STATISTICAL ANALYSIS PLAN

A Real-World Evidence study evaluating Quality of Life parameters following use of Emergen-C

Protocol Number:	300217
Phase:	4
Version:	2.0

This document contains confidentiality statements that are not relevant for this publicly available version

Document History

Document	Version Date	Summary of Changes (New analysis or Change in planned analysis)
Original Analysis Plan	07-MAR-2025	Not applicable (N/A)
V2.0	18-MAR-2025	Compliance definition updated following blind data review See Appendix 2 for more detail.

Amendments incorporate all revisions to date.

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1 Abbreviations

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
BDRM	Blind Data Review Meeting
CI	Confidence Interval
GEE	Generalized Estimation Equations
MFI	Multidimensional Fatigue Inventory
mITT	Modified Intent-To-Treat
MMRM	Mixed-effects Model for Repeated Measures
PT	Preferred Term
QoL	Quality of Life
SAE	Severe Adverse Event
SE	Standard error
SOC	System Organ Class
TEAE	Treatment-emergent adverse event

The purpose of this Statistical Analysis Plan is to describe the planned analyses and outputs to be included in the Clinical Study Report for Protocol 300217.

2 Summary of Key Protocol Information

The purpose of this trial is to demonstrate the efficacy and safety of Emergen-C Core Super Orange Powder to improve the symptoms of fatigue and quality of life (QoL). Efficacy will be demonstrated as superiority of the intervention vs. control group on the QoL assessments at 12 weeks. Safety will be demonstrated through comparison of intervention vs. control groups on incidence of treatment-emergent adverse events (TEAEs).

The study will follow a randomized, double-blind, parallel group, placebo-controlled, decentralized design with two treatment arms. After a screening period, subjects will be randomized to receive Emergen-C Core Super Orange Powder or a placebo according to a pre-specified randomization scheme.

2.1 Study Design

This is a randomized, double-blind, parallel group, placebo-controlled, decentralized clinical trial in healthy male and female subjects, aged 18-64 years, evaluating the over-time effects of 12-weeks daily-use of Emergen-C. Approximately 430 people, aged 18-64 years, will be screened for eligibility. The study expects to enroll about 300 eligible subjects across the United

States. Subjects will be randomized into one of two study groups (at a 1:1 ratio) and will take one sachet of study product (Emergen-C or placebo) once daily in the morning at approximately the same time each day for 12 weeks. A total of approximately 240 subjects are expected to complete the study (approximately 120 in each study group).

Subjects will be recruited through targeted advertising on social media platforms. This study is entirely decentralized, and subjects will not be required to physically attend any on-site visits (only virtual visits). All study data will be collected remotely through a study platform using the subject's personal mobile device, tablet or computer.

Detailed study procedures can be found in Section 5 of the protocol.

2.2 Study Objectives

Objectives	**Endpoints**
Primary Objective	**Primary Endpoint**
To evaluate the effect of daily supplementation with Emergen-C in improving QoL parameters as measured by the Multidimensional Fatigue Inventory (MFI) domains, compared to placebo at Week 12.	Change from Baseline at Week 12 in: • *General Fatigue* Domain score (items 1,5,12,16) • *Physical Fatigue* Domain score (items 2,8,14,20) • *Reduced Activity* Domain score (items 3,6,10,17) • *Reduced Motivation* Domain score (items 4,9,15,18) • *Mental Fatigue* Domain score (items 7,11,13,19)
Secondary Objectives	**Secondary Endpoints**
Efficacy	
To evaluate the effect of daily supplementation with Emergen-C in improving QoL parameters as measured by the MFI domains, compared to placebo at Week 4 and 8.	Change from Baseline at Week 4 and 8 in: • *General Fatigue* Domain score (items 1,5,12,16) • *Physical Fatigue* Domain score (items 2,8,14,20) • *Reduced Activity* Domain score (items 3,6,10,17) • *Reduced Motivation* Domain score (items 4,9,15,18)

Objectives	Endpoints
	• *Mental Fatigue* Domain score (items 7,11,13,19)
To evaluate the effect of daily supplementation with Emergen-C in improving QoL parameters as measured by the MFI individual items, compared to placebo at Week 4, Week 8 and Week 12.	• Change from Baseline at Week 4, Week 8 and Week 12 for each of the individual items in the MFI.
To evaluate the effect of daily supplementation with Emergen-C in improving additional QoL parameters as measured by additional QoL Questions, compared to placebo at Week 4, Week 8 and Week 12.	Change from Baseline at Week 4, Week 8 and Week 12 for: • Family support (Questions 1 and 2 on additional QoL questionnaire) • Resilience (Questions 3 and 4 on additional QoL questionnaire) • Ability to relax and unwind (Questions 5 and 6 on additional QoL questionnaire)
Safety	
To monitor the safety of the study treatment with daily use for 12 weeks.	• The number of TEAEs [1]
Exploratory Objectives	**Exploratory Endpoints**
To evaluate the effect of daily supplementation with Emergen-C in improving additional QoL parameters as measured by additional QoL Questions, compared to placebo at Week 4, Week 8 and Week 12.	Number of days reported at Week 4, Week 8 and Week 12, for: • Days feeling rundown • Days cancelling plans • Days with cold and flu symptoms • Days of work missed
Subgroup analyses for primary and secondary endpoints.	Subgroup analyses for: • Sex (male and female) • Age (18-34 and 35-64 years)

Footnotes: [1] Further details on safety outcomes and data collected in Section 5.7

2.3 Treatments

The investigational product "Emergen-C Core Super Orange Powder" will be provided to subjects in the intervention group, who are instructed to consume one sachet per day in the morning at approximately the same time each day. Subjects in the control group will receive a

placebo product, to be consumed in the same way as the investigational product. Both study products (treatment and placebo) are packaged in individual, unmarked, identical foil sachets.

2.4 Sample Size Calculation

This study will be conducted in healthy male and female subjects, aged 18-64 years (inclusive), and of any race/ethnicity. No discrimination of any kind (e.g. social class, gender, skin color, ethnicity) should preclude eligible participants from participating in the study. The study will aim to recruit a diverse population representative of the US census.

Sufficient subjects will be screened in order to enroll about 300 eligible subjects (approximately 150 subjects per study group) and approximately 240 subjects are expected to complete the study (approximately 120 subjects per study group, allowing for up to 20% dropouts). Potential participants will be recruited through targeted digital advertising campaigns.

3 Planned Analyses

3.1 Interim Analysis

No interim analysis is planned.

3.2 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 database has been locked.
3. All criteria for unblinding the randomization codes have been met and the randomization codes have been distributed.

4 Considerations for data analyses and Data Handling Conventions

4.1 Baseline Definition

For all endpoints, the baseline value will be the latest pre-dose assessment with a non-missing value.

4.2 Subgroups/Stratifications

The following subgroups will be constructed and analyzed for primary and secondary analyses as an exploratory outcome:

- Sex (male vs. female subjects)
- Age groups (18-34 years vs. 35-64 years).

4.3 Timepoints and Visit Windows

The timepoints and visits for this study are defined in the Table 1: Schedule of Activities. Any deviation from the study schedule may be reviewed on a case-by-case basis at the Blinded Data Review Meeting (BDRM) to determine whether the data should be excluded from the Per-Protocol (PP) analyses.

Table 1: Schedule of Activities

Visit		**Treatment Period**			
	Pre-screening	**Visit 1 Screening & Baseline**	**Treatment Initiation**	**Virtual Visit 2**	**Virtual Visit 3**	**Virtual Visit 4**
Study Day	**Day-7 to Day -2**	**Day -7 to Day -2**	**Day 1**	**Week 4 Day 28 (+5)**	**Week 8 Day 56 (+5)**	**Week 12 Day 84 (+5)**
Medical/Medication History[a]	X					
Demographics[a]	X					
MFI [a]	X			X	X	X
Informed Consent	X					

Visit			Treatment Period			
	Pre-screening	Visit 1 Screening & Baseline	Treatment Initiation	Virtual Visit 2	Virtual Visit 3	Virtual Visit 4
Study Day	**Day-7 to Day -2**	**Day -7 to Day -2**	**Day 1**	**Week 4 Day 28 (+5)**	**Week 8 Day 56 (+5)**	**Week 12 Day 84 (+5)**
ID Verification		X				
Inclusions/Exclusion criteria[c]		X				
Eligibility Assessment		X				
Randomization		X				
Participant Training		X				
Study Product Shipped		X				
Supplementary QOL questionnaire		X	X	X	X	X
Concomitant Medication Check		X		X	X	X
Adverse Event (AE/ Serious Adverse Event)	X	X	X	X	X	X
Study Product Administration[b]			X (Daily through Week 12 visit)			
Participant Daily eDiary[a]			X (Daily through Week 12 visit)			
Subject Conclusion/Subject Exit from Study						X

[a]Subject-reported (self-reported) assessments.

[b]Subject will take the study product in the morning of each day

[c]Subject will self-report pregnancy status during Visit 1

5 Data Analysis

Data analysis will be performed by PPD, independent biostatistics consultant CCI, with oversight from Haleon. The statistical analysis software used will be Stata Version 18 or later (StataCorp. 2023. *Stata Statistical Software: Release 18*. College Station, TX: StataCorp LLC).

Prior to database lock and unblinding, a BDRM will be conducted in which various aspects of the trial will be discussed and agreed.

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

5.1 Populations for Analysis

Tables described in this section will be produced for the mITT population, unless otherwise specified.

5.1.1 Subject Disposition

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. An enrolled subject is a subject who has signed the informed consent and is eligible to proceed beyond the screening visit.

The number of screened, enrolled, and randomized subjects will be presented in Table 14.1.1 (see Appendix 2) and a CONSORT diagram showing the flow of subjects through the study will be produced.

The number and percentage of screen failure subjects (subjects not randomized) with reasons why subjects are not randomized will be displayed. Percentages for screen failure subjects will be based on the total number of subjects screened.

The number and percentage of randomized subjects who complete and discontinue the study, broken down by reason for discontinuation, by study product and overall will also be displayed. The percentages will be based on the number of subjects randomized.

Table 14.1.1 will also present the number and percentage of subjects in each of the defined analysis populations (as defined in Section 4.1.3) by study product and overall. Percentages will be based on the number of subjects randomized.

Subject disposition will be listed for randomized subjects (Listing 16.2.1.1) by study product displaying:

- Subject number
- Demographic data (age, sex, race, and ethnicity)

- Screening date
- Study product start date and time
- Study product end date, and days of study product use
- Subject status (completer, Yes/No) – completer to be defined as providing MFI at week 12
- Study completion /withdrawal date
- Duration (in days) in the study (defined as [(date of completion or withdrawal – start date of study product) + 1]
- Primary reason for withdrawal, if applicable.

Subject disposition information will be listed for all screened, non-randomized subjects (Listing 16.2.1.2), displaying:

- Subject number
- Demographic information (age, sex, race and ethnicity)
- Screening date
- Reason for screen failure
- Any further details of reason for screen failure.

5.1.2 Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study. Data will be reviewed prior to unblinding and database lock to ensure all important deviations are captured and categorised. Subjects with important protocol deviations liable to influence the efficacy outcomes will have their affected data excluded from the PP analyses. Subjects may also be identified as having important protocol deviations not leading to exclusion of data from the PP 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 assessment process will be specified in the Blind Data Review Plan and subjects with important protocol deviations will be identified at the BDRM.

For all randomized subjects, Table 14.1.2 will present the number and percentage, by study product and overall, and Listing 16.2.2.1 will list:

- Subjects with at least one important protocol deviation
- Subjects with important protocol deviations not leading to exclusion from PP population with reasons for deviations and reasons why the deviation was not excluded from PP population
- Subjects with important protocol deviations leading to exclusion from the PP population with reasons for deviations.

All protocol deviations collected on the protocol deviation case report form page will be listed in Listing 16.2.2.2. The listing will present date of deviation, type of deviation, and deviation description.

5.1.3 Analysis Populations

Three analysis populations are defined.

Population	Definition / Criteria	Analyses Evaluated
Safety	• Comprise of all subjects who receive at least one dose of study product. • This population will be based on the treatment the subject actually received.	• Safety
Modified Intent-To-Treat (mITT)	• Comprise of all randomized subjects with completed baseline visit (visit 1), at least one completed post-baseline MFI domain assessment, and taken at least one dose of allocated product. • This population will be based on the treatment to which the subject was randomized.	• Demographics • Baseline Characteristics • Efficacy • Subgroup analyses

Population	Definition / Criteria	Analyses Evaluated
	• Any subject who receives a randomization number will be considered to have been randomized.	
Per-Protocol (PP)	• Comprised of all subjects in the mITT population who have adhered to treatment regime and were not affected by protocol deviations.	• Sensitivity (Primary endpoint)

Note: Please refer to Appendix 1: List of Data Displays which details the population to be used for each display being generated.

The numbers of subjects included in each of the analysis populations will be summarized (Table 14.1.1). Subjects excluded from any of the analysis populations will be listed in Listing 16.2.3.1, with the reason for exclusion.

The primary population for assessment of efficacy will be the mITT Population. A PP analysis will be performed for efficacy analysis of the primary endpoint if at least 10% of the mITT subjects are excluded from the PP Population. Efficacy data determined to have been potentially impacted by a protocol deviation will be excluded from the PP analysis. A decision on whether a protocol deviation impacts efficacy data and whether to perform a PP analysis will be made at the BDRM.

5.2 Subject Demographics and Other Baseline Characteristics

Demographic and baseline characteristics summaries will be produced for the mITT.

5.2.1 Demographic Characteristics

Demographic and baseline characteristics for each group will be reported for the mITT and Safety populations (and for the PP population, if a PP analysis is performed) using descriptive statistics. Categorical demographic variables are sex, smoking status and race. These variables will be summarized by the number and percentage of subjects with each relevant characteristic in each treatment group. Continuous variables (age, weight, and height) will be summarized by the arithmetic mean, standard deviation, median, minimum, and maximum values in each treatment group. All demographic information will be tabulated (Table 14.1.3.1) and listed (Listing 16.2.4.1).

5.2.2 General Medical History

Medical history/current medical conditions will be listed (see Listing 16.2.4.2) based on 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, dietary supplements and herbal remedies, that began before obtaining informed consent.

The presence/absence of any relevant medical history will also be listed in Listing 16.2.4.2, with start date and end date or ongoing at the start of study product.

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

Compliance data will be summarized for the mITT population. Exposure and other medications will be summarized on the safety population.

For all randomized subjects, 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).

5.3.1 Study Product Compliance and Exposure

Treatment compliance will be assessed daily during the 12-week treatment period – the end of the treatment period will be defined as the completion of the last virtual visit 4 MFI questionnaire. If the virtual visit 4 MFI questionnaire is not completed, the date used as the definition will be the treatment initiation date plus 84 days. Both definitions have an acceptable window of +/- 5 days. Compliance will be analyzed descriptively by reporting the absolute and relative frequency of subjects with 80% compliance to treatment per block of 4 treatment weeks and overall, for each group. A compliance score will be calculated for each subject by dividing the number of days the allocated treatment was taken by the number of days the treatment was allocated. The compliance score will be summarized for each group and compared between groups.

Additional information on number of doses taken, number of missed doses, number of expected doses, and dose compliance will be presented both in Table 14.2.1.1 and Listing 16.2.5.1 where:

- Number of doses taken is defined as:
    - Overall: Number of times daily diary indicates a dose was taken between treatment initiation and Week 12 MFI completion date. If the virtual visit 4 MFI questionnaire is not completed, the date used as the definition will be the treatment initiation date plus 84 days.
    - Treatment Start to Week 4: Number of times daily diary indicates a dose was taken between treatment initiation and Week 4 MFI completion date. If the virtual visit 2 MFI questionnaire is not completed, the date used as the definition will be the treatment initiation date plus 28 days.
    - Week 4 to Week 8: Number of times daily diary indicates a dose was taken between Week 4 MFI completion date and Week 8 MFI completion date. If the

virtual visit 3 MFI questionnaire is not completed, the date used as the definition will be the treatment initiation date plus 56 days.
    - Week 8 to Week 12: Number of times daily diary indicates a dose was taken between Week 8 MFI completion date and Week 12 MFI completion date. If the virtual visit 4 MFI questionnaire is not completed, the date used as the definition will be the treatment initiation date plus 84 days.
-

- Number of expected doses is defined as:
    - Overall: Week 12 MFI Completion Date - Treatment Start Date.
    - Treatment Start to Week 4: Week 4 MFI Completion Date - Treatment Start Date.
    - Week 4 to Week 8: Week 8 MFI Completion Date – Week 4 MFI Completion Date.
    - Week 8 to Week 12: Week 12 MFI Completion Date – Week 8 MFI Completion Date.
- Number of missed doses is defined as number of expected doses – number of actual doses taken for each time period.
- Dose compliance (%) = [100 x (Number of doses taken / Expected number of dose)].

Compliance will be tabulated using absolute and relative frequencies, and compliance score using mean, standard deviation, minimum and maximum values and median (see Table 14.2.1.1 and Listing 16.2.5.1).

5.3.2 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 listed (Listing 16.2.4.3)

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 [redacted].

Prior medications and prior non-drug treatments will be listed by subject, with drug name, CCI [redacted] 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 16.2.4.4) 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.

5.4 Analysis of Efficacy

5.4.1 Primary Efficacy Endpoint

5.4.1.1 Primary Efficacy Endpoint Definition

The primary efficacy variable are the MFI domain scores:

- *General Fatigue*: Items 1, 5, 12, 16
- *Physical Fatigue*: Items 2, 8, 14, 20
- *Reduced Activity*: Items 3, 6, 10, 17
- *Reduced Motivation*: Items 4, 9, 15, 18
- *Mental Fatigue*: Items 7, 11, 13, 19

Items are answered on a 5-point scale and recoded so that higher scores represent higher levels of fatigue.

Change from Baseline will be calculated at the subject level by subtracting the baseline score from scores assessed at 4, 8 and 12 weeks. The baseline score will be the screening (Day -7 to Day -2) MFI scores.

5.4.1.2 Statistical Hypothesis, Model, and Method of Analysis

The primary analyses assess the following hypothesis for each MFI domain score:

$$H_0: MFI_{12w-baseline_{Control}} = MFI_{12w-baseline_{Intervention}}$$
$$H_1: MFI_{12w-baseline_{Control}} \neq MFI_{12w-baseline_{Intervention}}$$

Where $MFI_{12w-baseline_{Control}}$ represents the change in MFI domain scores from baseline to 12 weeks in the control group, and $MFI_{12w-baseline_{Intervention}}$ refers to the change in the intervention group.

Change from baseline for each of the MFI domains listed above will be analyzed using a linear mixed-effects model for repeated measures (MMRM) with randomized treatment arm, timepoint as a factor and [treatment x timepoint] interaction as fixed effects, and the respective baseline MFI domain score as a covariate. Subject will be included as a repeated measure with an unstructured covariance matrix. Kenward-Rogers degrees of freedom will be applied (Kenward and Roger 1997). The difference between the least square mean change from baseline for the treatment compared to placebo group at Week 12 from the MMRM will be presented along with the two-sided p-value and 95% confidence interval (CI).

Using the above model, the adjusted mean change from baseline in MFI domains will also be reported by study product along with the 95% confidence intervals (CIs) and p-values testing for a non-zero change from baseline.

A significance level of 5% is used to evaluate the primary endpoint. To account for multiple comparisons, a Bonferroni-Holm correction will be applied to the p-values and CIs of the mean change between groups for the MFI domain scores at week 12. Change from Baseline in each of the MFI domain scores at earlier timepoints will only be assessed for confirmatory evidence if the change from the later timepoint achieves a statistically significant difference. Each domain will only be evaluated if the change from Baseline to 12 weeks (primary endpoint) was significant at the Bonferroni-Holm adjusted significance level. A significance level of 5% applies to all subsequent analyses of timepoints. This strategy will begin at Week 12, then move to Week 8, then to Week 4. There will be no further adjustments for multiplicity for other secondary endpoints. Both adjusted and non-adjusted p-values will be reported (where applicable).

The assumption of normality and homogeneity of variance in the MMRM will be investigated. In case of violation of these assumptions, a suitable non-parametric test (such as: Van Elteren Test) will be performed to assess the change from Baseline comparison. The results will be provided to support the MMRM results.

For each MFI domain listed above, the value at each timepoint (baseline, week 4, week 8 and week 12) and the corresponding change from baseline will be summarized descriptively for each treatment group. Raw means (+/- standard errors, SE) for each MFI endpoint at each assessment timepoint will be plotted by treatment group.

5.4.1.3 Supportive Analyses

A PP analysis will be performed on the primary endpoint if there is greater than or equal to a 10% difference in the number of subjects between the PP and mITT populations.

Primary and secondary endpoints will be analyzed separately for each subgroup.

5.4.2 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 (Ashbeck and Bell 2016; Baron et al. 2008).

Such complete case analysis requires a 'missing completely at random' assumption to remain unbiased and this is unlikely to hold, i.e., the fact that the data are missing is independent of the observed and unobserved data.

Using an MMRM, it will therefore be assumed that a subject with missing data at one post-baseline assessment visit would have obtained a similar efficacy result at that visit compared to a subject using the same investigational product with similar non-missing results at other timepoints (baseline and the other post-baseline assessment visits).

5.5 Analysis of Secondary Objectives

5.5.1 Efficacy (Secondary)

The secondary endpoints of each MFI domain at week 4 and week 8 will be summarized descriptively and analyzed as described for the primary endpoint. Non-adjusted *p*-values and 95%-CIs will be reported, which need to be interpreted in light of the results of the primary endpoint.

Similarly, the secondary endpoint for each of the individual MFI questions will be summarized descriptively and analyzed as described for the primary endpoint, but with baseline of the MFI domain score replace with the individual MFI question score at baseline for the respective MFI item for each timepoint (week 4, week 8 and week 12).

The secondary endpoint for the each of the supplementary quality of life (QoL) questions will also be summarized descriptively and analyzed using the same MMRM model described above, but with baseline of the MFI domain score replaced with the baseline of the respective quality of life question for each timepoint (week 4, week 8 and week 12).

5.6 Exploratory Analyses

The number of days reported at each timepoint for the previous 4 weeks (and total) will be listed and summarized by treatment group in the mITT population using descriptive statistics for:

- days feeling rundown
- days canceling plans
- days with cough and flu symptoms
- days of work missed

The exploratory endpoint for the each of the supplementary quality of life (QoL) questions will also be summarized descriptively and analyzed using the same MMRM model described above, but with baseline of the MFI domain score replaced with the baseline of the respective quality of life question for each timepoint (week 4, week 8 and week 12).

5.7 Analysis of Safety

5.7.1 Adverse Events and Serious Adverse Events

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 (visit 2). 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 AEs 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
- TEAEs by System Organ Class (SOC) and Preferred Term (PT)
- Treatment emergent treatment related AEs by SOC and PT
- Treatment emergent treatment related serious AEs by SOC and PT

Separate listings will be presented for:

- Deaths, Severe AEs (SAE) and any AEs leading to product or study discontinuation.
- Exposure to study product

5.8 Analysis of Other Variables

Not applicable.

6 Changes to the Protocol Defined Statistical Analysis Plan

Two questions outlined in the protocol section 9.10.2 were not included in this statistical analysis plan as they were not included in the study database build.

It was found that the below exploratory endpoints had been phrased differently within the database build:

- Days feeling unwell
- Days with cough and cold symptoms
- Days sick in bed

To better align with the question in the database build, the endpoints have been updated in this SAP to:

- Days feeling rundown
- Days with cold and flu symptoms
- Days of work missed

Ethnicity was also not explicitly captured within the database and has been removed from the SAP.

The definition of study product compliance was updated in the SAP to account for differences in end of treatment. In place of using the 12-week timepoint as the treatment period end, the date of last (completed) visit 4 MFI questionnaire has been used as the definition of the end of treatment. If the visit 4 MFI questionnaire was not completed, then the date of the virtual visit will be used.

7 References

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Appendix 1: List of Data Displays

CSR Section	TLF	Title	Population	Template	Topline
14.1 Demographic Data Summary Tables and Figures					
	Table	Subject Disposition	All Screened Subjects	14.1.1	Yes
	Table	Demographic and Baseline Characteristics	Safety Population	14.1.3.1	Yes
	Table	Demographic and Baseline Characteristics	mITT Population	14.1.3.2	Yes
14.2 Efficacy Data Summary Tables and Figures					
	Table	Summary of Product Compliance	mITT Population	14.2.1.1.1	---
	Table	Summary of MFI Domain Scores	mITT Population	14.2.2.1.1	Yes
	Table	Summary of MFI Individual Item Scores	mITT Population	14.2.3.1.1	Yes
	Table	Summary of Quality of Life (QoL) Questions (Secondary Endpoint)	mITT Population	14.2.4.1.1	
	Table	Summary of Quality of Life (QoL) Questions (Exploratory Endpoint)	mITT Population	14.2.5.1.1	
	Table	Summary of MFI Domain Scores – Sex Subgroup	mITT Population	14.2.2.1.3	
	Table	Summary of MFI Individual Item Scores– Sex Subgroup	mITT Population	14.2.3.1.3	
	Table	Summary of QoL Questions (Secondary Endpoint) – Sex Subgroup	mITT Population	14.2.4.1.3	
	Table	Summary of MFI Domain Scores – Age Subgroup	mITT Population	14.2.2.1.5	
	Table	Summary of MFI Individual Item Scores– Age Subgroup	mITT Population	14.2.3.1.5	

CSR Section	TLF	Title	Population	Template	Topline
	Table	Summary of QoL Questions (Secondary Endpoint) – Age Subgroup	mITT Population	14.2.4.1.5	
	Table	Statistical Analysis of Change from Baseline in Multidimensional Fatigue Inventory (MFI) Domains Over Time (MMRM)	mITT Population	14.2.2.1.2	Yes
	Table	Statistical Analysis of Change from Baseline in MFI Individual Item Scores Over Time (MMRM)	mITT Population	14.2.3.1.2	Yes
	Table	Statistical Analysis of Change from Baseline in Quality of Life (QoL) Questions (Secondary Endpoint) Over Time (MMRM)	mITT Population	14.2.4.1.2	
	Table	Statistical Analysis of Change from Baseline in Quality of Life (QoL) Questions (Exploratory Endpoint) Over Time (MMRM)	mITT Population	14.2.5.1.2	
	Table	Statistical Analysis of Change from Baseline in Multidimensional Fatigue Inventory (MFI) Domains Over Time (MMRM) – Sex Subgroup	mITT Population	14.2.2.1.4	
	Table	Statistical Analysis of Change from Baseline in MFI Individual Item Scores Over Time (MMRM) – Sex Subgroup	mITT Population	14.2.3.1.4	
	Table	Statistical Analysis of Change from Baseline in Quality of Life (QoL) Questions (Secondary Endpoint) Over Time (MMRM) – Sex Subgroup	mITT Population	14.2.4.1.4	
	Table	Statistical Analysis of Change from Baseline in Multidimensional Fatigue Inventory (MFI) Domains Over Time (MMRM) – Age Subgroup	mITT Population	14.2.2.1.6	
	Table	Statistical Analysis of Change from Baseline in MFI Individual Item Scores Over Time (MMRM) – Age Subgroup	mITT Population	14.2.3.1.6	

CSR Section	TLF	Title	Population	Template	Topline
	Table	Statistical Analysis of Change from Baseline in Quality of Life (QoL) Questions (Secondary Endpoint) Over Time (MMRM) – Age Subgroup	mITT Population	14.2.4.1.6	
	Figure	MFI Domain Score by Visit and Study Product – General Fatigue	mITT Population	14.2.2.1.1	Yes
	Figure	MFI Domain Score by Visit and Study Product - Physical Activity	mITT Population	14.2.2.1.2	Yes
	Figure	MFI Domain Score by Visit and Study Product – Reduced Activity	mITT Population	14.2.2.1.3	Yes
	Figure	MFI Domain Score by Visit and Study Product – Reduced Motivation	mITT Population	14.2.2.1.4	Yes
	Figure	MFI Domain Score by Visit and Study Product – Mental Fatigue	mITT Population	14.2.2.1.5	Yes
14.3 Safety Data Summary Tables and Figures					
14.3.1 Displays of Adverse Events					
	Table	Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population	14.3.1.1	
	Table	Treatment Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population	14.3.1.2	
	Table	Treatment Related Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Population	14.3.1.3	
14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events					
	Listing	Deaths	Safety Population	14.3.2.1	
	Listing	Non-Fatal Serious Adverse Events	Safety Population	14.3.2.2	

CSR Section	TLF	Title	Population	Template	Topline
	Listing	Treatment Emergent Adverse Events Leading to Study or Product Discontinuation	Safety Population	14.3.2.3	
APPENDIX					
16.1.7 Randomization Scheme and Codes (Subject identification and treatment assigned)					
	Listing	Randomization Information	All Randomized Subjects	16.1.7.1	
16.1.9 Documentation of Statistical Methods					
	Raw output	Statistical Analysis of Change from Baseline in Multidimensional Fatigue Inventory (MFI) Domains Over Time (MMRM) (Reference: Table 14.2.2.1.2)		R Output	Yes
	Raw output	Statistical Analysis of Change from Baseline in MFI Individual Item Scores Over Time (MMRM) (Reference: Table 14.2.3.1.2)	mITT Population	R Output	Yes
	Raw output	Statistical Analysis of Change from Baseline in Quality of Life (QoL) Questions (Secondary Endpoint) Over Time (MMRM) (Reference: Table 14.2.4.1.2)	mITT Population	R Output	
	Raw output	Statistical Analysis of Change from Baseline in Quality of Life (QoL) Questions (Exploratory Endpoint) Over Time (MMRM) (Reference: Table 14.2.5.1.2)	mITT Population	R Output	
	Raw output	Statistical Analysis of Change from Baseline in Multidimensional Fatigue Inventory (MFI) Domains Over Time (MMRM) – Sex Subgroup (Reference: Table 14.2.2.1.4)	mITT Population	R Output	

CSR Section	TLF	Title	Population	Template	Topline
	Raw output	Statistical Analysis of Change from Baseline in MFI Individual Item Scores Over Time (MMRM) – Sex Subgroup (Reference: Table 14.2.3.1.4)	mITT Population	R Output	
	Raw output	Statistical Analysis of Change from Baseline in Quality of Life (QoL) Questions (Secondary Endpoint) Over Time (MMRM) – Sex Subgroup (Reference: Table 14.2.4.1.4)	mITT Population	R Output	
	Raw output	Statistical Analysis of Change from Baseline in Multidimensional Fatigue Inventory (MFI) Domains Over Time (MMRM) – Age Subgroup (Reference: Table 14.2.2.1.6)	mITT Population	R Output	
	Raw output	Statistical Analysis of Change from Baseline in MFI Individual Item Scores Over Time (MMRM) – Age Subgroup (Reference: Table 14.2.3.1.6)	mITT Population	R Output	
	Raw output	Statistical Analysis of Change from Baseline in Quality of Life (QoL) Questions (Secondary Endpoint) Over Time (MMRM) – Age Subgroup (Reference: Table 14.2.4.1.6)	mITT Population	R Output	
16.2 Subject Data Listings					
16.2.1 Discontinued Subjects					
	Listing	Subject Disposition	All Randomized Subjects	16.2.1.1	---
	Listing	Subject Disposition	Non-Randomized Subjects	16.2.1.2	---
16.2.2 Protocol Deviations					

CSR Section	TLF	Title	Population	Template	Topline
	Table	Incidence of Important Protocol Deviations	All Randomized Subjects	14.1.2	---
	Listing	Important Protocol Deviations	All Randomized Subjects	16.2.2.1	---
	Listing	All Protocol Deviations	All Randomized Subjects	16.2.2.2	---
16.2.3 Patients Excluded from the Efficacy Analysis					
	Listing	Exclusion from Analysis Population	All Randomized Subjects	16.2.3.1	---
16.2.4 Demographic Data					
	Listing	Demographic and Baseline Characteristics	All Randomized Subjects	16.2.4.1	---
	Listing	Medical History and Current Medical Conditions	All Randomized Subjects	16.2.4.2	---
	Listing	Prior Medications	Safety Population	16.2.4.3	---
	Listing	Concomitant Medications and Significant Non-Drug Therapies	Safety Population	16.2.4.4	---
16.2.5 Compliance and/or Drug Concentration Data (if available)					
	Listing	Study Product Compliance	All Randomized Subjects	16.2.5.1	---

CSR Section	TLF	Title	Population	Template	Topline
16.2.6 Individual Efficacy Response Data					
	Listing	MFI Domain Scores	All Randomized Subjects	16.2.6.1	---
	Listing	MFI Individual Item Scores	All Randomized Subjects	16.2.6.2	---
	Listing	QoL Questions (Secondary Endpoint)	All Randomized Subjects	16.2.6.3	---
	Listing	QoL Questions (Exploratory Endpoint)	All Randomized Subjects	16.2.6.4	---
16.2.7 Adverse Event Listings					
	Listing	All Adverse Events	All Randomized Subjects	16.2.7.1	---
	Listing	All Adverse Events	Non Randomized Subjects	16.2.7.2	---
16.2.8 Other Listings and Listing of Laboratory Measurements, when required by regulatory authorities (if applicable)					
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16.4 Individual Subject Data Listings					
	NA				

Appendix 2: Addendum (Change in treatment compliance definition)

Rationale for changes:

During the Blind Data Review, a decision was made to alter the treatment compliance definition.

- The original version used was based on virtual visit dates. However, the main outcome uses the MFI questionnaire which may have been completed on a different date to the virtual visit. Therefore, the new treatment compliance definition uses MFI completion date, rather than virtual visit date.
- The original version stated that if the virtual visit 4 MFI questionnaire is not completed, the date used as the definition will be the final virtual visit date. However, to maintain measurement over a 12-week treatment period, in the new definition, if the virtual visit 4 MFI questionnaire is not completed, the date used as the definition will be the treatment initiation date plus 84 days.
- The daily diary that was used to record treatment compliance could only be completed once per day and therefore did not capture any additional doses. No additional doses were reported as a protocol deviation. Therefore, additional doses have been removed from the treatment compliance calculation.

Original version of treatment compliance section:

Treatment compliance will be assessed daily during the 12-week treatment period – the end of the treatment period will be defined as the completion of the last virtual visit 4 MFI questionnaire. If the virtual visit 4 MFI questionnaire is not completed, the date used as the definition will be the final virtual visit date. Both definitions have an acceptable window of +/- 5 days. Compliance will be analyzed descriptively by reporting the absolute and relative frequency of subjects with 80% compliance to treatment per block of 4 treatment weeks and overall, for

each group. A compliance score will be calculated for each subject by dividing the number of days the allocated treatment was taken by the number of days the treatment was allocated. The compliance score will be summarized for each group and compared between groups.

Additional information on both number of doses taken, number of expected doses taken, dose compliance, number of missed doses and number of additional doses presented both in Table 14.2.1.1 and Listing 16.2.5.1 where:

- Number of doses taken for 'Visit X – Visit Y' is defined as: [(date of Visit Y – date of Visit X) – number of missed doses between Visit X and Visit Y + number of additional doses between Visit X and Visit Y] by visit, and [(date of final visit – date of baseline visit) – number of missed dose + number of additional dose] for overall.
- Dose compliance (%) = [100 x (Number of doses taken / Expected number of dose)].
- Number of expected dose for 'Visit X – Visit Y' is defined as: [(date of Visit Y - date of Visit X)] by visit, and [(date of Final visit – date of Baseline visit)] for overall.

Final visit in the above definitions is the date the subject completed their week 12 MFI questionnaire (or the final virtual visit if not completed).

Compliance will be tabulated using absolute and relative frequencies, and compliance score using mean, standard deviation, minimum and maximum values and median (see Table 14.2.1.1 and Listing 16.2.5.1).

New version of treatment compliance section:

Treatment compliance will be assessed daily during the 12-week treatment period – the end of the treatment period will be defined as the completion of the last virtual visit 4 MFI questionnaire. If the virtual visit 4 MFI questionnaire is not completed, the date used as the definition will be the treatment initiation date plus 84 days. Both definitions have an acceptable window of +/- 5 days. Compliance will be analyzed descriptively by reporting the absolute and relative frequency of subjects with 80% compliance to treatment per block of 4 treatment weeks and overall, for each group. A compliance score will be calculated for each subject by dividing the number of days the allocated treatment was taken by the number of days the treatment was allocated. The compliance score will be summarized for each group and compared between groups.

Additional information on number of doses taken, number of missed doses, number of expected doses, and dose compliance will be presented both in Table 14.2.1.1 and Listing 16.2.5.1 where:

- Number of doses taken is defined as:
  - Overall: Number of times daily diary indicates a dose was taken between treatment initiation and Week 12 MFI completion date. If the virtual visit 4 MFI questionnaire is not completed, the date used as the definition will be the treatment initiation date plus 84 days.
  - Treatment Start to Week 4: Number of times daily diary indicates a dose was taken between treatment initiation and Week 4 MFI completion date. If the virtual visit 2 MFI questionnaire is not completed, the date used as the definition will be the treatment initiation date plus 28 days.
  - Week 4 to Week 8: Number of times daily diary indicates a dose was taken between Week 4 MFI completion date and Week 8 MFI completion date. If the virtual visit 3 MFI questionnaire is not completed, the date used as the definition will be the treatment initiation date plus 56 days.

- Week 8 to Week 12: Number of times daily diary indicates a dose was taken between Week 8 MFI completion date and Week 12 MFI completion date. If the virtual visit 4 MFI questionnaire is not completed, the date used as the definition will be the treatment initiation date plus 84 days.

- Number of expected doses is defined as:
  - Overall: Week 12 MFI Completion Date - Treatment Start Date.
  - Treatment Start to Week 4: Week 4 MFI Completion Date - Treatment Start Date.
  - Week 4 to Week 8: Week 8 MFI Completion Date – Week 4 MFI Completion Date.
  - Week 8 to Week 12: Week 12 MFI Completion Date – Week 8 MFI Completion Date.
- Number of missed doses is defined as number of expected doses – number of actual doses taken for each time period.
- Dose compliance (%) = [100 x (Number of doses taken / Expected number of dose)].

Compliance will be tabulated using absolute and relative frequencies, and compliance score using mean, standard deviation, minimum and maximum values and median (see Table 14.2.1.1 and Listing 16.2.5.1).

In section 5.1.4.2, reference to total MFI domain removed as not applicable to the endpoints (typo from draft version).