Statistical Analysis Plan

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Organization	Approval role	Role and name	Signature information in the source	Date
CLIPS BnC	Prepared by	PB / Kibyung Park	Electronically signed; kibyung park; 15:57:05 GMT+9	2026/06/16
CLIPS BnC	Reviewed by	MM / Haerim Lee	Electronically signed; 16:09:37 GMT+9	2026/06/16
CLIPS BnC	Reviewed by	STM / Daehan Kim	Electronically signed; Daehan Kim; 16:10:19 GMT+9	06/16/2026
Dasan Pharmaceutical Co., Ltd.	Reviewed by	PM / Hee-seon Eom	Electronically signed; 16:14:23 GMT+9	2026/06/16
Dasan Pharmaceutical Co., Ltd.	Approved by	Director / Dong-hyun Jeong	Electronically signed; 16:16:12 GMT+9	2026/06/16

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Revision History

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1.0	First document	Kibyung Park

Abbreviations

The following abbreviations and terms are used in this statistical analysis plan.

Term	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariances
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BSS	Bronchitis Severity Score
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CMH	Cochran Mantel Haenszel
COAT	Cough Assessment Test
CRF	Case Report Form
CS	Clinically Significant
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
HCG	Human Chorionic Gonadotropin
ICH	International Council for Harmonization
IMOS	Integrative Medicine Outcome Scale
IMPSS	Integrative Medicine Patient Satisfaction Scale
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
LSM	Least Square Mean
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
PPS	Per Protocol Set
PT	Preferred Term
RBC	Red Blood Cell
SADR	Serious Adverse Drug Reaction

Term	Definition
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing, Figure
UK	Unknown
WBC	White Blood Cell
WHO-ATC Index	World Health Organization - Anatomical Therapeutic Chemical Index

1. Introduction

This Statistical Analysis Plan (SAP) describes in detail the planned statistical analyses for clinical study DSP2505-CT4.

DSP2505-CT4 aims to evaluate efficacy and safety after 7 days of treatment with CANIUM Tab. (test drug) or Umckamin Tab. (comparator) in patients with acute bronchitis.

The following documents were reviewed in preparing this SAP:

- DSP2505-CT4 Protocol V3.1.
- DSP2505-CT4 CRF V3.0.
- The International Committee on Harmonization guideline on statistical principles for clinical trials.

The purpose of the SAP is to clarify statistical analysis procedures and provide guidance for consistent and reliable assessment of the final study results and conclusions, implementation, and all important details of the analyses presented.

1.1 Study Objectives

1.1.1 Primary Objective

To compare improvement in acute bronchitis symptoms using the change in Bronchitis Severity Score (BSS) at 7 days after study drug administration in patients with acute bronchitis, and to demonstrate noninferiority of the test drug to the comparator.

1.1.2 Secondary Objectives

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

1.2 Study Design

This is a multicenter, randomized, double-blind, active-controlled, parallel-group, Phase 4 clinical trial. Participants who provide written consent may undergo a screening period of up to 2 days. Those who satisfy the final eligibility assessment and meet the inclusion and exclusion criteria may participate.

Participants who pass screening and the final eligibility assessment will be randomized 1:1 to the test or control group at Visit 2. Randomized participants will 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

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

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)
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.

1.3 Procedures for Randomization and Stratification

Randomization is planned to prevent bias in treatment assignment and increase the likelihood that the two groups represent comparable populations.

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

Before the study begins, the randomization manager will provide the randomization codes to the sponsor's study drug packaging personnel and the Interactive Web Response System (IWRS) personnel.

1.4 Blinding

The study is double-blind for participants and investigators. Information about each participant's treatment assignment will be managed so that it is not disclosed to study personnel.

To maintain blinding, a double-dummy method will be used with placebos visually indistinguishable from the test drug and comparator. The principal investigator will retain the assignment details of the unique codes in sealed form without disclosure until study completion. Code assignments will be managed through the central registration center's IWRS.

In principle, individual treatment assignments must remain blinded until database locking is completed after study completion. Blinding may be broken if code access is unavoidable in an emergency, such as a serious adverse drug reaction, or if the sponsor considers it essential to protect a participant's rights and safety. Only that participant's unique code may be accessed.

Unblinding must be considered case by case and only for a serious medical emergency. In general, it should occur only if treatment assignment information will affect the participant's treatment. If the principal investigator considers unblinding necessary, the sponsor must be contacted and agreement obtained before unblinding. Every unblinding must be clearly justified, recorded, and retained as documentation. A participant whose randomization code has been unblinded cannot continue in the study.

2. Statistical Hypotheses

The primary objective is 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. The hypotheses are:

H_0: μT - μC ≥ δ versus H_1: μT - μC < δ

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

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

δ: Noninferiority margin.

3. Sample Size Determination

The sample size was calculated using the following assumptions:

1. Significance level α = 0.025 (one-sided test).

2. Power 1 - β = 0.8.

3. Test-to-control allocation ratio 1:1.

4. Noninferiority margin δ = 1.10.

5. Standard deviation σ = 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 participants per group. Allowing for 15% dropout, at least 109 participants per group, or 218 in total, will be enrolled.

4. Population (Analysis Sets) for Analysis

Efficacy data will be analyzed primarily in the Per-Protocol Set and supportively in the Full Analysis Set. Safety data will be analyzed in the Safety Set. Demographic and baseline characteristics will be analyzed in the Randomized Set.

Analysis set	Description	Study treatment assignment
Enrolled	All participants who sign the consent form	
Randomized Set	All participants randomized in the study	As randomized
Full Analysis Set (FAS)	Randomized participants who receive at least one dose and have both baseline and postdose results for the primary efficacy endpoint	As randomized
Per-Protocol Set (PPS)	FAS participants who complete the study according to the protocol without a major protocol violation	As randomized
Safety Set	All randomized participants who receive at least one dose of study drug	As treated

5. General Analysis Definitions

5.1 Visit Windows

For FAS efficacy analyses, data from scheduled visits outside the visit window and from participants who discontinue will be included using the analysis windows below. For PPS efficacy analyses, the visit windows below will be applied.

Scheduled visit	Output label	Target day	Visit window (days)	Analysis window (days)
1	Screening		NA	NA
2	Baseline	0	NA	NA
3	Day 7	7	±1 day (6 to 8)	2 to 8

If two observations fall within the visit window, the observation closest to the target time point will be used. If both are equally distant, the later observation will be used.

5.2 Data Handling Rules

5.2.1 Handling of Missing Data

Missing efficacy data for FAS analyses will be handled using last observation carried forward (LOCF), treating the most recently obtained data as the data at the missing time point. LOCF will be applied only to missing data after the first postbaseline visit.

Missing safety data and missing efficacy data for PPS analyses will not be imputed.

5.2.2 Handling of Incomplete Dates

Methods for handling missing dates in medical and surgical history, prior/concomitant medications, prior/concomitant treatments, and adverse events are described in the corresponding sections.

5.2.3 Handling of Invalid Values

If a laboratory value is collected with an inequality indicating that it is below a lower limit or above an upper limit, the numerical limit without the inequality sign will be used for analysis. Participant listings will show the value as recorded in the CRF.

- Values recorded as at least or greater than a limit (for example, ≥100 or >100) will be replaced by the minimum value, 100.
- Values recorded as below or at most a limit (for example, ≤4 or <4) will be replaced by the maximum value, 4.

5.3 Analysis Specifications

1) Significance level: Statistical significance tests will be two-sided at $\alpha = 5\%$.

2) Data presentation: Continuous data will be summarized using descriptive statistics (number of participants, mean, standard deviation, median, minimum, and maximum). Categorical data will be presented as frequencies and percentages.

3) Normality and statistical tests: The Shapiro-Wilk test p-value in each treatment group, evaluated at the 5% significance level, will determine whether parametric or nonparametric methods are used. Within-group comparisons of continuous data will use a paired t-test if normality is satisfied and the Wilcoxon signed-rank test otherwise. Between-group comparisons of categorical data will use Pearson's chi-square test, or Fisher's exact test if more than 20% of cells have expected frequencies below 5.

4) Decimals: Statistics will be rounded to two decimal places. Least square means estimated by ANCOVA and p-values will be presented to four decimal places; p-values below 0.0001 will be shown as <.0001. Frequencies will be integers. Arithmetic operations used to create analysis datasets will use the SAS ROUND function to six decimal places.

5.4 Protocol Violation

Major protocol violations are:

- Failure to obtain informed consent.
- Violation of inclusion or exclusion criteria.
- Randomization error.
- Use of prohibited concomitant medication.

Additional PPS exclusion criteria are:

- Treatment compliance below 80%.
- Violation of the Day 7 visit window.

For other participants considered to have a major protocol violation, the impact on the study will be reviewed comprehensively at a blinded review meeting before database lock to determine PPS exclusion. Protocol violation categories decided at the blinded meeting will be considered final for analysis. Analysis sets will reflect the PPS determined at that meeting.

5.5 Medical Dictionary and Version

The following medical coding dictionaries and versions will be used:

- Medical history, concomitant treatments, and adverse events: the latest version of MedDRA, classified by System Organ Class (SOC) and Preferred Term (PT).
- Medications: the latest WHO-ATC Index, classified by ATC Levels 1 and 2.

5.6 Software Version

All statistical analyses will be performed using SAS (Statistical Analysis System) version 9.4 or later.

6. Statistical Analyses

6.1 Participant Dispositions

6.1.1 Variable and/or Definition

Participant disposition is classified as follows:

- Screened: all participants who enter the study.
- Screening Failure: participants who discontinue before randomization.
- Randomized: all randomized participants.
- Treated: all participants who receive study drug.
- Withdrawn: randomized participants who discontinue early.
- Completed: participants who complete the study.

Primary reasons for noncompletion are classified as follows.

Screening failure reasons: failure to meet inclusion/exclusion criteria; withdrawal of consent; loss to follow-up; other.

Withdrawal/violation after randomization:

- Participant or representative withdrawal of consent.
- An inclusion/exclusion criterion violation discovered during the study.
- Inability to continue because of an adverse event or serious adverse event.
- Participant or representative request to stop because of unsatisfactory treatment effect.

- Failure to follow the principal investigator's or other investigator's instructions.
- Loss to follow-up.
- Pregnancy during the study.
- Continued participation otherwise considered inappropriate by the sponsor or investigator.
- Use of prohibited concomitant medication that may affect efficacy or safety assessments.

6.1.2 Analysis Methods

Counts will be presented for all screened participants, screening failures, and reasons for screening failure. Frequencies and percentages by treatment group will be presented for randomized, treated, withdrawn, and completed participants.

Frequencies and percentages by treatment group will also be presented for participants who discontinue after randomization and their reasons; participants with each major protocol violation and the reasons; randomized participants and participants in the Safety Set, FAS, and PPS; and reasons for exclusion from each analysis set.

6.2 Demographics and Baseline Characteristics

6.2.1 Variable and/or Definition

Demographic and target-disease variables are defined below.

Type	Variable	Unit / category	Derivation
Continuous	Age in completed years	Years	Automatically calculated in EDC
Continuous	Average daily smoking amount	Cigarettes	
Continuous	Weight	kg	Visit 1
Continuous	Height	cm	Visit 1
Continuous	BMI	kg/m²	Weight / (height / 100)², using Visit 1 values
Continuous	Disease duration	Days	(Consent signature date - acute bronchitis onset date) + 1
Categorical	Sex	Male / female	
Categorical	Childbearing potential	Yes / no	
Categorical	Pregnancy test method	Urine hCG / serum hCG	
Categorical	Pregnancy test	Positive / negative	Among participants with childbearing potential, any positive collected pregnancy test result
Categorical	Alcohol use	Yes / no	
Categorical	Smoking history	Yes / no	
Categorical	Stratum	BSS <8 / ≥8	

6.2.2 Analysis Methods

Demographic information will be analyzed in the Randomized Set. Continuous variables will be summarized by treatment group using number of participants, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by treatment group using frequencies and percentages.

6.3 Medical History

6.3.1 Variable and/or Definition

Past/current medical and surgical history will be coded by MedDRA SOC and PT.

- Past medical and surgical history: “No” for ongoing at screening.
- Current medical and surgical history: “Yes” for ongoing at screening.

6.3.2 Analysis Methods

Past/current medical and surgical history will be analyzed by treatment group in the Randomized Set. Frequencies, percentages, and numbers of events will be presented by MedDRA SOC and PT.

6.4 Prior and Concomitant Medications

6.4.1 Variable and/or Definition

Prior medications are those stopped before study drug administration. If a medication's end date is the same as the study drug start date, it will be considered concomitant. If the end day is “UK” and its year and month match the study drug start year and month, it will also be considered concomitant.

Concomitant medications are those started after the study drug start date or continued from before study participation.

6.4.2 Analysis Methods

Prior/concomitant medications will be analyzed by treatment group in the Randomized Set. Frequencies, percentages, and numbers of occurrences will be presented by ATC Levels 1 and 2.

6.5 Concomitant Non-drug Treatment

6.5.1 Variable and/or Definition

Prior/concomitant treatments will be coded by MedDRA SOC and PT.

Prior treatments are those ended before study drug administration. If the end date equals the study drug start date, the treatment will be considered concomitant. If the end day is “UK” and the year and month match the study drug start year and month, it will also be considered concomitant.

Concomitant treatments are those started after the study drug start date or ongoing from before study participation.

6.5.2 Analysis Methods

Prior/concomitant treatments will be analyzed by treatment group in the Randomized Set. Frequencies, percentages, and numbers of occurrences will be presented by MedDRA SOC and PT.

6.6 Treatment Compliance

6.6.1 Variable and/or Definition

Compliance will be assessed by comparing the number of tablets expected to be taken, including two doses on the first prescription day and one dose on the end-of-study visit day, with the quantity of study drugs returned by the participant.

Participants take two tablets per dose (test drug or comparator plus the matching placebo of the other drug), three times daily for 7 days.

Treatment compliance (%) = (Number of tablets actually taken / Number of tablets expected to be taken) × 100.

- Treatment duration (days) = study drug end date - study drug start date.

- Number actually taken = “Actual quantity taken” entered in EDC.
- Number expected to be taken = (Visit 3 date - Visit 2 date) × 3 × 2.

6.6.2 Analysis Methods

Descriptive statistics for treatment duration and compliance will be presented by treatment group in the Safety Set.

7. Efficacy

Endpoint	Description	Methodology
Primary: BSS total score change	Change from baseline at Day 7 (Visit 3)	Descriptive statistics; ANCOVA LSMs, difference between LSMs, 95% CI
Secondary: symptom-specific BSS changes	Change from baseline at Day 7 (Visit 3)	Descriptive statistics; ANCOVA LSMs, difference between LSMs, 95% CI
Secondary: BSS treatment response rate	Response at Day 7 (Visit 3) relative to baseline	Frequency and percentage; CMH test
Secondary: COAT total score change	Change from baseline at Day 7 (Visit 3)	Descriptive statistics; ANCOVA LSMs, difference between LSMs, 95% CI
Secondary: investigator overall improvement score	Investigator assessment of treatment response at Day 7 (Visit 3)	Frequency and percentage; logistic regression odds ratio and 95% CI; CMH test
Secondary: investigator overall improvement rate	Investigator assessment of treatment response at Day 7 (Visit 3)	Frequency and percentage; CMH test
Secondary: participant overall improvement rate	Participant assessment of treatment response at Day 7 (Visit 3)	Frequency and percentage; CMH test
Secondary: participant satisfaction	Participant satisfaction with treatment response at Day 7 (Visit 3)	Frequency and percentage; CMH test

7.1 Primary Endpoint Analysis

Change from baseline in BSS total score at Day 7 (Visit 3) after study drug administration.

7.1.1 Variable and/or Definition

The BSS will be assessed at every visit. The investigator rates the severity of each main acute bronchitis symptom, cough, sputum, rales/rhonchi, chest pain during coughing, and dyspnea, from 0 (absent) to 4 (very severe). The total is the sum of individual symptom 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

Change = value at Day 7 (Visit 3) - baseline value.

7.1.2 Analysis Methods

Descriptive statistics will be presented by treatment group for BSS total scores at baseline and Day 7 (Visit 3), and for the change from baseline at Day 7.

Between-group comparison of the change will use ANCOVA with treatment group as a fixed effect and baseline BSS total score as a covariate. Groups will be compared using the difference in least square means (LSMs). Each group's LSM, the between-group LSM difference, its 95% confidence interval, and p-value will be presented. Noninferiority of the test group to the control group will be demonstrated if the upper limit of the 95% confidence interval is below the noninferiority margin of 1.10.

Within-group changes from baseline will also be analyzed using a paired t-test or Wilcoxon signed-rank test, depending on whether normality is satisfied.

7.2 Secondary Endpoints Analysis

1. Change from baseline in each symptom-specific BSS score at Day 7 (Visit 3).
2. BSS treatment response rate at Day 7 (Visit 3) relative to baseline.
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 (IMPSS) at Day 7 (Visit 3).

7.2.1 Variable and/or Definition

BSS treatment response:

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

An overall treatment response is considered present if any one of these three conditions is satisfied.

The Cough Assessment Test (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 evaluate the effect of cough on quality of life. At Visits 2 and 3, the investigator administers it by interview. It covers cough frequency, interference with daily activities, sleep disturbance, fatigue, and airway hypersensitivity. Each item is rated from 0 to 4, giving a total score of 0 to 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

Change = value at Day 7 (Visit 3) - baseline value.

Overall improvement in treatment response (IMOS): At Day 7 (Visit 3), the investigator interviews the participant about treatment effects and integrates the findings to rate the change from baseline (Visit 2)

using the five-point Integrative Medicine Outcome Scale. The participant also independently rates overall improvement. 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

Overall improvement rate (%) = (Number rated “Major improvement” or “Complete recovery” / Number of participants in the relevant analysis set) × 100.

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 IMPSS.

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

7.2.2 Analysis Methods

1) Symptom-specific BSS changes: Descriptive statistics by treatment group will be presented for each symptom score at baseline and Day 7, and for its change from baseline. Between-group comparison will use ANCOVA with treatment group and baseline BSS stratum (<8 / ≥8) as fixed effects and the corresponding baseline symptom score as a covariate. Each group's LSM, the between-group 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: Frequencies and percentages will be presented by group for treatment response at baseline and Day 7. Between-group comparison will use logistic regression with treatment group as a fixed effect and baseline BSS total score as a covariate; the odds ratio, 95% CI, and p-value will be presented. In addition, a Cochran-Mantel-Haenszel (CMH) test accounting for baseline BSS stratum (<8 / ≥8) will be performed.

3) COAT total score change: Descriptive statistics by group will be presented for baseline and Day 7 total scores and the change from baseline. Between-group comparison will use ANCOVA with treatment group and baseline BSS stratum (<8 / ≥8) as fixed effects and baseline COAT total score as a covariate. 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. Changes in individual COAT item scores will additionally be analyzed using the same methods.

4) Investigator overall improvement score: Frequencies and percentages for each score at Day 7 will be presented by group. Between-group comparison will use a CMH test accounting for baseline BSS stratum (<8 / ≥8).

5) Investigator overall improvement rate and 6) participant overall improvement rate: Frequencies and percentages at Day 7 will be presented by group. Between-group comparisons will use CMH tests accounting for baseline BSS stratum (<8 / ≥8).

7) Participant satisfaction (IMPSS): Frequencies and percentages for each satisfaction score at Day 7 will be presented by group. Between-group comparison will use a CMH test accounting for baseline BSS stratum (<8 / ≥8).

8. Safety

Safety endpoints are adverse events, clinical laboratory tests, vital signs, physical examination, and ECG. All safety endpoints will be analyzed in the Safety Set.

8.1 Adverse Events

8.1.1 Variable and/or Definition

Adverse events occurring after study drug administration are defined as follows:

- Treatment-emergent adverse events (TEAEs): all adverse events occurring after study drug administration.
- Adverse drug reactions (ADRs): all TEAEs except those assessed as “Unlikely” or “Not-related” to the study drug.
- Serious adverse events (SAEs).
- Serious adverse drug reactions (SADRs).
- Adverse events leading to study discontinuation: events for which the action taken with study drug is “Drug withdrawn” and the withdrawal reason is inability to continue because of an adverse event or serious adverse event.

Assessment categories are:

- Severity: mild, moderate, severe.
- Causality: certain; probable/likely; possible; unlikely; conditional/unclassified; unassessable/unclassifiable; not-related.
- Outcome: recovered; recovering; not recovered; recovered with sequelae; death; unknown.
- Action taken with study drug: dose unchanged; dose increased; dose reduced; drug withdrawn; not applicable; unknown.
- Corrective treatment: none; drug treatment; nondrug treatment; drug and nondrug treatment.

All events will be classified by MedDRA SOC and PT.

8.1.2 Analysis Methods

For TEAEs, ADRs, SAEs, SADRs, and adverse events leading to discontinuation, the number of participants, incidence, and number of events will be presented by treatment group. Incidences will be compared between groups using Pearson's chi-square test or Fisher's exact test.

The number of participants, incidence, and number of events will also be presented by group and MedDRA SOC/PT, including breakdowns by severity and causality.

8.2 Clinical Laboratory Tests

8.2.1 Variable and/or Definition

The following tests will be performed at Visits 1 and 3.

Category	Tests
Hematology	RBC, hemoglobin, hematocrit, platelet count, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils
Blood chemistry	BUN, creatinine, eGFR, uric acid, total bilirubin, albumin, total protein, ALT, AST, glucose, total cholesterol, Na, Ca, K, Cl
Urinalysis	Protein (albumin), glucose, ketones, WBC, blood (RBC)

Normality and clinical significance categories are normal, abnormal not clinically significant (NCS), and abnormal clinically significant (CS).

Change from baseline = Visit 3 result - Visit 1 result.

8.2.2 Analysis Methods

For continuous hematology, blood chemistry, and urinalysis variables, descriptive statistics will be presented by visit and treatment group and for the pre- to posttreatment change by group.

For each test, results will be grouped as normal/NCS versus CS, and pretreatment-to-posttreatment shift tables will be presented. McNemar's test will be used for within-group comparisons. Data listings will be provided for tests with posttreatment CS abnormalities.

8.3 Vital Signs

8.3.1 Variable and/or Definition

At every visit, systolic/diastolic blood pressure (mmHg), pulse rate (beats/min), and tympanic temperature (°C) will be measured.

Change from baseline = Visit 3 result - Visit 2 result.

8.3.2 Analysis Methods

Descriptive statistics will be presented for each vital sign by visit and treatment group and for the change from pretreatment (Visit 2) to posttreatment (Visit 3) by group. If Visits 1 and 2 occur together, Visit 1 results will be used.

8.4 Physical Examination

8.4.1 Variable and/or Definition

The following will be examined at every visit: general appearance, skin, head/neck, chest/lungs, heart, abdomen, genitourinary system, extremities, musculoskeletal system, nervous system, lymph nodes, and other findings. Results will indicate whether a clinically significant abnormal finding is present.

8.4.2 Analysis Methods

Data listings will be provided for physical examination findings with posttreatment CS abnormalities.

8.5 Electrocardiogram

8.5.1 Variable and/or Definition

ECGs will be performed at Visits 1 and 3. Results will be classified as normal, abnormal NCS, or abnormal CS.

8.5.2 Analysis Methods

ECG findings will be grouped as normal/NCS versus CS, and pretreatment-to-posttreatment shift tables will be presented. McNemar's test will be used for within-group comparisons. Data listings will be provided for posttreatment CS ECG abnormalities.

9. Sub-group Analysis

Not applicable.

10. Interim Analysis and Data Monitoring Committee Review

No interim analysis or separate data monitoring committee is planned.

11. Changes in the Conduct of the Trial or Planned Analysis

There are two changes to the statistical analysis plan described in Protocol V3.1, as detailed below.

Protocol analysis plan	SAP analysis plan	Rationale for change
7.3.6.2 Secondary efficacy analysis; 2) BSS treatment response rate at Day 7 (Visit 3) relative to baseline; intervening text omitted; new addition	9.8.2 Secondary efficacy analysis; 2) BSS treatment response rate at Day 7 (Visit 3) relative to baseline; intervening text omitted. In addition, perform a CMH test accounting for baseline BSS stratum (<8 / ≥8).	Add a stratification-adjusted CMH test for direct between-group comparison of BSS response rates.
7.3.6.2 Secondary efficacy analysis; 3) COAT total score change from baseline at Day 7 (Visit 3); intervening text omitted; new addition	9.8.2 Secondary efficacy analysis; 3) COAT total score change from baseline at Day 7 (Visit 3); intervening text omitted. Additionally, present changes in each COAT item score using the same analysis methods.	Add analyses of changes in individual COAT item scores.

12. SAS Code Example

Statistical method	SAS code
Categorical variables	PROC FREQ DATA=<Dataset>; TABLE <variable>*<variable>; RUN;
Pearson's chi-square test	PROC FREQ DATA=<Dataset>; TABLE <variable>*<variable>/CHISQ; RUN;
Fisher's exact test	PROC FREQ DATA=<Dataset>; TABLE <variable>*<variable>/FISHER; RUN;
McNemar's test	PROC FREQ DATA=<Dataset>; TABLE <variable>*<variable>/AGREE; RUN;
Cochran-Mantel-Haenszel test	PROC FREQ DATA=<Dataset>; TABLE <variable>*<variable>*<variable>/CMH; RUN;
Numerical variables	PROC MEANS DATA=<Dataset> N MEAN STD Median MIN MAX; CLASS <variable>; VAR <variable(s)>; RUN;
Normality test / paired t-test / Wilcoxon signed-rank test	PROC UNIVARIATE DATA=<Dataset> NORMAL; CLASS <Independent variable>; VAR <Dependent variable>; RUN;
ANCOVA	PROC MIXED(or GLM) DATA=<Dataset>; CLASS <Independent variable>; MODEL <Dependent variable> = <Independent variable(s)>; RUN;
Logistic regression model	PROC LOGISTIC DATA=<Dataset>; CLASS <Independent variable>; MODEL <Dependent variable> = <Independent variable(s)>/FIRTH; RUN;

13. Table, Listing and Figure

TLF shells for the study's tables, listings, and figures are attached separately. TLF shells may be changed without revising the SAP version. TLF templates, such as footnotes, table layout, and typographic details, may differ from the TLFs containing actual analysis results. Template changes must not affect interpretation of the statistical analyses.

Final Audit Report

DSP2505-CT4_Statistical Analysis Plan_V1.0_Final_20260616

Final Audit Report: 2026-06-16

Created: 2026-06-16 (Korea Standard Time)

By: kibyung park (kbpark@clipsbnc.com)

Status: Signed

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History of “DSP2505-CT4_Statistical Analysis Plan_V1.0_Final_20260616”

Date and time (GMT+9)	Event
2026-06-16 15:48:54	Document created by kibyung park (kbpark@clipsbnc.com).
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2026-06-16 16:14:23	Document electronically signed by Hee-seon Eom (hseom@dspharm.com). Time source: server. Signature captured on a device with telephone number XXXXXXXX6063. Signature appearance: mobile drawing.
2026-06-16 16:14:26	Document emailed to best97@dspharm.com for signature.
2026-06-16 16:15:07	Email viewed by best97@dspharm.com.
2026-06-16 16:16:10	Signer best97@dspharm.com entered the name Dong-hyun Jeong when signing.
2026-06-16 16:16:12	Document electronically signed by Dong-hyun Jeong (best97@dspharm.com). Time source: server. Signature appearance: typed.
2026-06-16 16:16:12	Agreement completed.