Clinical Study Protocol

Protocol No. DSP2505-CT4

Version 3.1, 20 November 2025

Dasan Pharmaceutical Co., Ltd.

A Multi-center, Randomized, Double-blind, Active control, Parallel, Phase 4 Clinical Trial to Evaluate the Efficacy and Safety of CANIUM Tab. in Acute Bronchitis Patients.

Protocol number: DSP2505-CT4

Study phase: Phase 4

Test drug: CANIUM Tab.

Target disease: Acute bronchitis

Sponsor: Dasan Pharmaceutical Co., Ltd.

Protocol version: Version 3.1 dated 20NOV2025

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Protocol Development and Amendment History

No.	Version	Version date	Principal changes
1	1.0	24JUN2025	Initial version.
2	2.0	13OCT2025	1) Incorporated MFDS requests: removed early termination when clinical symptoms completely resolve within 7 days; lowered enrollment age based on comparator labeling; added protection for vulnerable participants following the age reduction; revised permitted contraception to methods considered highly effective; added a smoking exclusion to eliminate effects on cough and sputum; added prohibited concomitant medications from the exclusion criteria to the relevant section; recalculated sample size following the age reduction; added sensitivity analysis using a different missing-data method; added compliance and visit-window criteria for PPS exclusion. 2) Added omitted information and sections. 3) Added cited references. 4) Updated the appendix list.
3	3.0	18NOV2025	Incorporated MFDS requests: 1) adjusted the Visit 3 window; 2) adjusted treatment compliance; 3) detailed hormonal contraceptive methods; 4) reverted to V1.0 sample-size content after excluding the reference added as the basis for recalculation; 5) changed LOCF to apply to FAS analyses.
4	3.1	20NOV2025	Corrected a typographical error in Section 7.3.6.1.

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Table of Contents

Protocol Development and Amendment History 2
Table of Contents 3
Abbreviations and Terms 6
Protocol Synopsis 8
Synopsis Inclusion Criteria 8
Synopsis Exclusion Criteria 9
Synopsis Efficacy Assessments 10
Synopsis Safety Assessments 10
Schedule of Study Procedures 10
1. Introduction 12
1.1 Study Background 12
1.2 Rationale 12
1.2.1 Rationale for Study Design 12
1.2.2 Rationale for Test-Drug Dose Selection 13
1.2.3 Potential Risk-Benefit Assessment 13
2. Study Objectives 13
2.1 Primary Objective 13
2.2 Secondary Objective 13
3. Overall Study Design and Plan 13
3.1 Study Design 13
3.2 Participating Study Sites 14
3.3 Treatment Assignment and Allocation Procedures 14
4. Study Assessment Methods and Procedures 14
4.1 Assessment Methods 14
4.1.1 Efficacy Assessments 14
4.1.2 Safety Assessments 15
4.1.3 Other Assessments 16
4.2 Procedures by Visit 17
4.2.1 Visit 1 (Screening, within 2 days before Day 0) 17
4.2.2 Visit 2 (Randomization, Day 0) 17
4.2.3 Visit 3 (End of Study, Day 7 ±1 day) 18
4.2.4 Unscheduled Visits 18
5. Participant Selection and Withdrawal Criteria 18
5.1 Inclusion Criteria 18
5.2 Exclusion Criteria 19
5.3 Discontinuation and Withdrawal Criteria 19
5.4 Handling of Protocol Violations 20

CONFIDENTIAL

6. Investigational Products 20
6.1 Overview of Investigational Products 20
6.1.1 Test Drug 20
6.1.2 Comparator 20
6.1.3 Test-Drug Placebo 21
6.1.4 Comparator Placebo 21
6.2 Dose, Administration, and Treatment Duration 21
6.2.1 Dose and Administration 21
6.2.2 Treatment Duration 21
6.3 Manufacture, Packaging, and Labeling 21
6.4 Investigational Product Management 22
6.5 Maintenance and Breaking of the Blind 22
6.6 Study Drug Compliance Assessment 22
6.7 Concomitant Medications and Treatments 23
6.7.1 Prohibited Concomitant Medications and Treatments 23
6.7.2 Permitted Concomitant Medications and Treatments 23
7. Statistical Considerations 23
7.1 Sample Size and Rationale 23
7.1.1 Sample Size 23
7.1.2 Rationale 23
7.2 Endpoints 24
7.2.1 Primary Efficacy Endpoint 24
7.2.2 Secondary Efficacy Endpoints 25
7.2.3 Safety Endpoints 25
7.3 Statistical Analysis Plan 25
7.3.1 Analysis Populations 25
7.3.2 General Statistical Principles 25
7.3.3 Demographic Information 26
7.3.4 Medical and Surgical History 26
7.3.5 Prior and Concomitant Medications 26
7.3.6 Efficacy Analyses 26
7.3.7 Safety Analyses 27
7.3.8 Handling of Withdrawals and Missing Data 27
7.3.9 Planned Interim Analyses and Data Monitoring 27
8. Adverse Events 28
8.1 Definitions 28
8.2 Collection and Recording of Adverse Events 28
8.3 Assessment of Adverse Events 28

CONFIDENTIAL

8.3.1 Severity 28
8.3.2 Causality 29
8.4 Reporting of Serious Adverse Events 29
8.5 Reporting and Management of SUSARs 29
8.6 Pregnancy 30
9. Ethical Considerations and Administrative Procedures 30
9.1 Ethical and Regulatory Compliance 30
9.2 Protocol Compliance 30
9.3 Protocol Approval and Amendments 30
9.4 Informed Consent Procedures 30
9.5 Measures to Protect Participant Safety 31
9.6 Protection of Participants in Vulnerable Circumstances 31
9.7 Medical Care and Treatment after Study Completion 31
9.8 Compensation for Injury 31
9.9 Study Documents and Record Retention 32
9.9.1 Case Report Forms and Source Documents 32
9.9.2 Access to Source Data 32
9.9.3 Retention of Study Data 32
9.9.4 Audits and Inspections 32
9.10 Confidentiality of Study Documents and Participant Records 32
9.11 Study Site Monitoring 32
9.12 Early Termination or Suspension 33
9.12.1 Sponsor 33
9.12.2 Investigator 33
9.13 Clinical Study Report and Publication 33
10. References 33
11. List of Appendices 35

Abbreviations and Terms

Abbreviation	Term
ACEI	Angiotensin-Converting-Enzyme Inhibitor
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
ARB	Angiotensin Receptor Blocker
AST	Aspartate Aminotransferase
BSS	Bronchitis Severity Score
BUN	Blood Urea Nitrogen
Ca	Calcium
Cl	Chloride
COAT	Cough Assessment Test
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
ECG	Electrocardiogram
e-CRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOS	End Of Study
FAS	Full Analysis Set
γ-GTP	Gamma-glutamyl Transferase
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMOS	Integrative Medicine Outcome Scale
IMPSS	Integrative Medicine Patient Satisfaction Scale
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
IWRS	Interactive Web Response System
K	Potassium
LDH	Lactate Dehydrogenase

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Abbreviation	Term
MedDRA	Medical Dictionary for Regulatory Activities
Na	Natrium
NCS	Not Clinically Significant
P	Phosphorus
PPS	Per Protocol Set
PT	Preferred Term
PT	Prothrombin Time
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
UV	Unscheduled Visit
WBC	White Blood Cell

Protocol Synopsis

Study title: A Multi-center, Randomized, Double-blind, Active control, Parallel, Phase 4 Clinical Trial to Evaluate the Efficacy and Safety of CANIUM Tab. in Acute Bronchitis Patients.

Sponsor: Dasan Pharmaceutical Co., Ltd., Suite 1302, 70 Seonyu-ro, Yeongdeungpo-gu, Seoul, Republic of Korea (342 Deogamsan-ro, Dogo-myeon, Asan-si, Chungcheongnam-do, Republic of Korea).

Study sites and principal investigators: Coordinating investigator, Professor Kwang Ha Yoo, Division of Pulmonology, Konkuk University Medical Center. For all sites, see the protocol appendix “Study Sites and Sponsor Organization.”

Study duration: 18 months from institutional review board (IRB) approval.

Target disease: Acute bronchitis.

Objectives: To evaluate efficacy and safety after 7 days of CANIUM Tab. (test drug) or Umckamin Tab. (comparator) in patients with acute bronchitis.

Primary objective: To compare improvement in acute bronchitis symptoms using the change in BSS at Day 7 after study drug administration and demonstrate noninferiority of the test drug to the comparator.

Secondary objective: To compare treatment effects (efficacy) and safety using acute bronchitis assessment measures.

Phase and design: Multicenter, randomized, double-blind, active-controlled, parallel-group, Phase 4 clinical trial.

Methods: Participants providing written consent may undergo up to 2 days of screening. Those who satisfy the final eligibility assessment and inclusion/exclusion criteria may enter the study. Eligible participants will be randomized 1:1 at Visit 2, receive study drugs for 7 days, and return at Day 7 (Visit 3) for efficacy and safety assessments.

Visit 1	Visit 2	Visit 3
Within 2 days before Day 0	Day 0	Day 7 (±1 day)
Screening	Baseline; randomization; start of study drug administration	End-of-study visit; efficacy and safety assessments

Study drugs:

- Test drug: CANIUM Tab., Dasan Pharmaceutical Co., Ltd.; Pelargonium sidoides 11% ethanol dry extract (5.5-6.6:1).
- Comparator: Umckamin Tab., Hanwha Pharma Co., Ltd.; mixture (1:4.56) of Pelargonium sidoides 11% ethanol extract (1:8-10) and maltodextrin.

Dose, administration, and treatment duration: One active tablet orally three times daily. To maintain double-blinding, each dose will comprise the following:

Group	Administration per dose
Test	One test-drug tablet (●) plus one comparator placebo (□)
Control	One test-drug placebo (○) plus one comparator tablet (■)

Sample size: 218 participants, 109 per group, allowing for 15% dropout.

Synopsis Inclusion Criteria

1) Males and females aged 12 to 75 years, inclusive.

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2) Diagnosis of acute bronchitis and both of the following: onset within 48 hours before randomization; BSS ≥5 at both screening and randomization.

3) Women who could become pregnant and men who agree to use medically acceptable contraception throughout the study. Acceptable methods are combined hormonal contraception containing estrogen and progestogen that inhibits ovulation (oral, intravaginal, transdermal); progestogen-only hormonal contraception that inhibits ovulation (oral, injectable, implantable); an intrauterine device (IUD); an intrauterine hormone-releasing system (IUS); bilateral tubal ligation/salpingectomy; bilateral oophorectomy; a vasectomized partner; and sexual abstinence.

4) For women of childbearing potential, a negative pregnancy test before study drug administration.

5) Voluntary decision to participate and written consent after receiving and understanding a detailed explanation of the study. For minors aged 12 years or older and under 19 years, the legally authorized representative must also provide written consent.

Synopsis Exclusion Criteria

1) Fever with measured temperature >38.5°C at randomization.

2) A respiratory disease that, in the investigator's judgment, may affect efficacy assessment: (a) pneumonia, bronchial asthma, cystic fibrosis, viral influenza, active tuberculosis, chronic obstructive pulmonary disease, bronchiectasis, interstitial lung disease, or similar conditions; or (b) findings suggestive of pneumonia on chest X-ray, auscultation, or vital signs.

3) A history or condition considered likely to affect the study, including any of the following:

(a) A coagulation disorder, increased bleeding tendency, or coagulation test results outside the normal range at Visit 1.

(b) Malignancy diagnosed within 5 years before screening. Participation is permitted if at least 1 year has elapsed since complete resection of basal-cell/squamous-cell carcinoma, curative resection of papillary thyroid carcinoma, or successful treatment of cervical carcinoma in situ; or if the person was declared cured within the 5 years before screening and has not received, or is considered unlikely to require, treatment for the disease.

(c) Other clinically significant hepatic, renal, cardiovascular, respiratory, endocrine, or central nervous system disease or disorder identified by physical examination or laboratory testing.

(d) History of psychiatric illness, alcoholism, or drug abuse.

(e) Hereditary disorders such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

4) Use or planned use of the following medications during the specified periods:

(a) At Visit 1: ongoing anticoagulant use.

(b) From 2 weeks before Visit 2 through the end-of-study visit (Visit 3): systemic antibiotics or antivirals; systemic/inhaled glucocorticosteroids.

(c) From 1 week before Visit 2 through Visit 3: ACE inhibitors. For perindopril, the period starts 4 weeks before Visit 2. Participants already taking this class for an underlying disease may continue without a change in dose or regimen during the study.

(d) From 2 days before Visit 2 through Visit 3: expectorants (mucolytics or sputum-expelling agents); antitussives; herbal preparations with antitussive/expectorant effects.

(e) Throughout the study (Visits 1-3): antihistamines; anticholinergics, including bronchodilators; other symptomatic treatments for acute bronchitis; analgesics. Temporary acetaminophen for fever, up to 1.5 g/day, is allowed except within 24 hours before Visits 2 and 3.

5) Any of the following screening laboratory results: (a) ALT or AST >3 times the upper limit of normal; (b) eGFR <30 mL/min/1.73 m², calculated using the CKD-EPI equation from creatinine results.

6) History of hypersensitivity to any component of the study drugs.

7) Pregnancy or breastfeeding.

8) Smoking an average of at least 15 cigarettes/day during the previous 30 days.

9) Receipt of an investigational drug or use of an investigational medical device in another trial within 30 days before screening, or current participation in another interventional clinical trial.

10) Any other reason the investigator considers participation inappropriate.

Synopsis Efficacy Assessments

Primary endpoint: Change from baseline in BSS total score at Day 7 (Visit 3) after study drug administration. BSS rates cough, sputum, rales/rhonchi, chest pain during coughing, and dyspnea from 0 (absent) to 4 (very severe) each, summed to a maximum of 20.

Secondary endpoints:

1. Change from baseline in symptom-specific BSS scores at Day 7 (Visit 3).

2. BSS treatment response rate at Day 7 (Visit 3) relative to baseline. Response definitions: total score <3; a reduction of at least 7 points; or both a total score <3 and a reduction of at least 7 points.

3. Change from baseline in COAT total score at Day 7 (Visit 3).

4. Investigator-assessed overall improvement in treatment response at Day 7 (Visit 3).

5. Investigator-assessed overall improvement rate at Day 7 (Visit 3).

6. Participant-assessed overall improvement rate at Day 7 (Visit 3).

7. Participant satisfaction with treatment response at Day 7 (Visit 3).

Overall improvement is subjectively assessed as change from baseline using the five-point IMOS. Improvement is defined as “Major improvement” (2) or “Complete recovery” (1). Participant satisfaction with treatment effects relative to baseline is subjectively assessed using the five-point IMPSS.

Synopsis Safety Assessments

1. Adverse events.

2. Clinical laboratory tests (hematology, blood chemistry, urinalysis).

3. Vital signs.

4. Physical examination.

5. ECG.

Schedule of Study Procedures

Procedure	Visit 1 Screening	Visit 2 Randomization / Baseline	Visit 3 EOS[7]	UV[8]
Day / visit window	Day -2 to Day 0	Day 0	Day 7 / ±1 day	Unscheduled
Informed consent[1]	X			
Demographic information	X			
Medical / surgical history	X	X		
Prior / concomitant medications	X	X	X	X
Physical examination	X	X	X	(X)
Vital signs[3]	X	X	X	(X)
ECG[4]	X		X	(X)

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Procedure	Visit 1 Screening	Visit 2 Randomization / Baseline	Visit 3 EOS[7]	UV[8]
Chest X-ray	X			(X)
Weight and height	X			(X)
Clinical laboratory tests[5]	X		X	(X)
Pregnancy test[6]	X		X	(X)
Inclusion / exclusion criteria	X	X		
Randomization		X		
BSS assessment	X	X	X	
COAT questionnaire		X	X	
Overall improvement (IMOS), investigator and participant			X	
Participant satisfaction (IMPSS)			X	
Adverse events			X	X
Study drug dispensing		X		
Return of study drugs and compliance assessment			X	

1) Before study initiation, the purpose and details of the study will be explained fully to the participant and written consent obtained. Written consent must precede every study procedure and may be obtained before screening procedures.

2) If all eligibility criteria can be assessed at Visit 1, Visits 1 and 2 may be performed together. Duplicate procedures may be performed only once.

3) Blood pressure, pulse rate, and tympanic temperature will be measured, preferably before other scheduled tests and with the participant seated after 5 minutes of rest.

4) ECG results obtained at the same institution within 4 weeks before screening may be used.

5) Laboratory results obtained at the study site within 4 weeks before screening may be used. One repeat test during screening is allowed at the investigator's discretion. Tests are as follows:

- Hematology: RBC, hemoglobin, hematocrit, platelet count, WBC, and WBC differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
- Blood chemistry: BUN, creatinine, uric acid, total bilirubin, albumin, total protein, ALT, AST, glucose, total cholesterol, and electrolytes (Na, Ca, K, Cl).
- Urinalysis: protein (albumin), glucose, ketones, WBC, and blood (RBC).
- Coagulation, at Visit 1 only: PT (INR), aPTT (sec).
- Diagnostic testing: bacterial or viral tests may be performed if the investigator considers them necessary for differential diagnosis of acute bronchitis.

6) Serum or urine hCG testing will be performed only in women of childbearing potential. These are women who have experienced menarche and are neither successfully surgically sterilized (hysterectomy, bilateral tubal ligation/salpingectomy, or bilateral oophorectomy) nor postmenopausal. Menopause is defined as at least 12 months of amenorrhea after the final menstrual period without another cause.

7) Participants who withdraw after randomization should undergo end-of-study procedures whenever possible.

8) UV means unscheduled visit. Tests in addition to those indicated may be performed at the investigator's discretion.

1. Introduction

1.1 Study Background

According to 2023 health insurance medical care statistics in the Healthcare Big Data Open System, acute bronchitis is the second most frequent outpatient condition and a very common disease in Korea, with more than 16 million patients treated annually.[6] Overseas reports indicate that it affects approximately 5% of the general population each year.[7]

Acute bronchitis is caused by inflammation of the bronchial mucosa. Viral infections, such as influenza virus, parainfluenza virus, respiratory syncytial virus, and adenovirus, are the most common cause. Secondary bacterial infection, including Mycoplasma pneumoniae, Chlamydophila pneumoniae, Bordetella pertussis, and Bordetella parapertussis, may occur in fewer than 10% of cases. Noninfectious causes include cold air, dust, airway irritants, and harmful gases.[7] It is an acute respiratory illness lasting approximately 1-3 weeks, mainly characterized by cough with or without sputum.[9,10] Mucosal injury and inflammatory mediators may act together to cause transient airway obstruction or bronchial hyperresponsiveness. Cases caused by M. pneumoniae or C. pneumoniae may be accompanied by reduced lung function.[7]

Chest radiography can distinguish acute bronchitis from pneumonia.[9,10] Early in its course, differentiation from an acute upper respiratory infection is difficult; a diagnosis of acute bronchitis is recommended when symptoms persist for at least 7 days.[8] Diagnosis is clinical and based on symptoms, but other diseases, such as asthma, should be considered when symptoms persist for more than 3 weeks.[7]

Antibiotics are often used after diagnosis, but colored sputum does not clearly distinguish bacterial from viral lower respiratory tract infection.[11] Most acute bronchitis is viral, and antibiotics provide little or no clinical benefit and are not recommended.[9,11] Inappropriate antibiotic use therefore requires management,[8] and treatment in adults should aim to reduce antibiotic use and improve the condition.

Symptomatic treatment is the first-line approach to cough due to acute bronchitis. Although randomized controlled studies of antitussives such as codeine or dextromethorphan in acute bronchitis are lacking, short-term use may be tried because they are effective in chronic bronchitis. Evidence that expectorants relieve cough from acute bronchitis is limited. Routine antibiotics are not recommended because most cases are viral.[7] Accordingly, the FDA no longer calls for randomized studies of antibiotic use in acute bronchitis, and cough and cold medicines are not recommended in children under 6 years.[8,11]

Antitussives, expectorants, beta-2 bronchodilators, and alternative therapies used for acute bronchitis have not shown consistent study results,[12] and beta-2 agonists are not recommended for cough caused by acute bronchitis.[7] Studies are therefore being conducted to develop various treatments, including herbal medicine research based on traditional medical knowledge.[8] Pelargonium supplements are reported to help reduce acute bronchitis symptoms in adults.[9]

CANIUM Tab. (Pelargonium sidoides 11% ethanol dry extract [5.5-6.6:1]) contains an herbal extract derived from dried Pelargonium sidoides roots. It is a generic of Hanwha Pharma's marketed Umckamin Tab. (a mixture [1:4.56] of Pelargonium sidoides 11% ethanol extract [1:8-10] and maltodextrin). Development focuses on a generic medicine that achieves equivalent or better results in pharmaceutical equivalence testing compared with Umckamin Tab.

1.2 Rationale

1.2.1 Rationale for Study Design

This oral herbal film-coated tablet was approved for marketing by the MFDS on 30 April 2015. This trial is being conducted under the MFDS notice requiring reevaluation of pharmaceutical equivalence for products whose equivalence has not been demonstrated.

Because of the characteristics of herbal products, conventional bioequivalence data based on blood concentrations of active ingredients cannot be generated. Equivalence to Umckamin Tab. will therefore be reevaluated in a comparative clinical trial using a noninferiority design.

1.2.2 Rationale for Test-Drug Dose Selection

The product is a generic of marketed Umckamin Tab. (Pelargonium sidoides 11% ethanol extract [1:8-10] and maltodextrin mixture [1:4.56]) and uses a corresponding bioequivalent dose.

1.2.3 Potential Risk-Benefit Assessment

According to Umckamin labeling, a Korean postmarketing safety evaluation in 641 patients found an adverse event incidence of 0.47% (3 events in 3/641 patients), regardless of causality. There were no adverse drug reactions for which a causal relationship to Umckamin could not be excluded, and no serious adverse events or unexpected adverse drug reactions.

Liver injury and hepatitis have been reported overseas with liquid and syrup formulations containing the same active ingredient. Because these were spontaneous reports, a reliable incidence could not be determined.

Umckamin labeling states that interactions with other medicines have not been reported to date. An enhanced anticoagulant effect with coumarin drugs cannot be excluded because the product may affect coagulation factors, but available reports suggest that it can be used safely. Because the ingredient's safety and efficacy are recognized, the therapeutic benefits of conducting this trial are expected to outweigh the risks.

2. Study Objectives

To evaluate efficacy and safety after 7 days of CANIUM Tab. (test drug) or Umckamin Tab. (comparator) in patients with acute bronchitis.

2.1 Primary Objective

To compare improvement in acute bronchitis symptoms using the change in BSS at Day 7 after study drug administration and demonstrate noninferiority of the test drug to the comparator.

2.2 Secondary Objective

To compare treatment effects (efficacy) and safety between the test drug and comparator using assessment measures related to acute bronchitis.

3. Overall Study Design and Plan

3.1 Study Design

Participants providing written consent may undergo up to 2 days of screening. Those who satisfy the final eligibility assessment and inclusion/exclusion criteria may participate.

Eligible participants will be randomized 1:1 to the test or control group at Visit 2, receive study drugs for 7 days, and return to the study site at Day 7 (Visit 3) for efficacy and safety assessments.

Visit 1	Visit 2	Visit 3
Within 2 days before Day 0	Day 0	Day 7 (±1 day)
Screening	Baseline; randomization; start of study drug administration	End-of-study visit; efficacy and safety assessments

3.2 Participating Study Sites

The study will be conducted at multiple sites in Korea. Details are provided in Appendix 4, Study Sites and Sponsor Organization.

3.3 Treatment Assignment and Allocation Procedures

Participants who provide written consent will receive a screening number in the order of consent, consisting of [two-digit site number]-S-[three-digit sequential number]. Eligible participants will be stratified by baseline BSS score, <8 (stratum 1) or ≥8 (stratum 2), and randomized according to the randomization plan. In the order in which the investigator decides to enroll them, they will receive a unique randomization number, R-[stratum number][three-digit sequential number].

The investigator will use IWRS for randomization. Participants will be assigned to groups according to a pregenerated randomization list through IWRS.

Allocation will be 1:1. An independent randomization manager will generate the list using stratified block randomization with baseline BSS score (<8 / ≥8) as the stratification factor, using SAS® (SAS Institute Inc., Cary, NC, USA) version 9.4 or later.

Before study initiation, the randomization manager will provide codes to the sponsor's study drug packaging personnel and IWRS personnel.

4. Study Assessment Methods and Procedures

4.1 Assessment Methods

4.1.1 Efficacy Assessments

4.1.1.1 Bronchitis Severity Score (BSS)

BSS will be assessed at every visit. The investigator rates cough, sputum, rales/rhonchi, chest pain during coughing, and dyspnea from 0 (absent) to 4 (very severe) each. The total is the sum of individual scores, with a maximum of 20.

Symptom	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

For the Day 7 (Visit 3) treatment response rate, BSS response is defined as meeting any one of the following:

1. Total score <3.
2. A decrease of at least 7 points in total score.
3. Total score <3 and a decrease of at least 7 points.

4.1.1.2 Cough Assessment Test (COAT)

COAT is a five-item questionnaire developed by the Cough Study Group of the Korean Academy of Tuberculosis and Respiratory Diseases for easier use in Korean clinical practice to assess the effect of cough on quality of life.[7]

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At Visits 2 and 3, the investigator administers COAT by interview. It assesses cough frequency, interference with daily activities, sleep disturbance, fatigue, and airway hypersensitivity. Each item is rated 0-4, for a total score of 0-20.

Item	None	Mild	Moderate	Severe	Very severe
How often do you cough?	0	1	2	3	4
Does coughing interfere with your daily activities?	0	1	2	3	4
Does coughing make it difficult to sleep?	0	1	2	3	4
Does coughing make you tired?	0	1	2	3	4
Does your cough worsen with dust, irritating odors, or breathing cold air?	0	1	2	3	4

4.1.1.3 Overall Improvement in Treatment Response (IMOS)

At Day 7 (Visit 3), the investigator interviews the participant regarding treatment effects, integrates the results, and rates change from baseline (Visit 2) using the five-point Integrative Medicine Outcome Scale. The participant also independently assesses overall improvement.

Overall improvement is defined as “Major improvement” (2) or “Complete recovery” (1).

Score	IMOS
1	Complete recovery
2	Major improvement
3	Slight to moderate improvement
4	No change
5	Deterioration

4.1.1.4 Participant Satisfaction with Treatment Response (IMPSS)

At Day 7 (Visit 3), participants subjectively rate their satisfaction with treatment effects relative to baseline (Visit 2) using the five-point Integrative Medicine Patient Satisfaction Scale.

Score	IMPSS
1	Very satisfied
2	Satisfied
3	Neutral
4	Dissatisfied
5	Very dissatisfied

4.1.2 Safety Assessments

Clinically significant abnormal findings detected at screening or before study drug administration will be collected as medical history. Clinically significant postdose abnormalities meeting the definition of an adverse event will be collected as adverse events.

4.1.2.1 Adverse Events

Participants will be instructed to report adverse events spontaneously whenever they occur. The investigator will identify and record events through interviews at scheduled or additional visits.

Definitions and procedures for collection, recording, assessment, and reporting are provided in Section 8, Adverse Events.

4.1.2.2 Physical Examination

All participants will undergo inspection, palpation, percussion, and auscultation at each visit to assess health and adverse events. Examination includes general appearance, skin, head/neck, chest/lungs, heart, abdomen, genitourinary system, extremities, musculoskeletal system, nervous system, and lymph nodes.

4.1.2.3 Clinical Laboratory Tests

All participants will undergo laboratory testing at the study site's laboratory according to the study schedule to assess general health. Sample collection, management, and processing will follow each site's laboratory instructions and SOPs.

For Visits 1 and 3, when blood sampling is scheduled, participants should attend fasting if possible, with no food or beverages except water for 8 hours before testing. Screening results obtained at the site within 4 weeks before Visit 1 may be used. One repeat test during screening is permitted at the investigator's discretion; if repeated, final eligibility will be based on the repeat results.

Tests include the following; additional tests may be performed if the investigator considers them necessary.

- Hematology: RBC, hemoglobin, hematocrit, platelet count, WBC, and WBC differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
- Blood chemistry: BUN, creatinine, uric acid, total bilirubin, albumin, total protein, ALT, AST, glucose, total cholesterol, and electrolytes (Na, Ca, K, Cl).
- Urinalysis: protein (albumin), glucose, ketones, WBC, blood (RBC).
- Coagulation at Visit 1 only: PT (INR), aPTT.
- Diagnostic tests: bacterial or viral testing when necessary, in the investigator's judgment, for differential diagnosis of acute bronchitis.

4.1.2.4 Vital Signs

Blood pressure, pulse rate, and tympanic temperature will be measured at every visit according to the schedule, preferably before other planned tests, with the participant seated after 5 minutes of rest.

4.1.2.5 Electrocardiogram (ECG)

All participants will undergo a 12-lead ECG at Visits 1 and 3 to assess health. Screening ECG results obtained at the site within 4 weeks may be used. Normal/abnormal status and the clinical significance of abnormalities will be recorded in the CRF. Additional ECGs may be performed if considered necessary by the investigator.

4.1.3 Other Assessments

4.1.3.1 Participant Baseline Information

Before study entry, the purpose and details will be fully explained and written consent obtained. Screening numbers will be assigned in consent order, followed by collection of baseline information: consent status and date, sex, date of birth, age, alcohol use within the previous 30 days, smoking within the previous 30 days, and average daily cigarette consumption for those who smoked during that period.

4.1.3.2 Medical History

Medical history will be investigated in detail through interview and review of prior medical records. Past and current conditions, including surgery and allergies within 6 months before screening, will be recorded with onset year or year/month and whether ongoing at screening. For eligibility-related history,

the period specified in each criterion, or the participant's entire lifetime if no period is specified, will be reviewed.

4.1.3.3 Medication History

Medication use within 1 month (30 days) before screening and current use, including regimen, dose, and duration, will be investigated. Changes from the screening medication history will be assessed. Any change in concomitant medication must be documented in detail in source records.

4.1.3.4 Height and Weight

Height and weight will be measured at screening. Weight will be measured with outer clothing and shoes removed and pockets empty. Both values will be recorded to one decimal place, rounding the second decimal place if measured.

4.1.3.5 Pregnancy Testing

At screening and the end-of-study visit, women of childbearing potential, excluding those with confirmed sterilization or menopause (including surgical menopause), will undergo serum or urine hCG testing at the site laboratory. A positive urine test may be followed by a serum test for final confirmation. Women of childbearing potential have experienced menarche and have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) and are not postmenopausal. Menopause is at least 12 months of amenorrhea after the final menstrual period without another cause.

4.1.3.6 Chest X-ray

All participants will undergo a chest X-ray at Visit 1. Normal/abnormal status and the clinical significance of abnormalities will be recorded in the CRF. Additional X-rays may be performed if necessary in the investigator's judgment.

4.1.3.7 Rescreening

Participants who fail screening may be rescreened once. New written consent must be obtained, a new screening number assigned, and all Visit 1 procedures repeated.

4.2 Procedures by Visit

4.2.1 Visit 1 (Screening, within 2 days before Day 0)

Participants will complete the informed consent process and sign the consent form. A screening number will be assigned in enrollment order, followed by the procedures below. Consent may be obtained before Visit 1. Tests not completed at Visit 1 may be performed at another visit within the screening period.

- Collect and record demographic information, medical history (past/current conditions including surgery), and medication history.
- Perform physical examination and measure vital signs.
- Perform ECG and chest X-ray.
- Measure height and weight.
- Perform hematology, blood chemistry, urinalysis, and coagulation tests. Bacterial or viral tests may be performed if needed for differential diagnosis in the investigator's judgment.
- Perform pregnancy testing in women of childbearing potential.
- Assess BSS to determine acute bronchitis symptom severity.
- Check inclusion/exclusion criteria.
- Schedule the next visit.

4.2.2 Visit 2 (Randomization, Day 0)

This visit will occur within 2 days after the first visit. The following assessments will be performed:

- Check changes in medical and medication history since the previous visit.
- Perform physical examination and measure vital signs.
- Assess BSS and administer COAT.
- Review all test and assessment results, including laboratory results, to confirm final eligibility.
- Randomize the participant and assign a randomization number.
- Dispense study drugs and explain administration.
- Schedule the next visit.

4.2.3 Visit 3 (End of Study, Day 7 ±1 day)

This is the final efficacy assessment visit for participants who have completed study drug administration. The permitted window is 1 day before or after the target day. These assessments will also be performed if participation ends early:

- Check changes in medication history since the previous visit.
- Investigate adverse event occurrence and details.
- Perform physical examination and measure vital signs.
- Perform ECG.
- Perform hematology, blood chemistry, and urinalysis.
- Perform pregnancy testing in women of childbearing potential.
- Assess BSS and administer COAT.
- Obtain investigator and participant IMOS assessments.
- Assess participant satisfaction with treatment response using IMPSS.
- Collect, count, and record remaining study drugs returned by the participant.

4.2.4 Unscheduled Visits

Additional visits may occur whenever requested by the participant or representative or considered necessary by the investigator. At regular visits, the investigator will inform participants of this possibility and instruct them to make immediate contact if an adverse event occurs. Unscheduled visits must not change the scheduled timetable.

Changes in medication use and adverse event occurrence will be investigated. The investigator may select and perform additional tests as necessary.

5. Participant Selection and Withdrawal Criteria

5.1 Inclusion Criteria

Participants must satisfy all of the following criteria to be eligible for enrollment.

1) Males and females aged 12 to 75 years, inclusive.

2) Diagnosis of acute bronchitis and both of the following: onset within 48 hours before randomization; BSS ≥5 at both screening and randomization.

3) Women who could become pregnant and men who agree to use medically acceptable contraception throughout the study. Acceptable methods are combined hormonal contraception containing estrogen and progestogen that inhibits ovulation (oral, intravaginal, transdermal); progestogen-only hormonal contraception that inhibits ovulation (oral, injectable, implantable); an intrauterine device (IUD); an intrauterine hormone-releasing system (IUS); bilateral tubal ligation/salpingectomy; bilateral oophorectomy; a vasectomized partner; and sexual abstinence.

4) For women of childbearing potential, a negative pregnancy test before study drug administration.

5) Voluntary decision to participate and written consent after receiving and understanding a detailed explanation of the study. For minors aged 12 years or older and under 19 years, the legally authorized representative must also provide written consent.

5.2 Exclusion Criteria

Participants meeting any of the following criteria must be excluded from enrollment.

1) Fever with measured temperature >38.5°C at randomization.

2) A respiratory disease that, in the investigator's judgment, may affect efficacy assessment: (a) pneumonia, bronchial asthma, cystic fibrosis, viral influenza, active tuberculosis, chronic obstructive pulmonary disease, bronchiectasis, interstitial lung disease, or similar conditions; or (b) findings suggestive of pneumonia on chest X-ray, auscultation, or vital signs.

3) A history or condition considered likely to affect the study, including any of the following:

(a) A coagulation disorder, increased bleeding tendency, or coagulation test results outside the normal range at Visit 1.

(b) Malignancy diagnosed within 5 years before screening. Participation is permitted if at least 1 year has elapsed since complete resection of basal-cell/squamous-cell carcinoma, curative resection of papillary thyroid carcinoma, or successful treatment of cervical carcinoma in situ; or if the person was declared cured within the 5 years before screening and has not received, or is considered unlikely to require, treatment for the disease.

(c) Other clinically significant hepatic, renal, cardiovascular, respiratory, endocrine, or central nervous system disease or disorder identified by physical examination or laboratory testing.

(d) History of psychiatric illness, alcoholism, or drug abuse.

(e) Hereditary disorders such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

4) Use or planned use of the following medications during the specified periods:

(a) At Visit 1: ongoing anticoagulant use.

(b) From 2 weeks before Visit 2 through the end-of-study visit (Visit 3): systemic antibiotics or antivirals; systemic/inhaled glucocorticosteroids.

(c) From 1 week before Visit 2 through Visit 3: ACE inhibitors. For perindopril, the period starts 4 weeks before Visit 2. Participants already taking this class for an underlying disease may continue without a change in dose or regimen during the study.

(d) From 2 days before Visit 2 through Visit 3: expectorants (mucolytics or sputum-expelling agents); antitussives; herbal preparations with antitussive/expectorant effects.

(e) Throughout the study (Visits 1-3): antihistamines; anticholinergics, including bronchodilators; other symptomatic treatments for acute bronchitis; analgesics. Temporary acetaminophen for fever, up to 1.5 g/day, is allowed except within 24 hours before Visits 2 and 3.

5) Any of the following screening laboratory results: (a) ALT or AST >3 times the upper limit of normal; (b) eGFR <30 mL/min/1.73 m², calculated using the CKD-EPI equation from creatinine results.

6) History of hypersensitivity to any component of the study drugs.

7) Pregnancy or breastfeeding.

8) Smoking an average of at least 15 cigarettes/day during the previous 30 days.

9) Receipt of an investigational drug or use of an investigational medical device in another trial within 30 days before screening, or current participation in another interventional clinical trial.

10) Any other reason the investigator considers participation inappropriate.

5.3 Discontinuation and Withdrawal Criteria

Randomized participants unable to participate for the entire study for any reason will be classified as withdrawn. Participants may stop at their own request at any time or may be withdrawn at the investigator's or sponsor's discretion for safety, behavioral, or administrative reasons. The investigator

must ask the reason, request a final visit, and make every effort to follow unresolved adverse events when applicable. Participants must return all unused study drugs.

When discontinuation or withdrawal is decided, participants should attend the site for final-visit procedures whenever possible. Withdrawn participants cannot reenter the study.

Participation may end at the participant's request or after discussion between the investigator and sponsor in the following circumstances:

1. Participant or representative withdrawal of consent.
2. An inclusion/exclusion criterion violation discovered during the study.
3. An adverse event or serious adverse event makes continued participation difficult.
4. Participant or representative request to stop because of unsatisfactory treatment effect.
5. Failure to follow the principal investigator's or other investigator's instructions.
6. Loss to follow-up.
7. Pregnancy during the study.
8. Continued participation otherwise considered inappropriate by the sponsor or investigator.
9. Use of prohibited concomitant medication that may affect efficacy or safety assessment.

5.4 Handling of Protocol Violations

The principal investigator and study staff must thoroughly understand and comply with the protocol to prevent violations. To ensure adherence to dosing and testing schedules, staff must take appropriate measures, such as written notification of the next appointment or telephone monitoring, to ensure attendance on the required day. Unavoidable violations must be reported to the monitor or sponsor and appropriately reported within the time limits required by each site's IRB.

6. Investigational Products

6.1 Overview of Investigational Products

6.1.1 Test Drug

- Product name: CANIUM Tab.
- Generic name of active ingredient: Pelargonium sidoides 11% ethanol dry extract (5.5-6.6:1).
- Manufacturer: Dasan Pharmaceutical Co., Ltd.
- Appearance and dosage form: reddish-brown, round, film-coated tablet.
- Storage: airtight container, room temperature (1-30°C).
- Shelf life: 36 months from manufacture.

Ingredient	Quantity	Unit	Specification	Notes
Pelargonium sidoides 11% ethanol dry extract (5.5-6.6:1)	20	mg	In-house specification	Total phenolic compounds, as epicatechin: 2.0-10.0 mg

6.1.2 Comparator

- Product name: Umckamin Tab.
- Manufacturer: Hanwha Pharma Co., Ltd.
- Appearance and dosage form: reddish-brown, round, film-coated tablet.
- Storage: airtight container, room temperature (1-30°C).
- Shelf life: 36 months from manufacture.

Ingredient	Quantity	Unit	Specification	Ingredient information
Mixture (1:4.56) of Pelargonium sidoides 11% ethanol extract (1:8-10) and maltodextrin	111.111	mg	In-house specification	Equivalent to 20 mg dry matter of Pelargonium sidoides 11% ethanol extract (1:8-10)

6.1.3 Test-Drug Placebo

- Product name: placebo matching the test drug.
- Manufacturer: Dasan Pharmaceutical Co., Ltd.
- Appearance and dosage form: tablet visually identical to and indistinguishable from the test drug.
- Storage: airtight container, room temperature (1-30°C).
- Shelf life: 36 months from manufacture.

6.1.4 Comparator Placebo

- Product name: placebo matching the comparator.
- Manufacturer: Dasan Pharmaceutical Co., Ltd.
- Appearance and dosage form: tablet visually identical to and indistinguishable from the comparator.
- Storage: airtight container, room temperature (1-30°C).
- Shelf life: 36 months from manufacture.

6.2 Dose, Administration, and Treatment Duration

6.2.1 Dose and Administration

The test drug and comparator are each administered as one tablet orally three times daily. To maintain double-blinding, each dose comprises:

Group	Administration per dose
Test	One test-drug tablet (●) plus one comparator placebo (□)
Control	One test-drug placebo (○) plus one comparator tablet (■)

Do not take the tablets while lying down.

6.2.2 Treatment Duration

7 days.

6.3 Manufacture, Packaging, and Labeling

The sponsor will manufacture or purchase the study drugs and supply them to the investigational pharmacist at each site.

Placebos will be identical in appearance and characteristics to the corresponding active product, with no visually observable or weight differences. Packaging personnel will apply identical labels to maintain participant and investigator blinding.

Labels will comply with Annex 11, Manufacture of Investigational Medicinal Products, of the Regulations on Pharmaceutical Manufacturing and Quality Control, and include:

1. A statement restricting use to clinical trials, such as “For clinical trial use.”

2. Product name or identification.

3. Batch or code number identifying the contents and packaging operation.

4. Name, address, and telephone number of the sponsor (holder of clinical trial approval).

5. Expiration date.

6. Storage conditions.

7. “Keep out of reach of children.”

8. Reference code identifying the trial.

9. Subject Identification No., Treatment No., and Visit No.*

10. Investigator name and instructions for use, if the sponsor considers them necessary.

*These may be omitted if the sponsor recognizes and documents a study-specific reason why they are unnecessary.

If primary and secondary packaging are supplied together, or a container is too small for all information, only the minimum required information may appear on the primary label under Annex 11. All information must appear on secondary packaging.

6.4 Investigational Product Management

- Store study drugs at room temperature (1-30°C). They must not be used without instructions or a prescription from the principal investigator or study investigator.
- In consultation with the principal investigator, the sponsor must deliver study drugs directly to the investigational pharmacist and obtain and retain a receipt.
- The pharmacist must store and manage study drugs to prevent nonstudy use, handle receipt, inventory, participant dispensing and returns, record these activities, and regularly inform the principal investigator.
- During the trial, the sponsor must check quantities and storage conditions and take measures to support proper study conduct.
- If the study is suspended or completed, a product problem occurs, or a use-by or expiration date is reached, the sponsor must retrieve and dispose of unused products. The pharmacist must return unused products and retain the return receipt.

6.5 Maintenance and Breaking of the Blind

To maintain double-blinding, the study will use a double-dummy method with placebos visually indistinguishable from the active products. The principal investigator will retain unique-code assignment details in sealed form without disclosure until study completion.

Assignments will be managed through the central registration center's IWRS. In principle, treatment assignments must remain blinded until database locking is completed after study completion. Unblinding may occur if access is unavoidable in an emergency such as a serious adverse drug reaction, or if the sponsor considers it essential for participant rights and safety. Only the affected participant's unique code may be accessed.

Unblinding must be considered case by case and only for a serious medical emergency. It should generally occur only if treatment information will affect care. The principal investigator must contact the sponsor and obtain agreement before unblinding. All unblinding must be clearly justified, documented, and retained. Participants whose codes are unblinded cannot continue in the study.

6.6 Study Drug Compliance Assessment

Compliance will be assessed by comparing the expected number of tablets, including two doses on the first prescription day and one dose on the end-of-study day, with the quantity returned by the participant. Remaining drugs must be returned to the pharmacy and entered in accountability records. Any discrepancy between quantities prescribed, returned, and taken must be explained and recorded.

Overall compliance (%) = (Number of tablets actually administered during the study / Total number expected to be administered during the study) × 100.

6.7 Concomitant Medications and Treatments

Concomitant treatments used for other diseases, adverse events, examinations, or similar purposes during the trial must be recorded in detail in the CRF. For medications, record product name, indication, dose and unit, treatment period (start/end dates), and route. For nondrug treatments, record treatment name, purpose, and period (start/end dates).

6.7.1 Prohibited Concomitant Medications and Treatments

The following are prohibited during the specified periods:

1. Visit 1 through Visit 3: anticoagulants.

2. Two weeks before Visit 2 through Visit 3: systemic antibiotics and antivirals; systemic/inhaled glucocorticosteroids.

3. One week before Visit 2 through Visit 3: ACE inhibitors. For perindopril, prohibition starts 4 weeks before Visit 2. Participants already receiving an ACE inhibitor for an underlying disease may continue without changing the dose or regimen.

4. Two days before Visit 2 through Visit 3: secretolytics/mucolytics or expectorants; antitussives; herbal preparations with antitussive/expectorant effects.

5. Throughout Visits 1-3: antihistamines; anticholinergics, including bronchodilators; other symptomatic treatments for acute bronchitis; analgesics. Temporary acetaminophen for fever, up to 1.5 g/day, is permitted except within 24 hours before Visits 2 and 3.

6.7.2 Permitted Concomitant Medications and Treatments

The following are permitted:

1. Medications used before participation that the investigator considers unlikely to affect interpretation of results.

2. Medications used temporarily for other diseases or adverse events after consultation with the investigator.

3. Temporary acetaminophen for fever, up to 1.5 g/day, except within 24 hours before Visits 2 and 3.

Other medications used for treatment or examination of other diseases may be permitted at the investigator's discretion if they are considered unlikely to affect interpretation of results.

7. Statistical Considerations

7.1 Sample Size and Rationale

7.1.1 Sample Size

To obtain the 92 participants per group required to demonstrate the primary objective, at least 109 per group and 218 in total will be enrolled, allowing for 15% dropout.

7.1.2 Rationale

The primary objective is to compare improvement in acute bronchitis symptoms using BSS change at Day 7 and demonstrate noninferiority of the test drug to the comparator. The hypotheses are:

H_0: $\mu T - \mu C \geq \delta$ versus H_1: $\mu T - \mu C < \delta$

μT: Day 7 change in BSS total score in the test group.

μC: Day 7 change in BSS total score in the control group.

δ: Noninferiority margin.

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Sample size was based on published studies in acute bronchitis of Pelargonium sidoides (EPs 7630), the same active ingredient as the study drugs.

Reference	Treatment	N	Mean change	Difference	SD	Upper 95% confidence limit
15	EPs 7630 (Pelargonium sidoides)	64	-7.20	-2.30	3.10	
15	Placebo	60	-4.90		2.70	
16	EPs 7630 (Pelargonium sidoides)	233	-5.90	-2.70	2.90	
16	Placebo	235	-3.20		4.10	
17	EPs 7630 (Pelargonium sidoides)	108	-7.60	-2.30	2.20	
17	Placebo	109	-5.30		3.20	
18	EPs 7630 (Pelargonium sidoides)	101	-6.10	-3.40	2.10	
18	Placebo	102	-2.70		2.30	
Pooled	Pelargonium sidoides	506	-6.47	-2.72	2.65	-2.34
Pooled	Placebo	506	-3.75		3.46	-2.34

After 7 days of Pelargonium sidoides, BSS total score changes ranged from -5.9 to -7.6, with a weighted mean of -6.47. The test and control groups are assumed to have the same Day 7 change. The standard deviation is assumed to be 2.65, the pooled standard deviation for Pelargonium sidoides.

A conservative statistical margin can be derived from the upper limit of the 95% CI in placebo-controlled studies. However, a statistically acceptable noninferiority margin may be clinically unacceptable. The clinical margin was therefore considered as 50% of the statistical margin.

The weighted mean Day 7 changes were -6.47 for Pelargonium sidoides and -3.75 for placebo. The upper 95% confidence limit of the difference was -2.34. The corresponding statistical margin is 2.34; 50% is 1.17. A more conservative margin of 1.10 was selected for this study.

The sample-size assumptions are:

1. Significance level $\alpha = 0.025$, one-sided.

2. Power $1 - \beta = 0.8$.

3. Allocation ratio 1:1.

4. Noninferiority margin $\delta = 1.10$.

5. Standard deviation $\sigma = 2.65$.

6. Dropout rate 15%.

Calculation formula: $n = 2(Z\alpha + Z\beta)^2\sigma^2 / (\varepsilon - \delta)^2$.

The minimum required sample size is 92 per group. Allowing for 15% dropout, at least 109 per group and 218 in total will be enrolled.

7.2 Endpoints

7.2.1 Primary Efficacy Endpoint

Change from baseline in BSS total score at Day 7 (Visit 3) after study drug administration. BSS rates cough, sputum, rales/rhonchi, chest pain during coughing, and dyspnea from 0 (absent) to 4 (very severe) each; the sum has a maximum of 20.

7.2.2 Secondary Efficacy Endpoints

1. Change from baseline in symptom-specific BSS scores at Day 7 (Visit 3).

2. BSS treatment response rate at Day 7 (Visit 3) relative to baseline. Response definitions: total score <3; decrease of at least 7 points; or total score <3 together with a decrease of at least 7 points.

3. Change from baseline in COAT total score at Day 7 (Visit 3).

4. Investigator-assessed overall improvement in treatment response at Day 7 (Visit 3).

5. Investigator-assessed overall improvement rate at Day 7 (Visit 3).

6. Participant-assessed overall improvement rate at Day 7 (Visit 3).

7. Participant satisfaction with treatment response at Day 7 (Visit 3).

Overall improvement (IMOS) is subjectively rated as change from baseline using a five-point scale. Improvement means “Major improvement” (2) or “Complete recovery” (1). Participant satisfaction (IMPSS) is subjectively rated on a five-point scale relative to baseline treatment effects.

7.2.3 Safety Endpoints

Adverse events; clinical laboratory tests (hematology, blood chemistry, urinalysis); vital signs; physical examination; ECG.

7.3 Statistical Analysis Plan

7.3.1 Analysis Populations

Efficacy data will be analyzed primarily in the PPS and supportively in the FAS. Safety analyses will use the Safety Set (SS).

Analysis set	Definition
SS	All randomized participants receiving at least one dose of study drug.
FAS	Randomized participants receiving at least one dose and having baseline and postdose results for the primary efficacy endpoint.
PPS	FAS participants completing the study according to the protocol without major protocol violations.

PPS exclusions for major violations: failure to obtain consent; violation of inclusion/exclusion criteria; randomization error; prohibited concomitant medication use.

Other PPS exclusions: compliance <80%; violation of the Day 7 visit window.

Other major violations or circumstances considered likely to affect results will be reviewed comprehensively at a blinded meeting before database lock to determine whether PPS exclusion is warranted.

7.3.2 General Statistical Principles

Unless otherwise specified, statistical significance tests will use α = 5%. Noninferiority testing will use a 97.5% one-sided confidence interval, equivalent to the upper limit of a 95% two-sided confidence interval.

Continuous data will be summarized using number of participants, mean, standard deviation, minimum, median, and maximum. Categorical data will be summarized using frequencies and percentages. Two-sided 95% confidence intervals will be provided when needed.

Statistics with decimal values, including means, standard deviations, and percentages, will be rounded to two decimal places. Efficacy endpoint confidence intervals and p-values will be presented to four decimal places; values below 0.0001 will be shown as “<0.0001.”

Normality will be assessed in each treatment group using the Shapiro-Wilk test at a 5% significance level to choose parametric or nonparametric methods.

7.3.3 Demographic Information

Continuous demographic data will be summarized using descriptive statistics by group, and categorical data using frequencies and percentages by group.

7.3.4 Medical and Surgical History

History will be coded using the latest MedDRA version by SOC and PT. Participant counts, percentages, and numbers of occurrences will be presented by treatment group.

7.3.5 Prior and Concomitant Medications

Medications will be classified using the latest WHO-ATC Index. Participant counts, percentages, and numbers of occurrences will be presented by treatment group.

7.3.6 Efficacy Analyses

7.3.6.1 Primary Efficacy Analysis

The endpoint is change from baseline in BSS total score at Day 7 (Visit 3). Each symptom, cough, sputum, rales/rhonchi, chest pain during coughing, and dyspnea, is rated 0 (absent) to 4 (very severe), for a maximum total of 20.

Descriptive statistics will be presented by group for baseline and Day 7 total scores and their change. ANCOVA with baseline BSS total score as a covariate will compare groups. Each group's LSM, the between-group LSM difference, its 95% CI, and p-value will be presented. Noninferiority will be demonstrated if the upper limit of the 95% CI is below 1.10. Within-group changes will be analyzed using a paired t-test or Wilcoxon signed-rank test according to normality.

7.3.6.2 Secondary Efficacy Analyses

1) Symptom-specific BSS changes at Day 7: Descriptive statistics will be presented by group for baseline and Day 7 symptom scores and their changes. ANCOVA will include the corresponding baseline symptom score and baseline BSS stratum (<8 / ≥8) as covariates. Each group's LSM, the LSM difference, its 95% CI, and p-value will be presented. Within-group changes will use a paired t-test or Wilcoxon signed-rank test according to normality.

2) BSS treatment response rate at Day 7: Response definitions are a total score <3, a decrease of at least 7 points, or both. Frequencies and percentages will be presented by group for response at baseline and Day 7. Logistic regression including baseline BSS total score as a fixed effect will compare groups; the odds ratio, 95% CI, and p-value will be presented.

3) COAT total score change at Day 7: Descriptive statistics will be presented by group for baseline and Day 7 scores and their change. ANCOVA will include baseline COAT total score and baseline BSS stratum (<8 / ≥8) as covariates. Each group's LSM, the LSM difference, its 95% CI, and p-value will be presented. Within-group changes will use a paired t-test or Wilcoxon signed-rank test according to normality.

4) Investigator overall improvement score; 5) investigator overall improvement rate; 6) participant overall improvement rate; and 7) participant satisfaction, all at Day 7: IMOS subjectively rates change from baseline on a five-point scale, with improvement defined as “Major improvement” (2) or “Complete recovery” (1). IMPSS subjectively rates satisfaction relative to baseline on a five-point scale. Frequencies and percentages will be presented by group for these outcomes. Between-group comparisons will use CMH tests accounting for baseline BSS stratum (<8 / ≥8).

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7.3.7 Safety Analyses

7.3.7.1 Adverse Events

TEAEs occurring after study drug administration will be summarized in detail. Frequencies, percentages, and event counts will be presented by group for TEAEs, ADRs, SAEs, and events leading to study discontinuation. Incidences will be compared using Pearson's chi-square test, or Fisher's exact test if more than 20% of cells have expected frequencies below 5.

Frequencies, percentages, and event counts will also be presented by group and MedDRA SOC/PT, and by event characteristics such as severity and causality.

7.3.7.2 Clinical Laboratory Tests

Descriptive statistics will be presented by visit and treatment group for continuous hematology, blood chemistry, and urinalysis variables and by group for pre- to posttreatment changes.

Results will be classified as normal/NCS versus CS. Pretreatment-to-posttreatment shift tables will be presented and within-group comparisons performed using McNemar's test. Data listings will be provided for posttreatment CS abnormalities.

7.3.7.3 Vital Signs

Descriptive statistics for blood pressure, pulse, and tympanic temperature will be presented by visit and group and for pre- to posttreatment changes by group.

7.3.7.4 Physical Examination

Data listings will be provided for posttreatment clinically significant abnormal findings.

7.3.7.5 ECG

ECG results will be classified as normal/NCS versus CS. Pretreatment-to-posttreatment shift tables will be presented, with McNemar's test for within-group comparison. Data listings will be provided for posttreatment clinically significant abnormalities.

7.3.8 Handling of Withdrawals and Missing Data

Missing safety data and missing efficacy data in PPS analyses will not be imputed. Missing efficacy data in FAS analyses will be handled by LOCF, treating the most recent data as the value at the missing time point. Pretreatment (baseline) results will not be carried forward as posttreatment results.

7.3.9 Planned Interim Analyses and Data Monitoring

No interim analysis or data monitoring committee is planned. Based on study risk, the principal investigator will act as Protocol Safety Manager (PSM). Each site's principal investigator will monitor participant safety according to the protocol.

When an SAE or ADR occurs, the principal investigator will collect and review the participant's data and safety information. Adverse events, unanticipated problems, and protocol noncompliance will be reported to the sponsor (including the CRO), IRB, and, when necessary, the MFDS in accordance with the protocol, local IRB requirements, GCP, and applicable regulations.

Under Section 9.12, efficacy or safety information materially affecting study continuation will be reported promptly to the sponsor. The sponsor will discuss and decide whether to continue according to its SOPs.

8. Adverse Events

8.1 Definitions

1) Adverse event (AE): Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease in a participant receiving study drug, whether or not causally related to that drug.

2) Adverse drug reaction (ADR): Any harmful and unintended response at any study drug dose for which a causal relationship cannot be excluded.

3) Unexpected ADR: A reaction whose nature or severity differs from available product information, such as the investigator's brochure or package insert.

4) Serious AE/ADR: An event or reaction at any dose that meets any of the following:

(a) Results in death or is life-threatening.

(b) Requires hospitalization or prolongation of hospitalization.

(c) Causes persistent or significant disability or incapacity.

(d) Causes a congenital anomaly or birth defect.

(e) Is another medically important event, such as drug dependence, abuse, or a blood disorder.

The following hospital visits are not considered SAEs in this study: hospitalization planned before study entry; hospitalization for health screening, cosmetic purposes, or convalescence; an emergency department visit lasting no more than 24 hours, although the investigator may still consider it serious.

Other situations considered to materially affect a participant's well-being or health may be classified as serious based on the medical judgment of the treating physician and relevant specialists, and appropriate action will be taken.

5) Suspected unexpected serious adverse reaction (SUSAR): A reaction in a participant receiving study drug that meets both the serious ADR definition in Section 8.1(4) and the unexpected ADR definition. Unexpectedness means that the nature or severity differs from available information such as the investigator's brochure or package insert.

8.2 Collection and Recording of Adverse Events

- Events will be collected from study drug administration through the end-of-study visit. Medical events before administration will be recorded as medical history.
- Reports must include event term, duration (start and resolution dates), severity, relationship to study drug, outcome, action taken with study drug, corrective treatment, and seriousness.
- Investigators should use a comprehensive diagnosis or symptom in standard medical terminology rather than recording individual signs and symptoms separately.
- Events should be followed, whenever possible, until resolution, stabilization, or loss to follow-up. Follow-up of events without a known resolution date at the last visit is at the investigator's discretion.
- Events arising after study completion will be reported only if serious and related to study drug.

8.3 Assessment of Adverse Events

8.3.1 Severity

Each AE and SAE will be graded as follows:

- Mild: minimal discomfort, easily tolerated, and no interference with normal activities of daily living or function.
- Moderate: discomfort that significantly interferes with normal daily activities or function.
- Severe: prevents normal daily activities or function.

Activities of daily living (ADL) are daily self-care activities, such as bathing, dressing and undressing, eating, taking medication, hygiene, and toileting.

Both AEs and SAEs may be severe under these definitions. Severity must not be confused with seriousness; a severe event is not necessarily serious.

8.3.2 Causality

The investigator will assess the relationship to study drug using the criteria below. Events assessed in any category other than “Unlikely” or “Not-related” are ADRs.

1. Certain: A plausible temporal relationship to drug administration/use, not explained by other medicines, chemicals, or concurrent disease; a clinically plausible response to withdrawal; and, if rechallenge is necessary, a pharmacologically or phenomenologically definitive response.

2. Probable/likely: A reasonable temporal relationship, unlikely to be explained by other medicines, chemicals, or concurrent disease, and a clinically reasonable response to withdrawal; no rechallenge information.

3. Possible: A reasonable temporal relationship, but also explainable by other medicines, chemicals, or concurrent disease; withdrawal information is insufficient or unclear.

4. Unlikely: A temporal relationship that makes causality unlikely, with a plausible alternative explanation involving other medicines, chemicals, or underlying disease.

5. Conditional/unclassified: More information is needed for an adequate assessment, or additional data are under review.

6. Unassessable/unclassifiable: Insufficient or conflicting information prevents judgment and cannot be supplemented or verified.

7. Not-related: The temporal sequence is implausible or the event is plausibly explained by factors other than the study drug.

8.4 Reporting of Serious Adverse Events

All SAEs occurring from the start of adverse event collection during the study must be reported to the sponsor or designee by telephone, fax, or email within 24 hours of investigator awareness, regardless of relationship. Reports to the site's IRB must follow its required timelines.

Safety reporting contact	Telephone	Email	Fax
Hee-seon Eom, Dasan Pharmaceutical Co., Ltd.	02-2679-5206	hseom@dspharm.com	02-2679-5208
Medisafe Co., Ltd.	-	PV@medisafe.kr	02-6915-8005

Events occurring after study completion will be reported only if serious and related to study drug.

To protect confidentiality, SAE reports to the sponsor must use the participant identification code instead of name, resident registration number, address, or other identifying information. If copies of medical records are requested, identifying information other than the study code will be masked.

Investigators must provide follow-up reports when additional information becomes available and periodically follow the event until resolution, stabilization, or loss to follow-up, reporting to the sponsor and IRB.

8.5 Reporting and Management of SUSARs

The sponsor must report SUSARs to investigators, the Commissioner of the MFDS, and, when necessary, the IRB within the periods below. For details, refer to Annex 4, Korean Good Clinical Practice, of the Rules on the Safety of Pharmaceuticals, etc., and the MFDS guidance “Considerations for Safety Assessment and Reporting by Sponsors of Clinical Trials of Medicinal Products.”

1. Fatal or life-threatening unexpected ADRs must be reported as soon as possible by telephone, fax, or written report, within 7 days after the sponsor first receives the report or becomes aware. If the initial

report is incomplete, a detailed follow-up report must be submitted within 15 days of first receipt or awareness.

2. All other SUSARs must be reported within 15 days after receipt or awareness.

The principal investigator and study staff must protect participant safety and promptly take appropriate measures to minimize the reaction. The sponsor must report additional information until the reaction is closed, meaning resolved or no longer possible to follow. In multicenter studies, the sponsor must promptly inform sites through the principal investigators.

8.6 Pregnancy

Pregnancy in a female participant is not an AE. An uncomplicated elective abortion (excluding therapeutic abortion) or hospitalization for normal delivery of a healthy infant is also not an AE.

If a female participant becomes pregnant during the study, she must discontinue. The investigator must complete a pregnancy report and notify the sponsor within 24 hours of awareness. The mother and fetus must be followed through delivery even if the participant withdraws or completes the study.

If a male participant's female partner or spouse becomes pregnant during participation, information must be collected after obtaining her consent to provide pregnancy information. Maternal and fetal outcomes must be followed through delivery. The investigator must submit a pregnancy report within 24 hours after written consent from the pregnant partner or spouse.

Serious maternal complications, spontaneous abortion, ectopic pregnancy, stillbirth, neonatal death, or congenital anomalies must be treated as SAEs and reported under Section 8.4.

9. Ethical Considerations and Administrative Procedures

9.1 Ethical and Regulatory Compliance

The study must comply with ethical principles based on the Declaration of Helsinki, GCP, and applicable laws and regulations. Participant rights, safety, and welfare take priority.

9.2 Protocol Compliance

Investigators must conduct the trial according to the protocol. Deviations are prohibited except to eliminate an immediate hazard to a participant, and any deviation and its reason must be documented. Even if an investigator believes a deviation would improve study conduct, it must not be implemented before sponsor agreement and IRB approval, including MFDS approval when required.

9.3 Protocol Approval and Amendments

The protocol or amendment must receive IRB approval for the applicable study phase and MFDS approval when necessary before initiation or implementation. Participants cannot enter before approval. No amendment may be implemented without written IRB approval, except to eliminate a clear and immediate hazard.

9.4 Informed Consent Procedures

The participant information sheet and consent form may be used only after IRB approval. Consent must follow the Declaration of Helsinki and Korean GCP. Before any study procedure, the investigator must fully explain the trial to the participant or representative and obtain written consent. The original signed form must be retained in the investigator file, and a copy of the signed form and the information sheet provided to the participant or representative.

If the participant cannot consent because of impaired understanding or ability to express a decision, consent must be obtained from a representative. Under Article 34-2(3)(3) of the Pharmaceutical Affairs Act, the order is the legally authorized representative or, if none, spouse, lineal ascendant, then lineal descendant. Multiple ascendants or descendants must agree on a representative; if they cannot, the oldest serves as representative.

If neither the participant nor representative can read, an impartial witness must attend the entire consent process. After oral consent and a handwritten signature if possible, the witness signs to attest that the information was accurately explained and understood.

Any revised information sheet or consent form must be reapproved by the IRB before use, and ongoing participants or representatives must be reconsented. The investigator must record whom they informed, when, and what information was provided in source documents.

9.5 Measures to Protect Participant Safety

Investigators must conduct the study with regard for participant rights and welfare under the Declaration of Helsinki and be familiar with Korean GCP and the protocol. Sufficient time must be devoted to interviews and examinations to thoroughly assess eligibility and adverse events.

The principal investigator will periodically report adverse events, progress, status, and results to the sponsor. The sponsor will periodically oversee study progress.

9.6 Protection of Participants in Vulnerable Circumstances

Vulnerable participants include persons whose voluntary decision may be influenced by anticipated benefits or fear of disadvantage from a hierarchical superior if they refuse, such as medical, Korean medicine, pharmacy, dental, and nursing students; healthcare institution or research institute employees; pharmaceutical company employees; and military personnel. They also include persons with incurable disease; residents of institutions under Article 27 of the Rules on the Safety of Pharmaceuticals, etc.; unemployed or impoverished persons; emergency patients; ethnic minorities; itinerant or homeless persons; refugees; minors; and those unable to give voluntary consent.

Before enrollment, the investigator must determine whether the participant has adequate capacity and whether additional consent procedures are necessary. The importance of voluntary participation must be emphasized, and participants must be free to choose. No form of coercion is permitted.

Because this trial includes minors, investigators must ensure:

1. Recruitment without inappropriate inducement of the minor or legally authorized representative.

2. Consent from the legally authorized representative under applicable laws and regulations.

3. Consent/assent from the minor whenever possible; the age at which this is possible is determined by the relevant IRB.

9.7 Medical Care and Treatment after Study Completion

Poststudy care will follow usual standards for acute bronchitis. Investigators must guide participants who withdraw or do not achieve a satisfactory effect toward appropriate alternative treatment. Participants completing the study must also receive appropriate alternative treatment if continued care is needed.

Participants must be able to obtain care at any time as instructed by the investigator for unexpected adverse events. If a study-related injury qualifies for sponsor compensation under the compensation policy, medical costs may be compensated after study completion depending on whether the injury persists.

9.8 Compensation for Injury

For adverse events caused by study drugs or injury occurring during corrective treatment of such events, the sponsor will compensate participants for injury directly caused by study drugs under the compensation policy.

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9.9 Study Documents and Record Retention

9.9.1 Case Report Forms and Source Documents

Data will be collected using electronic case report forms (e-CRFs) in accordance with FDA 21 CFR Part 11 and/or MFDS guidance on electronic clinical trial data processing. Investigators and/or designees must complete training and receive unique EDC accounts. When a user no longer participates, the investigator must notify the sponsor, including the CRO, so access can be disabled. The investigator is responsible for accuracy, completeness, clarity, and timeliness of e-CRF information.

An e-CRF will be completed for each participant as promptly as possible. Data must agree with source documents. The investigator must review and electronically sign all site e-CRFs.

Monitors will compare CRFs with source records, notify investigators of discrepancies, and request appropriate correction. Only investigators and/or designees may enter or amend CRFs and source documents.

9.9.2 Access to Source Data

The sponsor, monitors, and auditors may review participant records for monitoring, auditing, and study oversight. By entering the study agreement, the investigator acknowledges that sponsor or CRO monitors and auditors may inspect participant charts and CRFs to verify data. Information must remain confidential, with appropriate secure facilities and management standards. The investigator must provide necessary support to the CRO and sponsor.

The investigator must permit authorized representatives of the sponsor, regulatory authorities, and IRB direct access to original medical records to verify study procedures and data.

9.9.3 Retention of Study Data

Investigators must securely retain study materials and records for 5 years after study completion. After the clinical study report is completed, study documents must be transferred to the designated custodian. The sponsor must be notified in advance of destruction or relocation of records.

Retention may be extended at the MFDS Commissioner's direction or if the sponsor considers it necessary. The sponsor must inform investigators and institutional heads in writing of the need for retention and its duration, and notify the principal investigator and institutional head in writing when retention is no longer required.

9.9.4 Audits and Inspections

The sponsor or designee may conduct quality assurance audits to ensure GCP and regulatory compliance, and the MFDS may conduct inspections. After appropriate notice, investigators must cooperate, permit direct access to all study documents, and allocate time to discuss findings and related matters.

9.10 Confidentiality of Study Documents and Participant Records

All study results and documents are confidential. Investigators and CRO personnel must not disclose study information without written sponsor approval.

Identifying records, including participant names and medical record numbers, will be kept confidential under the principal investigator's responsibility in a separate locked area with restricted access. CRFs and other study documents will identify participants by code rather than name. Identity will remain confidential in publications.

9.11 Study Site Monitoring

Monitoring will protect participant rights and welfare; verify accuracy, completeness, and verifiability of reported data against source records; and confirm compliance with the approved protocol, Article 30 of the Rules on the Safety of Pharmaceuticals, etc., and Annex 4, Korean GCP.

Sponsor-designated monitors will conduct regular site visits and telephone contacts, assess progress, and verify investigators' protocol and regulatory obligations. They will review original participant records, CRFs, drug accountability records, and study document storage, discussing discrepancies or problems with investigators.

9.12 Early Termination or Suspension

9.12.1 Sponsor

If a site, investigator, or sponsor designee fails to meet basic obligations, including GCP, protocol, contracts, and applicable laws and regulations, the sponsor will take immediate corrective action. The sponsor may terminate the entire trial or a site's participation early for:

1. Failure to enroll the target number overall or at a particular site.

2. Efficacy or safety information materially affecting continuation.

3. Site or investigator violations of GCP, protocol, contracts, or laws/regulations serious enough to compromise continuation.

4. Other administrative reasons materially affecting continuation.

The sponsor must promptly report early termination or suspension and its reasons in writing to the principal investigator and MFDS Commissioner. In a multicenter trial, other sites' principal investigators must also be notified in writing.

9.12.2 Investigator

If the sponsor terminates or suspends the study, the principal investigator must immediately inform the IRB, provide a detailed explanation, and promptly notify participants to ensure appropriate care and follow-up.

If the principal investigator intends to terminate or suspend the study, the sponsor must be informed in advance. The decision and reasons must be promptly reported to the IRB with a detailed written explanation.

9.13 Clinical Study Report and Publication

After complete analysis of all sites' data, the sponsor will prepare a report and inform investigators of the results.

All study data and results belong to the sponsor, which has the right to publish them at any time. Investigators must not publish, present, or disclose results without prior written sponsor consent and must ensure study staff comply. To ensure use of accurate, verified data, all draft publications and presentations must be submitted to the sponsor for discussion before release and withheld until written approval.

In a multicenter study, investigators agree not to publish results from their own or selected sites before publication of the combined results, unless all principal investigators and the sponsor formally agree.

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11. List of Appendices

Appendix 1. Participant Information Sheet and Informed Consent Form.

Appendix 2. Information Sheet and Consent Form for a Participant's Pregnant Partner or Spouse.

Appendix 3. Compensation Policy for Study-Related Injury.

Appendix 4. Study Sites and Sponsor Organization.

Appendix 5. Expected Adverse Reactions and Precautions for Study Drugs.

Appendix 6. Adolescent Participant Information Sheet and Consent Form.