HALEON

STATISTICAL ANALYSIS PLAN
Amendment

A Real-World Evidence study evaluating Quality of Life parameters following treatment with Robitussin

Protocol Number: 300233

Phase: 4

Authorisation of Statistical Analysis Plan and Tables, Figures, Listing Shells:

Position	Name	Signature	Date
Statistician (Haleon)	PPD		
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Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan (V1.0)	19-Feb-2025	Not applicable (N/A)
Amendment to Original Analysis Plan (V2.0)	04 Mar 2025	Section 4.4.1, study product compliance was updated to reflect that end of treatment is defined as day 7, or last day study treatment was used – whichever comes first.
Amendment to Original Analysis Plan (V3.0)	10 Mar 2025	Updated Section 5 to add information about the additional of the QSSPID data flag, and why it has been implemented.

Amendments incorporate all revisions to date.

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Abbreviations

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
BDR	Blind Data Review
CI	Confidence Interval
CSR	Clinical Study Report
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
MMRM	Mixed-effects Model for Repeated Measures
NCCM	Non-Common Cold Medication
PT	Preferred Term
QoL	Quality of Life
SAE	Severe Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SAE	Serious Adverse Event
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
WURSS	Wisconsin Upper Respiratory Symptom Survey

The purpose of this Statistical Analysis Plan is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusion regarding the study objectives.

This SAP is based on the following documents:

1 Summary of Key Protocol Information

This decentralized study is designed to generate real world data from subjects with cough associated with the common cold, evaluating the effects in two arms with commercially available cough syrups on health-related quality of life (QoL). Arm 1 includes one cough syrup (which can be used day or night) and Arm 2 includes the daytime cough syrup and a nighttime cough syrup.

Robitussin Maximum Strength Cough and Chest Congestion DM (Dextromethorphan HBr, USP 20 mg; Guaifenesin, USP 400 mg) and Robitussin Maximum Strength Cough and Chest Congestion DM + Robitussin Maximum Strength Nighttime Cough DM (Dextromethorphan HBr, USP 30 mg; Doxylamine Succinate, USP 12.5 mg) are marketed cough and congestion syrups used for treatment of cough associated with common cold. Although this is a non-life-threatening condition, it impacts individuals' ability to function normally in day-to-day activities (physical, social, occupational, and emotional).

This study will generate data to support the effectiveness of the Robitussin syrups in the real-world setting to suppress cough among individuals with common cold to understand how the effect can influence their QoL.

1.1 Study Design

This is a longitudinal, randomized, open-label, decentralized clinical study evaluating the effect on QoL factors in subjects with cough associated with the common cold in two arms using Robitussin Maximum Strength in a real-world setting.

Subjects will be randomized into one of two study groups (at a 1:1 ratio):

- Group 1 will take Robitussin Maximum Strength Cough and Chest Congestion DM
- Group 2 will take Robitussin Maximum Strength Cough and Chest Congestion DM + Robitussin Maximum Strength Nighttime Cough DM.

1.2 Study Objectives

Each of the treatment groups will be analyzed separately; there is no comparison between the study groups (daytime product only and daytime/nighttime product combination).

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
To evaluate the over-time effects of Robitussin on QoL factors and common cold symptoms among individuals	Score change from Baseline to each treatment day in: • WURSS-21 total score

Objectives	Endpoints
experiencing cough associated with common cold, following up to 8 days of treatment using WURSS-21.	• WURSS-21 total symptom domain score • WURSS-21 total QoL domain Score • Each of the WURSS-21 symptom scores (10 items in total) [a] • Each of the WURSS-21 QoL scores (9 items in total)
Secondary Objectives	**Secondary Endpoints**
To evaluate the over-time effects of Robitussin on QoL factors among individuals experiencing cough associated with common cold, following up to 8 days of treatment, using specific QoL questions.	Score change from Baseline to each treatment day in: • social activities • feeling self-conscious around people • coughing in public • falling asleep • sleeping through the night • energy • motivation
To evaluate the over-time effects of Robitussin on specific QoL questions among individuals experiencing cough associated with common cold, following up to 8 days of treatment, using categorized QoL factors.	Score change from Baseline to each treatment day in: • Sleep quality • Vitality • Physical activities • Social activities
Safety	
To record adverse events (AEs) during study period	Number and percent of patients reporting AEs or serious AEs (SAEs) while on treatment: • Related to product • Not related to product
Exploratory Objectives	**Exploratory Endpoints**
Subgroup analyses for primary and secondary endpoints.	Subgroup: Exclude subjects who took concomitant medications that are known to have an impact on common cold symptoms

1.3 Treatments

Subjects will be randomized into one of the two study groups:

Group 1: Subjects in this group will take Robitussin Maximum Strength Cough and Chest Congestion DM

- Subjects will be instructed to take per label instructions for up to 8 days or until resolution of symptoms, whichever occurs first
- Dosing: Oral tablets Up to 20 ml (Not to exceed 6 doses in any 24 hour period)

Group 2: Subjects in this group will take Robitussin Maximum Strength Cough and Chest Congestion DM + Robitussin Maximum Strength Nighttime Cough DM

- Subjects will be instructed to take the following per label instructions for up to 8 days or until resolution of symptoms, whichever occurs first:
- Dosing: Taken as Oral tablets
  - Robitussin Maximum Strength Cough and Chest Congestion DM (Daytime) - Up to 20 ml*
  - Robitussin Maximum Strength Nighttime Cough DM - Up to 20 ml*

*Not to exceed 4 doses of daytime + 1 dose of nighttime OR 3 doses of daytime in any 24 hour period

Dosing instructions will be followed as listed on the study product commercial label.

1.4 Sample Size Calculation

Sufficient individuals (approximately 372) will be screened to enrol approximately 260 eligible subjects assuming an estimated 23% drop out rate. It is believed that for this study, approximately 200 completed subjects (100 per treatment group) are deemed sufficient to observe an improvement in the WURSS-21.

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2 Planned Analyses

2.1 Interim Analysis

No interim analysis is planned.

2.2 Blinded Data Review (BDR):

After completion of database soft lock, a BDR will be conducted. The details of the BDR will be compiled in a separate document. The purpose of the BDR is to assign the study populations outlined in Section 4.2.3 of this SAP. As this study is open label, the term "blind" is used to denote that the population determination will be done without respect to treatment. To ensure analyses are blind, the treatment allocation will not be accessed by the statistician prior to the database hard lock. The BDR will be undertaken on this dataset without the treatment variable.

2.3 Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities including any external data reconciliation have been completed and the database has been locked.

3. All criteria for the database hard lock have been met and the randomization codes have been distributed.

After the database has been locked, the final analyses will consist of two main analyses:

Topline TLFs: After completion of database hard lock, a subset of all TLFs will be generated intended to identify key results of the study as outlined in Appendix 1.

Final Analysis: The final analysis is planned to be completed after completion of Topline TLFs and will include all Topline TLFs.

3 Considerations for data analyses and Data Handling Conventions

3.1 Baseline Definition

For all endpoints the baseline value will be self-completed during the screening and enrolment phase. It will, at a minimum, be the latest pre-treatment scores available for the participant.

3.2 Subgroups/Stratifications

There are no planned subgroup analyses for this study. Any subgroups included in the CSR will be post-hoc and labelled as such.

3.3 Timepoints and Visit Windows

The timepoints and visits for this study are defined in the Table 1: Schedule of Activities. Table 1 will present baseline characteristics of study variables categorized by measurement type. For continuous variables, means and standard deviations (SD) will be reported; for categorical variables, frequencies (n) and percentages (%) will be presented. Supplementary tables may also be generated to display related variables grouped by similar characteristics.

Table 1 Schedule of Activities

All assessments are completed online. Subjects will receive links via email/text to complete questionnaires per the Schedule below.

	May occur same-day [a]									
Counterparty Assessments	**Pre-screening**	**Day 0 (Baseline) (N)**	**Day 1 (N)**	**Day 2 (N)**	**Day 3 (N)**	**Day 4 (N)**	**Day 5 (N)**	**Day 6 (N)**	**Day 7 (N)**	**2 Days after Last Dose [j] (N)**
Pre-screening Survey	X									
Informed consent (self consent)	X									

	May occur same-day [a]									
Counterparty Assessments	**Pre-screening**	**Day 0 (Baseline) (N)**	**Day 1 (N)**	**Day 2 (N)**	**Day 3 (N)**	**Day 4 (N)**	**Day 5 (N)**	**Day 6 (N)**	**Day 7 (N)**	**2 Days after Last Dose [j] (N)**
Medical/Medication history [b]		X								
Demographics		X								
ID Verification		X								
WURSS–21 questionnaire [cf] (Baseline, pre-treatment)		X								
Specific QoL Questions (Baseline, pre-treatment)		X								
Eligibility Assessment		X								
Randomization		X								
Study product shipped [e]		X								
Study product use [eg]		X	X	X	X	X	X	X	X	
WURSS–21 questionnaire [f] (post-treatment)			X	X	X	X	X	X	X	
Specific QoL Questions (post-treatment)			X	X	X	X	X	X	X	
Product Usage Diary[h]		X	X	X	X	X	X	X	X	
End of Study Survey [i]									X	
Concomitant Medication Check			X	X	X	X	X	X	X	
Adverse Event/Serious Adverse Event			X	X	X	X	X	X	X	X

QoL, quality of life; WURSS–21, Wisconsin Upper Respiratory Symptom Survey-21.

[a] Pre-screening, Screening and Baseline can occur same day if product is received by subject same day

[b] Medical history including medication history will be self-reported by participant during the virtual visit.
[c] Participant eligibility to be confirmed through assessment of inclusion/exclusion criteria and cold symptoms of at least mild intensity reported on the Baseline WURSS-21 assessment at the time of Screening.
[d] Participant to confirm receipt of study product for study enrollment confirmation and read through detailed instructions regarding product dosing; Counterparty staff will be available to answer any queries regarding product use.
[e] Robitussin: Group 1: Subjects in Group 1 will be instructed to take up to 20 ml of Robitussin per label instructions for up to 8 days or until resolution of symptoms, whichever occurs first. Group 2: Subjects in Group 2 will be instructed to take the following per label instructions for up to 8 days or until resolution of symptoms, whichever occurs first: - up to 20 ml of Robitussin Maximum Strength Cough and Chest Congestion DM - up to 20 ml of Robitussin Maximum Strength Nighttime Cough DM
[f] WURSS–21 to be completed at the time of Baseline/Screening to confirm eligibility as well as daily during treatment (from Day 1 up to Day 7).
[g] Study product (Robitussin) to be shipped only after screening/baseline assessments are completed and eligibility is confirmed; up to 8 days' worth of study product(s) will be shipped together to ensure there is no interruption in study timeline or treatment duration.
[h] Participant will complete an eDiary documenting Robitussin use each day directly through the Citrus ePRO module.
[i] Participant-reported End of Study Survey will be completed at the end of study directly through the Citrus ePRO module. Participants ending product use early will complete the survey one day after their last reported dose; participants dosing on Day 7 will complete the survey on Day 7.
[j] Participant-reported Change in Health will be recorded two days after last study product administration.

4 Data Analysis

Data analysis will be performed by CCI [redacted] with oversight from Haleon. It is anticipated that the statistical analysis software used will be *R* version 4.4.2 or newer; Stata Version 18 or later (StataCorp. 2023. *Stata Statistical Software: Release 18*. College Station, TX: StataCorp LLC); or another validated statistical software.

Prior to database closure a Blind Data Review (BDR) meeting will be conducted in which various aspects of the trial will be discussed and agreed, including the exact definitions for the Non-Common-Cold-Medication (NCCM) population. Treatment labels will be masked for this review to avoid any potential sources of bias.

Except as described below, all listings will be produced for all randomized subjects.

4.1 Data Quality

Data cleaning will be ongoing throughout the study lifecycle and will be completed by a data manager prior to completion of the final analysis, raising queries and resolving them prior to the final database lock.

Analysis related to the primary, secondary, and safety objectives will be validated by a second biostatistician. Any discrepancies identified during the output review will be corrected or

documented until there are no findings, unless findings can be explained and are agreed upon by the study team. At the end of the study, all data sets used for analysis and final output will be archived.

4.2 Populations for Analysis

4.2.1 Subject Disposition

Subject disposition, including the number of subjects screened, enrolled, and reasons for non-randomization will be summarized in Table 14.1.1. The table will also present the number of subjects who completed the study and reasons for discontinuation. Listing 16.2.1.1 will present subject disposition.

4.2.2 Protocol Deviations

Protocol deviations will be reported as numbers and percentages, with deviations grouped into important and non-important deviations. Important deviation will be summarized (Table 14.1.2) and all deviations will be listed (Listing 16.2.2.1) produced for all randomized subjects.

Subjects with important protocol deviations liable to influence the primary and secondary endpoints may have their affected data excluded from analyses in exceptional circumstances as decided at the BDR meeting. Subjects may also be identified as having important protocol deviations not leading to exclusion of data from analyses.

Important deviations of the protocol procedures may include, but will not necessarily be limited to the following:

- Consent procedures
- Inclusion/Exclusion criteria
- Concomitant medication/therapy
- Study procedures
- Randomization procedures
- Study drug dosing/study product administration/study product compliance
- Visit schedule/interval
- Other

The specific details of the important protocol deviations will be listed and assessment process will be specified in the BDR meeting and subjects with important protocol deviations will be identified at the BDR meeting.

4.2.3 Analysis Populations

The following analysis populations are defined.

Population	Definition / Criteria	Analyses Evaluated
Enrolled Population	All subjects who meet inclusion/exclusion criteria Due to the nature of this study, the enrolled population is equivalent to the randomized subjects .	Enrollment summaries and subject disposition

Population	Definition / Criteria	Analyses Evaluated
Safety Population	All subjects who use either study product at least once. Population will be based on actual study product used (regardless of group).	Analysis of safety variables, subject demographics and baseline characteristics
Modified Intention-to-Treat (mITT) Population	All subjects who use the study product at least once and have at least one post-baseline QoL questionnaire for at least one primary endpoint assessment to support at least one of the primary endpoint assessments	Primary and secondary endpoints. All analyses will be mITT unless otherwise stated.
Non-Common-Cold-Med (nCCM) Population	All subjects in the mITT population who have not used other medicinal products which might influence reported symptom severity. Reported concurrent medications will be assessed in a Blind Data Review (BDR) meeting to identify potentially interfering medications prior to analysis.	Exploratory endpoints

4.3 Subject Demographics and Other Baseline Characteristics

Demographic and baseline characteristics summaries will be produced for the Safety Population.

4.3.1 Demographic Characteristics

Demographic and baseline characteristics for each group will be reported for the Safety Population using descriptive statistics. For categorical variables (sex, smoking status, race, and ethnicity), the number and percentage of subjects in each category will be reported by treatment group. For continuous variables (age, weight, and height), summary statistics will include arithmetic mean, standard deviation, median, interquartile range, and minimum/maximum values by treatment group. All demographic data will be presented in Table 14.1.3 and Listing 16.2.4.1. For repeatedly collected measurements, data will be described at each timepoint.

4.3.2 General Medical History

Self-reported relevant medical and/or surgical history (in the previous 12 months) including allergies or drug sensitivity and prior medications/treatments, including prescription and non-prescription drugs, vaccines, dietary supplements and herbal remedies, that began before obtaining informed consent will be recorded as the Medical History/Current Medical Conditions.

Medical History will be coded using MedDRA. Medical Histories will be summarized by System Organ Class (SOC) and Preferred Term (PT) listed for the safety population (Table 14.1.4). The presence/absence of any relevant medical history will be listed in Listing 16.2.4.2 with start date and end date or ongoing at the start of study product.

4.4 Treatments (Study Product, other Concomitant Therapies, Compliance)

Compliance data will be summarized for the safety population, exposure and other medications will also be summarized on the safety population.

Randomization details will be listed, including the randomization number, the planned study product, the actual study product the subject received and the randomization date (Listing 16.1.7.1) for all randomized subjects.

4.4.1 Study Product Compliance and Exposure

Compliance will be assessed as the number of days subjects reported to have adhered to the treatment regime up the end of treatment. For compliance and analysis tables, the end of treatment will be defined as the last day the subject used the study product or day 7. The number of compliant days will be tabulated using absolute and relative frequencies as well as the mean, standard deviation, minimum and maximum values, median, and quantiles (Table 14.1.6 and Listing 16.2.5.1). A summary of daily product use will also be presented (Table 14.1.7 and Listing 16.2.5.1). Listing 16.2.5.1 will show all study product uses, including subjects who use the study product after Day 7.

4.4.2 Prior and Concomitant Medication

Prior medications/non-drug therapies and concomitant medications/significant non-drug therapies used prior to treatment initiation and in the treatment phase will be tabulated and listed (Table 14.1.5 and Listing 16.2.4.2).

Prior medications/treatments, including prescription and non-prescription drugs, dietary supplements and herbal remedies, taken in the last 30 days and prior to signing the informed consent form, will be documented in the CRF. The prior and concomitant medications will be coded using a validated medication dictionary, CCI
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Prior medications and prior non-drug treatments will be listed by subject, with drug name, CCI Drug Synonym, reason for medication, route, dose, frequency, start date, start day relative to the study product start date, end date and end day relative to the study product start date (Listing 16.2.4.3) for all safety subjects. Prior medications are defined as those which stopped before the first use of the study product.

Concomitant medications and concomitant non-drug therapies taken during treatment will be listed similarly (Listing 16.2.4.2) for all safety subjects with either ongoing or end date displayed. Concomitant medications are defined as medications that started or stopped on or after the first use of the study product or are ongoing.

Unknown dates will not be imputed. However, if the start or stop date is unknown, then it will be assumed to be concomitant medication unless the partial start date or stop date indicates differently.

4.5 Analysis

4.5.1 Primary Endpoint

4.5.1.1 Primary Endpoint Definition

The primary endpoint will be measured using the Wisconsin Upper Respiratory Symptom Survey (WURSS); 21 question daily symptom report.

WURSS-21 scores will be reported as:

- Total score: sum of questions 2 through to 20
- Total symptoms domains score: sum of the items (questions 2 – 11) in the symptom section (10 individual items on cold symptoms answered on a 0 (does not have this symptom) - 7 (severe scale))
- Total QoL domain score: sum of the domains (questions 12 – 20) in the QoL section (9 individual items on cold interference to QoL answered on a 0 (not at all) - 7 (severely scale)
- Individual symptom item score (10 items)
- Individual QoL item score (9 items)

Change from baseline (Day 0) will be calculated for each subject by subtracting the baseline score from scores at subsequent treatment timepoints (Days 1-7 after baseline) regardless of study product use compliance as long as they have used it at least once and at end of treatment (defined as the last day of study product use or day 7 – whatever event comes first). The percentage improvement will be calculated at each timepoint (Days 1-7, and end of treatment), any timepoints after Day 7 will not be included in the analysis tables but will be included in the subject listings. Results will be presented for both the mITT and NCCM populations in:

- Tables 14.2.1.1.1 through 14.2.1.5.2
- Figures 14.2.3.1 through 14.2.6.2

4.5.1.2 Statistical Hypothesis, Model, and Method of Analysis

Changes in WURSS-21 domain and total scores from baseline will be analyzed using a linear mixed-effects model for repeated measures (MMRM) with subjects as the clustering unit. The model will include treatment day (as a categorical variable up to day 7) and baseline WURSS-21 score as fixed effects, with a random intercept for each subject. The model will employ an unstructured covariance matrix for within-subject variance-covariance errors, Kenward-Rogers degrees of freedom, and restricted maximum likelihood estimation (REML). For each treatment group, the following will be reported at each treatment day: estimated marginal mean differences from baseline on the original scale, standardized effect sizes (where applicable) with 95% confidence intervals, and nominal p-values. Primary endpoints will be evaluated at the 5% significance level. Given the study design, no adjustments for multiple comparisons will be made.

The distribution of outcome measures will be assessed for normality using Q-Q plots for each treatment group. While linear mixed-models are generally robust to modest departures from normality, substantial deviations (as assessed through visual inspection of Q-Q plots and formal tests including Shapiro-Wilk test) will prompt complementary analyses using

non-parametric methods. The Wilcoxon signed-rank test will be conducted at each timepoint, including end of treatment, as a sensitivity analysis to the primary MMRM analysis. If substantial discrepancies (defined as >20% difference in effect estimates or divergent statistical significance at α=0.05) are observed between the MMRM and Wilcoxon signed-rank test results, both sets of results will be reported with appropriate discussion of the differences. For the primary analysis, the MMRM results will be considered primary, with non-parametric results serving as supportive evidence. Model diagnostics will include assessment of heteroscedasticity through residual plots. If significant heteroscedasticity is detected (defined as systematic patterns in residual plots or significant Breusch-Pagan test results at α=0.05), Huber-White robust standard errors will be applied to ensure valid inference. All model assumption violations and remedial measures will be documented in the statistical analysis report.

For each domain and item, the value at each timepoint and corresponding change from baseline and % improvement will be summarised descriptively for each treatment group. Raw means (with standard deviations) for each endpoint at each assessed timepoint (day 1-7) will be plotted by treatment group. Change from baseline to end of treatment, as defined as either the last day subject uses study product or day 7 (whichever event comes first), will also be calculated and presented. Each WURSS-21 domain and individual item will be analyzed with comprehensive summary statistics presented by treatment group at each timepoint (Days 1-7) and at end of treatment (defined as either the last day of study product use or day 7 (whichever event comes first)). These statistics will encompass observed values, including mean, standard deviation, median, interquartile range, and 95% confidence intervals. Additionally, changes from baseline will be characterized through mean change, standard deviation of change, median change, and 95% confidence intervals for mean change, along with percent improvement calculations including mean percentage, standard deviation, median percentage, and associated confidence interval. Longitudinal profile plots, which will display mean values and mean changes from baseline (both with ±1 standard error) over time by treatment group, will be provided. Median values and interquartile ranges will also be plotted to provide a complete assessment of distributional characteristics throughout the study period.

4.5.2 Handling of Missing Values

MMRM analyses account for missing data using 'a missing at random' assumption, i.e., there is a systematic relationship between the propensity for missing values and the observed data, but not the missing data. Under such assumptions, MMRM is shown to provide unbiased estimates of the treatment effect whilst analysis of only complete cases using analysis of covariance (ANCOVA) is biased.

As such missing values will not be imputed.

4.6 Analysis of Secondary Objectives

4.6.1 Secondary Endpoint: Specific QoL Scores

Measurements of health related QoL indicators will be evaluated using the specific QoL scores and categorized QoL scores change from baseline to each treatment day to determine the effectiveness of the two treatment groups (Daytime, Daytime+Nighttime).

The Specific QoL Scores consist of 7 separate questions on QoL, scored 0 ('not at all') to 7 ('severely'). Lower scores represent better outcomes. Each specific question covers one of the following topics:

- Social activities
- Feeling self-conscious around people
- Coughing in public
- Falling asleep
- Sleeping through the night
- Energy
- Motivation

Changes from baseline in Quality of Life (QoL) domain scores (Sleep Quality, Social Activities, Physical Activities, and Vitality) will be analyzed longitudinally using the same methodological approach as the primary outcome. The analysis will be conducted for the mITT population, with results presented in Tables 14.2.2.1.(1-2) and Figures 14.2.4.(1-2); 14.2.5.(1-2) A linear mixed-effects model for repeated measures (MMRM) will be fitted separately for each QoL domain. Each model will include treatment day as a categorical fixed effect, baseline QoL score as a continuous covariate, and a random intercept for subject to account for within-subject correlation. The models will employ an unstructured covariance matrix, Kenward-Rogers degrees of freedom adjustment, and restricted maximum likelihood estimation (REML) to ensure valid inference. For each QoL domain and treatment group, the following estimates will be reported at each timepoint: estimated mean changes from baseline with 95% confidence intervals, between-treatment differences in mean changes with 95% confidence intervals, standardized effect sizes (Cohen's d) with 95% confidence intervals, and associated p-values for treatment comparisons. Statistical significance will be evaluated at α=0.05 level. Given the exploratory nature of the QoL analyses, p-values will be reported without adjustment for multiplicity, but interpretations will consider the potential impact of multiple testing on Type I error rates. Sensitivity analyses for the robustness of results to missing data and distributional assumptions will follow the same approach as specified for the primary outcome.

4.6.2 Secondary Endpoint: Categorized QoL Scores

Measurements of health related QoL indicators will be evaluated using the categorized QoL scores change from baseline to each treatment day to determine the effectiveness of the two treatment groups (Daytime, Daytime+Nighttime).

All individual questions are scored from 0-7 with lower scores representing better health outcomes. The QoL scores (sum of individual questions per category) will be categorized as below:

1. Sleep Quality
    - Sleep Well – WURSS-21 Q13
    - Falling asleep – QoL Q4
    - Sleep through the night – QoL Q5
2. Social Activities
    - Interact with others – WURSS-21 Q19

- Less comfortable in social activities – QoL Q1
- Self-conscious around others – QoL Q2
- Coughing in public – QoL Q3

3. Physical Activities
   - Breathe easily - WURSS-21 Q14
   - Walk, climb stairs, exercise - WURSS-21 Q15
   - Accomplish daily activities - WURSS-21 Q16
4. Vitality
   - Energy – QoL Q6
   - Motivation – QoL Q7
   - Feel tired - WURSS-21 Q11

Changes from baseline in mean Quality of Life (QoL) scores will be analyzed using a mixed-effects model for repeated measures (MMRM). The model will include fixed effects for treatment, visit (as a categorical variable), treatment-by-visit interaction, and baseline QoL score, with subject as a random effect. An unstructured covariance matrix will be employed to model the within-subject errors. The model will utilize restricted maximum likelihood (REML) estimation with Kenward-Rogers approximation for degrees of freedom. The analysis will be conducted for both the modified intention-to-treat (mITT) and non-cancer cachexia mortality (NCCM) populations, with results presented in Tables 14.2.2.2.(1-2). For each treatment group, the analysis will report estimated marginal means at each visit, mean changes from baseline with corresponding 95% confidence intervals, and nominal p-values for between-group comparisons. Statistical significance will be evaluated at the 5% level, with no adjustments for multiplicity. If the unstructured covariance matrix fails to converge, alternative covariance structures (compound symmetry, autoregressive) will be considered and documented in the statistical analysis report.

4.7 Exploratory Analyses

A Non-Common-Cold-Med (NCCM) population will include all patients in the mITT population who have not used other medicinal products which might influence reported symptom severity. Reported concurrent medications will be assessed in a Blind Data Review (BDR) meeting to identify potentially interfering medications. The NCCM population will be created, and the decision to perform analyses on this population will be made during the BDR meeting. There is no pre-defined threshold on differences between the mITT population and the NCCM population.

The NCCM population will exclude participants with potentially contraindicating medications. This population will be used for the primary and secondary endpoint analyses, and results will be presented in the same Table format as the primary and secondary endpoints, with Table numbers ended in '.2'.

4.8 End of study satisfaction survey

At the end of the study (either Day 7, or the day after the last treatment dose) subjects are asked the following question in an exit survey:

- Would you use Robitussin to treat your cough/cold again? (Y/N)

Results from these exit survey question will be summarized descriptively using frequencies and absolute percentages in Table 14.2.2.4.

4.9 Analysis of Safety

4.9.1 Adverse Events and Serious Adverse Events

All AEs will be coded using MedDRA. AEs will be categorized as related or unrelated by Lindus Health prior to database lock. The number of AEs/SAEs and the number of subjects with AEs/SAEs will be listed and tabulated.

The absolute and relative frequency of adverse events (AEs) in each group will be reported, including the total number of events, the total number of patients experiencing at least one event, and the frequency of events by severity and AE category. Safety analyses will be performed on the Safety population, according to investigational product received. AEs will be regarded as 'treatment emergent' if they occur on or after the first use of investigational product at baseline (Day 0, pre-randomization). In the event of a missing start date, an AE will be assumed to be 'treatment emergent' unless the end date is prior to starting treatment. In case of misallocation compared to the randomization schedule, TEAEs will be associated with the most recent investigational product received.

A listing of all Treatment Emergent AEs (TEAEs) will be presented for all subjects in the Safety population with the following AE summaries (number of distinct AEs and frequency/proportion of subjects affected) presented by treatment group and overall:

- TEAEs—Overview (Table 14.3.1.1)
- TEAEs by System Organ Class (SOC) and Preferred Term (PT) (Table 14.3.1.2)
- TEAE by Relationship, System Organ Class and Preferred Term (Table 14.3.1.3)
- TEAE by System Organ Class, Preferred Term and Worst Severity (Table 14.3.1.4)
- Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term (Table 14.3.1.5)

4.10 Analysis of Other Variables

Not applicable.

5 Changes to the Protocol Defined Statistical Analysis Plan

Rules to halt diary entries being sent out were not in place for all participants and therefore a subset of participants will have reported outcome and compliance data after they responded

that they had stopped study treatment. To highlight this, the data exports will flagged under the variable QSSPID, with each issue noted.

Data flagged in the QSSPID variable will be excluded from all analysis tables and aggregated data. However, this data will be available in all relevant listings, with the QSSPID flag visible for each relevant participant. Information about how the flagged data will be excluded from the analysis datasets will be available in the analysis dataset specifications.

6 References

FDA, Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (Aug. 2023), https://www.fda.gov/media/171667/download.

Appendix 1: List of Data Displays

CSR Section	TLF	Number	Title	Population	Topline
14.1 Demographic Data, Subject Disposition and Subject Characteristics Summary Tables and Figures					
	Table	14.1.1	Subject Disposition	All Screened Subjects	T
	Table	14.1.2	Incidence of Important Protocol Deviations	All Randomized Subjects	
	Table	14.1.3	Demographic and Baseline Characteristics	Safety Population	T
	Table	14.1.4	Summary of Medical History	Safety Population	
	Table	14.1.5	Summary of Concomitant Medications	Safety Population	
	Table	14.1.6	Summary of Product Compliance	Safety Population	
	Table	14.1.7	Summary of Daily Product Use	Safety Population	
14.2 Primary and Secondary Endpoint Summary Tables and Figures					
	Table	14.2.1.1.1	Primary Endpoint: Summary and Statistical Analysis of WURSS-21 Total Scores	mITT Populaton	T
	Table	14.2.1.1.2	Primary Endpoint: Summary and Statistical Analysis of WURSS-21 Total Scores	NCCM Populaton	
	Table	14.2.1.2.1	Primary Endpoint: Summary and Statistical Analysis of WURSS-21 Total Symptom Domain	mITT Population	T
	Table	14.2.1.2.2	Primary Endpoint: Summary and Statistical Analysis of WURSS-21 Total Symptom Domain	NCCM Population	

CSR Section	TLF	Number	Title	Population	Topline
	Table	14.2.1.3.1	Primary Endpoint: Summary and Statistical Analysis of WURSS-21 Total QoL Domain	mITT Population	T
	Table	14.2.1.3.2	Primary Endpoint: Summary and Statistical Analysis of WURSS-21 Total QoL Domain	NCCM Population	
	Table	14.2.1.4.1	Primary Endpoint: Summary and Statistical Analysis of WURSS-21 Individual Symptom Domains	mITT Population	T (cough symptom only)
	Table	14.2.1.4.2	Primary Endpoint: Summary and Statistical Analysis of WURSS-21 Individual Symptom Domains	NCCM Population	
	Table	14.2.1.5.1	Primary Endpoint: Summary and Statistical Analysis of WURSS-21 Individual QoL Domains	mITT Population	T
	Table	14.2.1.5.2	Primary Endpoint: Summary and Statistical Analysis of WURSS-21 Individual QoL Domains	NCCM Population	
	Table	14.2.2.1.1	Secondary Endpoint: Summary and Statistical Analysis of Specific QoL questions	mITT population	T
	Table	14.2.2.1.2	Secondary Endpoint: Summary and Statistical Analysis of Specific QoL questions	NCCM population	
	Table	14.2.2.2.1	Secondary Endpoint: Summary and Statistical Analysis of Categorized QoL factors	mITT population	

CSR Section	TLF	Number	Title	Population	Topline
	Table	14.2.2.2.2	Secondary Endpoint: Summary and Statistical Analysis of Categorized QoL factors	NCCM population	
	Table	14.2.2.3.1	Summary of Secondary Endpoint (effect of Robitussin on specific QoL questions)	mITT Population	
	Table	14.2.2.3.2	Summary of Secondary Endpoint (effect of Robitussin on specific QoL questions)	NCCM Population	
	Figure	14.2.3.1	Summary WURSS-21 Total Score	mITT Population	
	Figure	14.2.3.2	Summary WURSS-21 Total Score	NCCM Population	
	Figure	14.2.4.1	Summary of WURSS-21 Total Symptom Domain	mITT Population	
	Figure	14.2.4.2	Summary of WURSS-21 Total Symptom Domain	NCCM Population	
	Figure	14.2.5.1	Summary of WURSS-21 Total QoL Domain	mITT Population	
	Figure	14.2.5.2	Summary of WURSS-21 Total QoL Domain	NCCM Population	
	Figure	14.2.6.1	Summary of WURSS-21 Question 7 (Cough)	mITT Population	
	Figure	14.2.6.2	Summary of WURSS-21 Question 7 (Cough)	NCCM Population	
	Table	14.2.2.4	Summary of End of Study Questionnaire	Safety Population	
14.3 Safety Data Summary Tables and Figures					

CSR Section	TLF	Number	Title	Population	Topline
14.3.1 Displays of Adverse Events and Serious Adverse Events					
	Table	14.3.1.1	Treatment-Emergent Adverse Events (TEAE) – Overview including Treatment death, Severity AEs, Serious Adverse Event(SAEs)	Safety Population	T
	Table	14.3.1.2	Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population	T
	Table	14.3.1.3	TEAE by Relationship, System Organ Class and Preferred Term	Safety Population	
	Table	14.3.1.4	TEAE by System Organ Class, Preferred Term and Worst Severity	Safety Population	
	Table	14.3.1.5	Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Population	
14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events					
	Listing	14.3.2.1	Listing of Death	Safety Population	---
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events					
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14.3.4 Other Observations Related to Safety and Abnormal Laboratory Values					
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CSR Section	TLF	Number	Title	Population	Topline
APPENDIX					
16.1.6 Listing of Subjects Receiving Test Drug(s)/Investigational Product(s) from Specific Batches, where more than one batch was used					
	NA				
16.1.7 Randomization Scheme and Codes (Subject identification and treatment assigned)					
	Listing	16.1.7.1	Randomization Information	All Randomized Subjects	
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16.1.9 Documentation of Statistical Methods					
	Raw output	16.1.9.1.1 through 16.1.9.16.1	Statistical Analysis of Primary and Secondary Endpoints (Reference: Tables 14.2.1.1.1 - 14.2.2.3.2)	mITT Population,	T (for topline tables only as defined above)
		16.1.9.1.2 through 16.1.9.16.2	Statistical Analysis of Primary and Secondary Endpoints (Reference: Tables 14.2.1.1.1 - 14.2.2.3.2)	NCCM Population	
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16.2 Subject Data Listings **16.2.1 Discontinued Subjects**					
	Listing	16.2.1.1	Subject Disposition	Enrolled Population / All randomized subjects	
16.2.2 Protocol Deviations					
	Listing	16.2.2.1	Important Protocol Deviations	All Randomized Subjects	

CSR Section	TLF	Number	Title	Population	Topline
	Listing	16.2.2.2	All Protocol Deviations	All Randomized Subjects	
16.2.3 Patients Excluded from Analysis Populations					
	Listing	16.2.3.1	Exclusions from Analysis Populations	All Randomized Subjects	
16.2.4 Demographic Data					
	Listing	16.2.4.1	Demographic and Baseline Characteristics	All Randomized Subjects	
	Listing	16.2.4.2	Medical History and Current Medical Conditions	All Randomized Subjects	
	Listing	16.2.4.3	Prior Medications	Safety Population	
	Listing	16.2.4.4	Concomitant Medications and Significant Non-Drug Therapies	Safety Population	
16.2.5 Compliance and/or Drug Concentration Data (if available)					
	Listing	16.2.5.1	Study Product Compliance	Safety Population	
16.2.6 Individual Response Data					
	Listing	16.2.6.1	WURSS-21	mITT Population	
	Listing	16.2.6.2	QoL Questionnaire (Secondary outcome)	mITT Population	
	Listing	16.2.6.3	End of study satisfaction survey	Safety Population	
16.2.7 Adverse Event Listings					
	Listing	16.2.7.1	All Adverse Events	Safety Population	
16.2.8 Other Listings and Listing of Laboratory Measurements, when required by regulatory authorities (if applicable)					

CSR Section	TLF	Number	Title	Population	Topline
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16.4 Individual Subject Data Listings					
	NA				

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