should not change the schedule of clinical trial.

## **4. Protocol violation, criteria for discontinuation/dropout and termination of clinical trial**

### **4.1. Protocol violation**

If it is known that the protocol has been violated during the clinical trial, an investigator should notify the sponsor of the violation as soon as possible and decide whether the relevant subject should continue to participate in the clinical trial or not. If a subject drops out of the trial due to the protocol violation, the details should be recorded in the CRF. The following cases are considered major protocol violation:

- 1) Violation of inclusion and exclusion criteria which may affect the efficacy and safety evaluation
- 2) Administration of contraindicated concomitant drugs or conduct of contraindicated therapies which may affect the efficacy and safety evaluation during the screening and treatment period (Visit 1 ~ Visit 4)



- 3) <75% or >130% of compliance with the investigational products during the treatment period
- 4) Other violations considered to be major protocol violation

## **4.2. Criteria for discontinuation/dropout**

### **4.2.1. Criteria for the dropout of an individual subject**

Subjects who have received the investigational products but cannot participate in the trial during the entire period for any reason are classified as 'dropout'. When a subject requests for dropout or an investigator judges that the subject's dropout is inevitable, the subject can drop out of the trial regardless of the time. The reasons for dropout of individual subjects are as follow:

- 1) Subject or his/her representative withdraws consent
- 2) It is difficult to continue the trial due to adverse events
- 3) The violation of inclusion and exclusion criteria is confirmed
- 4) Contraindicated concomitant drugs are taken during the screening and treatment periods (Visit 1 ~ Visit 4), or it is judged treatment with the contraindicated concomitant drugs is required
- 5) It is impossible to follow up subjects
- 6) It is judged by an investigator that it is difficult for subjects to continue the trial

In order not to miss the fact that AEs occur without a subject's knowledge, a subject who refuses to visit should make every effort to contact the subject by all methods such as phone and e-mail, etc. The reasons of dropout should be recorded in the CRFs. A final evaluation should be performed even for those who drop out of the trial. Subject who have dropped out cannot re-participate in the trial.

### **4.2.2. Criteria for the discontinuation of clinical trial**

The sponsor may discontinue the entire trial or trial at a specific institution in early stages. The reasons for discontinuing the clinical trial by the sponsor are as follows:

- 1) It fails to enroll the target number of subjects in all or a specific institutions
- 2) Efficacy/safety information that may have a significant impact on the continuation of the clinical trial occurs
- 3) The violation of GCP, clinical trial protocol, or contract by an institution or investigator causes problems in the continuation of the clinical trial

- 4) There are other administrative reasons that may have a significant impact on the continuation of the trial

## **5. Efficacy evaluation criteria and method**

### **5.1. Primary efficacy endpoints**

Each control group is evaluated compared to the test group. If the superiority of the test group to each control group is demonstrated, the effect of the test group is also demonstrated.

- Changes in total BSS on Day 4 after administration compared to before administration

### **5.2. Secondary efficacy endpoints**

With respect to the following efficacy endpoints, each control group is comparatively evaluated with the test group.

- 1) Changes in total BSS at Day 7 after administration compared to before administration:
- 2) Changes in BSS by symptom on Day 4 and Day 7 after administration compared to before administration
- 3) Response rate on Day 4 and Day 7 after administration<sup>†</sup>  
<sup>†</sup>Response:  $\leq 3$  points of Total BSS, or reduction of  $\geq 7$  points compared to before administration
- 4) Overall improvement evaluated by an investigator and a subject on Day 4 and Day 7 after administration
- 5) Therapeutic efficacy rate according to the overall improvement evaluated by an investigator and a subject<sup>††</sup>  
<sup>††</sup>Effective: Cure or Significant improvement
- 6) Overall satisfaction evaluated by a subject on Day 4 and Day 7 after administration

With respect to the following efficacy endpoints, the control group 1 and control group 2 are comparatively evaluated.

- 7) Changes in total BSS on Day 4 after administration compared to before administration

### **5.3. Efficacy evaluation method**

#### **5.3.1. Bronchitis Severity Score**

Bronchitis severity score (BSS) is an evaluation scale which an investigator evaluates the severity of each symptom on a scale of 0-4 for the main symptoms of bronchitis such as cough, sputum, rales/rhonchi, chest pain during coughing and dyspnea (Table 3). The total score is a maximum of 20 points, calculated as the sum of individual symptom scores. As a result of the BSS evaluation, the proportion of subjects whose total score decreased by 3 points or less or by 7 points or more compared to before administration was defined as the treatment response rate.

Table 3 Bronchitis severity score (BSS)

Symptom	Score				
	absent	mild	moderate	severe	very severe
Cough	0	1	2	3	4
Sputum	0	1	2	3	4
Rales/rhonchi	0	1	2	3	4
Chest pain during coughing	0	1	2	3	4
Dyspnea	0	1	2	3	4

### 5.3.2. Overall improvement and therapeutic efficacy rate according to overall improvement

The overall improvement is evaluated on a 5-step scale, and is defined as follows.

In the evaluation of overall improvement, the proportion of subjects evaluated as '4. Cure' or '3. Significant improvement' is defined as therapeutic efficacy rate (Table 4).

Table 4 Overall improvement

Score	Definition
4	Cure
3	Significant improvement
2	Improvement
1	Some improvement
0	Non-improvement or worsening of symptoms

### 5.3.3. Overall satisfaction

The overall satisfaction is evaluated on a 5-step scale, and is defined as follows (Table 5).

Table 5 Overall satisfaction

Score	Definition
4	Very satisfied
3	Satisfied
2	Neutral
1	Dissatisfied
0	Very dissatisfied

## 6. Safety (including adverse events) evaluation criteria and method and reporting method

### 6.1. Definition of adverse events

'Adverse event(AE)' refers to any harmful and unintended signs (including abnormal laboratory findings) and symptoms, or diseases which occur in subjects receiving the investigational products, and does not necessarily have to have a causal relationship with the investigational products.

'Adverse drug reaction(ADR)' refers to any harmful and unintended reactions which occurs at any dose of investigational products and whose causal relationship with the investigational products cannot be denied.

'Serious AE(SAE)' refers to any of the following AEs occurring at any dose of investigational product:

- ① Results in death or life-threatening risk
- ② Requires hospitalization or the prolongation of existing hospitalization

However, a visit to the hospital for the following reasons is not considered SAE:

- Hospitalization or the prolongation of existing hospitalization for diagnosis or selective surgery for pre-existing diseases
- Hospitalization or the prolongation of existing hospitalization for measuring the effect of clinical trial
- Hospitalization or the prolongation of existing hospitalization for the scheduled treatment for the indications of clinical trial
- When visiting an emergency room, the visit time does not pass 24 hours

- ③ Results in persistent or significant disability/incapacity

- ④ Results in a congenital anomaly/birth defect
- ⑤ Is other medically important event: In addition to cases ① to ④, medically important conditions such as drug dependence or abuse or hematological diseases occur

'Unexpected adverse drug reaction' refers to a difference in the pattern of adverse drug reactions or the degree of harm in light of available drug-related information, such as package insert.

## 6.2. Criteria for the collection of adverse events and documentation

- Adverse events are collected during the entire trial period from the subject's consent to the telephone visit. All medical events occurring prior to the administration of investigational products should be recorded as medical history.
- The time of collection of SAEs is the same as the time of collection of AEs.
- AEs should be reported including the name of AE, duration(start date and end date), severity, causal relationship with the investigational products, relevant measures, outcome, medical treatment and whether the event is serious or not.
- When documenting adverse events, an investigator should record a comprehensive diagnosis or symptom rather than each symptoms or sign, using standard medical term.
- Adverse events which occurs during the clinical study, should be followed up until they are resolved or become stable condition, or the follow up of subject fails.
- Adverse events which occurs after the completion of the trial should be reported only when they are serious and causally related to the investigational products.

### 6.2.1. Severity of adverse events

- 1) Grade 1 (mild): Easily tolerated AEs
- 2) Grade 2(moderate): Causes significant trouble to activities of daily living(ADL)
- 3) Grade 3(severe): Unable to live a routine ADL

\*Definition of Activities of daily living(ADL): All activities that occur in daily life to take care of one's own body (e.g.: taking a bath, putting on and taking off clothes, eating, taking medicines, hygiene management, personal care, etc.)

### 6.2.2. Causal relationship with the investigational products

An investigator evaluates the causal relationship between AEs and the investigational products in two steps:

- 1) Definitely related
  - (1) The adverse event is most probably explained by administration of the test drug than any other reason, or the sequence of administration of the drug and onset of AEs is proper
  - (2) AEs disappear or become vague by discontinuation of administration (dechallenge)
  - (3) Rechallenge (if possible) is found to be positive
  - (4) AEs show consistent aspects with known information about this drug or the same class of the drug
- 2) Definitely not related
  - (1) There is another cause for an adverse event that is more plausible
  - (2) The adverse event did not disappear by the discontinuation of investigational products

#### **6.2.3. Measures against the investigational products**

- 1) Discontinuation
- 2) Dose increase
- 3) Dose decrease
- 4) None
- 5) Not known
- 6) Not applicable

#### **6.2.4. Treatment of adverse events**

- 1) Drug therapy: Drug therapy is done for AEs.
- 2) Non-drug therapy: Non-drug therapy is done for AEs.
- 3) Drug/Non-drug therapy: Drug and Non-drug therapies are done together for AEs.
- 4) No therapy performed: Drug and/or Non-drug therapies are not done for AEs.

#### **6.2.5. Outcomes of adverse events**

- 1) Recovered(resolved)
- 2) In recovery(resolution)

- 3) Not recovered(resolved)
- 4) Recovered(resolved) with sequelae
- 5) Death
- 6) Not known

## **7. Statistical analysis method**

### **7.1. Definition of analysis set**

In the efficacy evaluation analysis for this trial, the analysis of full analysis set (FAS) is performed as a main analysis, and the analysis of per-protocol set (PPS) as an auxiliary analysis. Safety evaluation analysis is performed in the safety set. Demographic information and medical history data are analyzed using FAS.

#### **7.1.1. Efficacy evaluation group**

##### **Full Analysis Set (FAS)**

It is defined as subjects who received the investigational products after randomization and in whom BSS is measured after administration.

##### **Per-Protocol Set (PPS)**

It is defined as subjects who complete a clinical trial without the major violation of clinical trial protocol among those included in the FAS. Reasons for the exclusion from the PPS are as follows:

- 1) Dropout
- 2) Violation of inclusion/exclusion criteria
- 3) Administration of contraindicated concomitant drugs and/or conduct of contraindicated therapies during the screening and treatment period(Visit 1~ Visit 4)
- 4) <75% or >130% of compliance with the investigational products during the treatment period
- 5) Other major protocol violation

#### **7.1.2. Safety evaluation group**

##### **Safety set**

It is defined as subjects who received the investigational products more than once.

## 7.2. General principle of result analysis

Descriptive statistics of endpoints for each group are presented, and unless otherwise specified, all tests are, in principle, two-sided tests under the significance level of 5%. In the case of FAS analysis, if a missing value occurs in the efficacy endpoints, the analysis is performed using last observation carried forward (LOCF) method. Others do not replace the missing value. For all  $p$ -values, up to 4 decimal places are presented, and  $<0.05$  is considered significant. Except for  $p$ -value, up to 2 decimal places are presented for figure with value below decimal point such as mean $\pm$ SD and percentage, etc.

## 7.3. Demographic information and medical history data

The demographic information and medical history data for subjects included in this clinical trial are summarized for each group. As continuous variables, the number of observed subjects, mean $\pm$ SD and median(range) are presented and analyzed using two sample  $t$ -test or Wilcoxon's rank sum test depending on whether the normality assumption is satisfied. As categorical variables, frequency and percentage are presented and analyzed using Pearson's chi-square test or Fisher's exact test.

## 7.4. Efficacy endpoints

### 7.4.1. Primary efficacy evaluation

Descriptive statistics(number of observed subjects, mean $\pm$ standard deviation, median(range)) of total BSS before administration and on Day 4 after administration in each group and of Changes in total BSS on Day 4 after administration (total BSS on Day 4 after administration – total BSS before administration) are presented, and the comparison of changes between the experimental and each control group is analyzed by the analysis of covariance(ANCOVA) in which baseline score is adjusted with covariate.

A 95% two-sided confidence interval and  $p$ -value of the difference in the least squares means (LS means) between the groups are presented. If the upper limit of the confidence interval is less than 0, it is judged that the superiority of the test group to the control group has been demonstrated, the effect of the test group is also demonstrated(If the superiority of the test group to each control group has been demonstrated, it represents the effect of the test group is



also demonstrated).

#### **7.4.2. Secondary efficacy evaluation**

- 1) Changes in total BSS at Day 7 after administration compared to before administration

Descriptive statistics(number of observed subjects, mean±standard deviation, median(range)) of total BSS before administration and on Day 7 after administration in each group and of Changes in total BSS on Day 7 after administration (total BSS on Day 7 after administration – total BSS before administration) are presented, and the comparison of changes between the experimental and each control group is analyzed by the analysis of covariance(ANCOVA) in which baseline score is adjusted with covariate.

- 2) Changes in BSS by symptom on Day 4 and Day 7 after administration compared to before administration

Descriptive statistics(number of observed subjects, mean±standard deviation, median(range)) of BSS by symptom before administration and on Day 4 & 7 after administration in each group and of Changes in BSS by symptom after administration (BSS after administration – BSS before administration) are presented, and the comparison of changes between the experimental and each control group is analyzed by the analysis of covariance(ANCOVA) in which baseline score is adjusted with covariate.

- 3) Response rate on Day 4 and Day 7 after administration

For the response rate on Day 4 & 7 after administration, the frequency and percentage by group are presented, and whether there are differences between the test group and each control group is tested using Pearson's chi-square test or Fisher's exact test.

- 4) Overall improvement evaluated by an investigator and a subject on Day 4 and Day 7 after administration

For the overall improvement evaluated by an investigator and a subject on Day 4 and Day 7 after administration, the frequency and percentage by group are presented, and whether there are differences between the test group and each control group is tested using Pearson's chi-square test or Fisher's exact test.

- 5) Therapeutic efficacy rate according to the overall improvement evaluated by an investigator

and a subject

For the overall improvement evaluated by an investigator and a subject, the frequency and percentage by group are presented, and whether there are differences between the test group and each control group is tested using Pearson's chi-square test or Fisher's exact test.

6) Overall satisfaction evaluated by a subject on Day 4 and Day 7 after administration

For the overall satisfaction evaluated by a subject on Day 4 and Day 7 after administration, the frequency and percentage by group are presented, and whether there are differences between the test group and each control group is tested using Pearson's chi-square test or Fisher's exact test.

7) Changes in total BSS on Day 4 after administration compared to before administration

The comparison of total BSS changes between the control group 1 and control group 2 on Day 4 after administration is analyzed by the analysis of covariance(ANCOVA) in which baseline score is adjusted with covariate

## 7.5. Safety endpoints

### 7.5.1. Adverse events

For AE, TEAE, ADRs and SAEs, the frequency and percentage by group are presented, and whether there are differences between the test group and each control group is tested using Pearson's chi-square test or Fisher's exact test.

AEs, TEAEs, ADRs and SAEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) in accordance with system organ class (SOC) and preferred term (PT), and the number of subjects with the coded Aes, incidence and number of occurrence are presented for each group.

### 7.5.2. Laboratory test, Vital signs

As continuous variables, descriptive statistics such as baseline value, value at the end and the difference between the baseline value and value at the end are presented, and depending on whether the normality assumption is satisfied, intragroup comparison is analyzed by paired *t*-test or Wilcoxon's signed rank test and comparison between the test group and each control group by two sample *t*-test or Wilcoxon's rank sum test. As categorical variables, frequency and percentage are presented, and intragroup comparison is analyzed by McNemar's test and

comparison between the test group and each control group by Pearson's chi-square test or Fisher's exact test.

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