CLINICAL PROTOCOL

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

Protocol Number:	**300217**
Compound/Product Name:	**Emergen-C Core Super Orange Powder**
Phase:	**IV**

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

Sponsor Information

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Document History

Document	Version	Summary of Changes
Original protocol	**1.0**	**Not applicable (N/A)**
Amendment 1	**2.0**	**Section 4.2 Inclusion Criteria: Criteria #4 updated to clarify MFI scoring for eligibility is during pre-screening.** **Table 5-1 Schedule of Activities** • **MFI completion has been moved from Visit 1 (Screening & Baseline) to Pre-screening.** • **To correct error in time of collection of Adverse Events to align with section 9.1.3. AEs are to be collected from date of randomization, not date of ICF completion.** **Section 5.1 Schedule of Activities: Footnote added for MFI** **Section 5.2 Pre-screening: removal of language to schedule a screening and baseline visit as a pre-screening activity. A screening and baseline visit will only be scheduled for those who satisfy the MFI inclusion criteria.** **Section 5.3 Pre-screening Assessments: MFI completion moved from Visit 1 (Screening & Baseline) to Pre-screening.** **Section 5.4 Screening & Baseline: Virtual Visit 1. MFI completion removed from this section.** **Section 9.9 Schedule of Activities Schematic: MFI completion has been moved from Virtual Visit 1 to pre-screening activities.** **Section 9.10.2 Additional QoL Questions: The possible responses to questions have been added to the table.**

Principal Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol and any amendments according to the current Good Clinical Practice guidelines (GCP).
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.
- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

Protocol Version/Date	**Version 2.0**
Investigator Name:	PPD
Investigator Qualifications:	PPD
Investigator Signature:	PPD
Date of Signature/Agreement:	PPD

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1 INTRODUCTION

1.1 Background & Study Rationale

Adequate nutrition and appropriate nutritional interventions, like dietary supplements, can play an important role in maintaining a person's immune defenses. While frank nutrient deficiencies are not common in the United States, sub-optimal intake of several micronutrients important for the immune response has been documented in the literature. The consumption of nutrient dense foods like fruits and vegetables help individuals meet the daily recommended intakes, as established by the Institute of Medicine (IOM). The Dietary Guidelines for Americans (2020-2025) states the average intake of total vegetables, total fruits and total dairy is less than recommended intake ranges for ages 14 and up (1). Additional supplementation of essential nutrients at levels well-below upper safety levels as established by the IOM, provides an effective way to supplement the diet, optimize micronutrient status, and support immune function.

The human immune system is the body's natural way to protect itself. It is constantly working to protect the body from infection, injury, and disease. Vitamins and minerals are essential for the integrity and optimum function of the immune system (2,3). An adequate supply of nutrients is required for the immune system's baseline functions as well as for ramping up its activity when necessary. It is well established that micronutrient status plays an important role in the immune response and that deficiencies in one or more essential micronutrients can diminish immune function (2,3).

Vitamin C is an essential nutrient that plays an important role in the immune system. In addition to vitamin C, Emergen-C products contain a variety of additional immune supporting nutrients to provide a more comprehensive immune support formula compared to products just containing vitamin C.

Emergen-C core powders contain a variety of nutrients (vitamin C, zinc, vitamin B6, vitamin B12, folate, manganese) that are critical for maintaining proper immune function. Vitamin C, zinc, and manganese are powerful antioxidants. The oxidant-antioxidant balance is an important determinant of immune cell function, including maintaining the integrity and functionality of membrane lipids, cellular proteins, and nucleic acids and controlling signal transduction and gene expression in immune cells. Optimal amounts of antioxidants are needed to maintain and support the immune response across all age groups.

Vitamin B12, folate and vitamin B6 have an essential role in the production and development of all new cells in the body, including immune cells. This process is crucial for the immune system to maintain its normal functions and to ramp up production when needed to respond to foreign invaders.

Much of the research investigating high vitamin C supplementation has focused on its impact on the common cold (4-9). In 1971, Linus Pauling carried out a meta-analysis of vita-min C and the common cold, including the four placebo-controlled trials available at that time. He

found very strong evidence that vitamin C decreased morbidity caused by the common cold (P = 0.000022) (10,11). Subsequent larger and methodologically more robust randomized controlled trials (RCTs) supported Pauling's conclusions. In a recent Cochrane review on vitamin C and the common cold, regular vitamin C supplementation of ≥ 0.2 g/day shortened the duration of colds by 9.4% (P < 0.00001) (10,11).Nevertheless, despite the strong evidence indicating that vitamin C has physiological effects on the common cold, there is a persistent wide-spread belief that vitamin C is of no benefit.

While the available evidence shows that vitamin C can affect colds, the optimal doses and the size of maximal benefit are not known, although two controlled trials indicated that 6–8 g/day of vitamin C might be twice as effective as 3–4 g/day (12-17).

Despite the research there are no current clinical recommendations that support the possibility of the potential impact on the risk of infection and of significantly reducing the severity of respiratory infections, by using high-dose supplements of vitamin C in a well-nourished general population. Only in restricted subgroups (e.g., athletes or the military) and in subjects with a low plasma vitamin C concentration may a supplementation be justified. Furthermore, in categories at high risk of infection (i.e., the obese, diabetics, the elderly, etc.), vitamin C supplementation can modulate inflammation, with potential positive effects on immune response to infections. The impact of an extra oral intake of vitamin C on the duration of a cold and the prevention or treatment of pneumonia is still questioned.

Other research into high doses of vitamin C has investigated how supplements have impacted physical and emotional measures of health. The B-vitamins are widely accepted as playing a role in brain function, and there is evidence to suggest that B-vitamins may have a modifying effect on cognitive function. Therefore, much of the research into B12 and B6 has investigated the impact of these vitamins on cognition as well as mood and stress.

Vitamins and minerals and their impact on quality of life in terms of energy and cognition is an area of increasing interest (18). A recent meta-analysis of vitamin C supplementation on mood status in adults showed that it may be beneficial in certain populations (19). A meta-analysis of the effects of vitamin and mineral supplementation on stress, mild psychiatric symptoms, and mood in nonclinical samples showed that subjects taking supplements with high levels of vitamin C and B-vitamins had lower levels of stress, improved mood, and better energy than placebo (20).

An extensive literature review investigating the research behind immune supplements (with high levels of vitamin C and the B-vitamins) showed that high doses of vitamin C can lead to increased levels of perceived energy. Twenty-nine studies have looked at the impact of supplement brands on various aspects of physical health, psychological health, and emotional including supplements such as Berocca, Supradyn, Elevit, and Centrum. Berocca and Supradyn (manufactured by Bayer) contain high levels of vitamin C and the B-vitamins and make similar claims to Emergen-C regarding immunity support and energy. There are 6 studies (21-26) on Berocca and Supradyn that are particularly pertinent to our proposed research investigating

various parameters of perceived physical and mental energy as well as mood and stress. These studies have run from 28 days, 33 days, 4 weeks, 9 weeks, and 90 days. Physical and mental energy measured by validated tools such as the General Health Questionnaire-12 (GHQ-12) appear to be positively impacted more quickly than parameters like stress and emotional wellbeing as measured by scales such as the Profile of Mood States (POMS) as outlined in the table below.

Competitor supplement brands and their impact on physical and emotional measures of health.

Study	*Brand*	*Duration*	*Results*
1.Vitamins and psychological functioning: a mobile phone assessment of the effects of a B vitamin complex, vitamin C and minerals on cognitive performance and subjective mood and energy. *Human Psychopharmacology, Haskell et al. 2010.*	*Berocca*	*28 days*	*Participants in the vitamin/mineral group rated themselves as having greater 'physical stamina' across assessments and weeks. They also rated themselves as having had greater 'concentration' and 'mental stamina' during the working day. Participants in this group also reported greater subjective 'alertness' on Bond-Lader mood scales during the post-work assessment on day 14 and both the pre- and post-work assessments on day 28.*
2.Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males. *Psychopharmacology, Kennedy et al. 2010.*	*Berocca*	*33 days*	*Vitamin/mineral supplementation led to significant improvements in ratings on the Perceived stress scale (PSS), General Health Questionnaire (GHQ-12) and the 'vigor' subscale of the Profile of Mood States (POMS). The vitamin/mineral group also performed better on the Serial 3s subtractions task and rated themselves as less 'mentally tired' both pre-and post-completion of the cognitive demand battery.*
3.Acute and chronic effects of multivitamin/mineral supplementation on objective and subjective energy measures *Nutrition and Metabolism, Dodd et al. 2024.*	*Berocca*	*28 days*	*These findings extend on existing knowledge, demonstrating increased carbohydrate oxidation and increased energy expenditure in males following supplementation for the first time. Importantly, they show modulation of energy expenditure and subjective tiredness following a single dose, providing further evidence for acute effects of supplementation. Differential effects in men and women suggest that sex may play an important role in the effects of supplementation on energy metabolism.*
4.Effects of Four-Week Supplementation with a Multi-Vitamin/Mineral Preparation on Mood and Blood Biomarkers in Young Adults: A	*Berocca Performance*	*4 weeks*	*Compared to placebo, supplementation was associated with significantly lowered homocysteine and increased blood B-vitamin levels (p < 0.01). Supplementation treatment was also associated with*

Randomized, Double-Blind, Placebo-Controlled Trial. Nutrients, White et al, 2015.			***significantly improved mood, as measured by reduced scores on the "depression-dejection" subscale of the Profile of Mood States (p = 0.018). These findings suggest that the four weeks of supplementation may have beneficial effects on mood, underpinned by elevated B-vitamins and lowered homocysteine in healthy young adults.***
5.Effects of a multi-vitamin/mineral supplement on cognitive function and fatigue during extended multi-tasking ***Brain Performance and Nutrition Research, Haskell et al, 2015.***	***Supradyn***	***9 weeks***	***Those in the supplement group exhibited an attenuation of the negative effects of extended task completion on mood/fatigue. Multi-tasking performance for this group was also improved in terms of accuracy across all tasks, and on two of the individual tasks (Mathematical Processing and Stroop) in terms of both faster and more accurate responses.***
6. The effect of 90-day administration of a high dose vitamin B-complex on work stress. ***Human Psychopharmacology Stough et al. 2011.***	***Supradyn***	***90 days***	***After individual differences in personality and work demands were statistically controlled, the vitamin B complex treatment groups reported significantly lower personal strain and a reduction in confusion and depressed/dejected mood after 12 weeks.***

Consumer insights research points to the fact that consumers are interested in learning more about the scientific rationale behind the brand and want to understand the benefits of taking Emergen-C on a routine or daily basis. A study was developed to examine the effects of consistent daily Emergen-C use for 12 weeks during a fall/winter season. This timeframe was selected given the greater demand on the immune system during this time with higher incidence of cough, cold, and flu. The aim of this research is to determine how Emergen-C use can improve QoL in a real-world setting, that can be communicated to help consumers and healthcare professionals better understand the science behind the brand.

The aim of this randomized double-blind placebo-controlled clinical trial is to evaluate the effectiveness of daily consumption (over 12 weeks) of Emergen-C core super orange powder Emergen-C core powders on QoL in a real-world setting. This study will enroll a healthy adult population (aged 18-64 yrs.) in the United States into one of two study arms (study product, or placebo). It is hypothesized the study group will demonstrate a significant decrease in MFI (Multidimensional Fatigue Inventory) domain scores (i.e. meaning an improvement of energy level) from baseline compared to the placebo group following 12 weeks of daily supplementation.

2 STUDY OBJECTIVES AND ENDPOINTS

Table 2-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
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	
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 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) ● *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 Multidimensional Fatigue Inventory (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 ● Resilience ● Ability to relax and unwind
Exploratory	
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 unwell ● days canceling plans ● days with cough and cold symptoms ● days sick in bed

Subgroup analyses for primary and secondary endpoints.	**Subgroup analyses for** • **sex (male and female)** • **age (18-34 and 35-64 years)**
Safety	
To monitor the safety of the study treatment with daily use for 12 weeks.	**The number of Treatment-emergent adverse events (TEAEs)**

This study will be considered successful if daily use of Emergen-C supplementation improves QoL (as measured by any of the individual domain scores), compared to placebo at Week 12.

3 STUDY DESIGN

This is a randomized, double-blinded, placebo-controlled clinical trial in healthy male and female subjects, aged 18-64 years, evaluating the over-time effects of 12-weeks Emergen-C supplementation on QoL parameters in a real-world setting. A sufficient number of adults (approximately 430), 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 enrolled 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.

4 STUDY POPULATION

4.1 Type and Planned Number of Subjects

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.

The study will be sufficiently powered to demonstrate statistically significant differences between Emergen-C core super orange powder compared to Placebo for QoL parameters as measured by the MFI at Week 12 (primary objective). A sample size of 120 evaluable subjects per treatment group will provide over 90% power to detect a mean difference of 0.5 standard deviations (27) Cohen's *d*), using a 2-tailed 2-sample t-test with a 1% significance level (Bonferroni-adjusted *p*-value). This effect is in line with the estimated minimal clinically important difference for the MFI in patients with lupus erythematosus (28).

The sample size calculation was performed using R software version 4.4.1.

This study can fulfill its objectives only if appropriate subjects are enrolled. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a subject is suitable for this protocol. Subject eligibility to participate in the clinical study should be reviewed and documented by a delegated member of the investigator's study team before subjects are included in the study. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate.

4.2 Inclusion Criteria

An individual must meet all the following inclusion criteria to be eligible to be included into the study:

1. Individual's provision of a signed and dated electronic informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Healthy Adults, 18-64 years of age at the time of electronic consent (does not exclude any ethnicities, races, or gender identities)
3. Individual is seeking to improve their energy/less fatigue levels
4. Individuals whose baseline score (assessed during pre-screening) is ≥10 on the dimension of general fatigue of the Multidimensional Fatigue Inventory (MFI) and a score ≥3 for at least ten of the 20 questions of the MFI
5. Individuals who are willing and able to comply with all study related activities as shown in the Schedule of Activities.
6. Individuals who reside in the United States (except for Hawaii and Alaska)
7. Individuals who own a mobile device, tablet or computer with access to stable internet connection and are willing to use their device to complete study surveys and assessments

4.3 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from the study:

1. Individuals who are an employee of CCI [redacted], either directly involved in the conduct of the study or a member of their immediate family; or a Haleon employee directly involved in the conduct of the study or a member of their immediate family.
2. Individuals who have participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days prior to study entry and/or during study participation.

3. Individuals who are pregnant, lactating, or plan to be pregnant or lactating during the course of the study (self-report).
4. Individuals with known or suspected intolerance or hypersensitivity to any study materials (or closely related compounds) or any of their stated ingredients.
5. Individuals who are hypertensive or salt-sensitive should be excluded from this study.
6. Individuals who report being a heavy drinker (defined as drinking 3 or more alcoholic beverages per day).
7. Individuals who are unable to read and understand English.
8. Individuals who report current and/or recent (up to 3 months ago) major illnesses and/ or major surgery
9. Individuals who report a planned surgery during the study duration.
10. Individuals who report a diagnosis of heart failure, heart rhythm disturbances, severe liver disease, severe mental health diagnosis, or severe renal failure.
11. Individuals who report taking medications (in the previous 21 days) that have well established moderate or severe interaction with any of the study product ingredients: Anticoagulants, antihypertensives, anxiolytics, antidepressants, chemotherapy, immunotherapy, sedative hypnotics, medications that warn against grapefruit consumption, corticosteroids at doses greater than 5 mg per day, diabetic medications, oral anti-infectives (antibiotics, antifungals, antivirals) to treat an acute infection, antipsychotics, Monoamine Oxidase Inhibitors (MAOIs), or thyroid products.
12. Individuals who are currently taking a multivitamin or have taken a multivitamin in the past 30 days & are not willing to stop taking a multivitamin for the duration of the trial.
13. Individuals who are currently taking other Vitamin C or B supplements or have taken Vitamin C or B supplements in the past 30 days & are not willing to stop taking other Vitamin C or B supplements for the duration of the trial.
14. Individuals who are currently consuming energy drinks or energy shots or have consumed an energy drink or energy shot in the past 30 days & are not willing to stop consuming energy drinks and energy shots for the duration of the trial.
15. A subject who has previously been enrolled in this study.
16. A subject who, in the opinion of the investigator or delegate, should not participate in the study.

4.4 Lifestyle Considerations

As a real-world evidence study, there will be no lifestyle considerations.

5 STUDY PROCEDURES

This section lists the procedures and assessments to be completed at each planned study time point. However, as per nature of Real World Evidence (RWE) studies, if a subject fails to complete their daily questionnaire at any time point post-baseline, subjects will be permitted to continue in the study. The timing of each procedure is listed in the Table 5-1 Schedule of Activities section.

5.1 Schedule of Activities

The Schedule of Activities (Table 5-1) provides an overview of the subjects virtual visits, study procedures and assessments. The investigator may schedule additional (unplanned) virtual visits to conduct additional evaluations or assessments required to protect the well-being of the subject. A detailed schematic of the Schedule of Activities is located in section 9.9 Schedule of Activities Schematic.

Table 5-1 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					
Informed Consent	X					
Subject ID Verification		X				
Inclusions/Exclusion Criteria[c]		X				
Eligibility Assessment		X				
MFI [a]	X			X	X	X
Supplementary QOL questionnaire [a]		X		X	X	X
Randomization		X				
Participant Training		X				
Study Product Shipped		X				
Concomitant Medication Check		X		X	X	X
Adverse Event (AE/ Serious Adverse Event)		X	X	X	X	X
Study Product Administration[b]			X (Daily through Week 12 visit)			
Participant Daily eDiary[d]			X (Daily through Week 12 visit)			
Subject Conclusion/Subject Exit from Study						X
Exit Survey[a]						X

Footnotes:

[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
[d]Subject-reported (self-reported) they took the investigational product on that day.

The virtual site may contact subjects prior to study visits, either as part of pre-screening activities or as a reminder of the approaching scheduled visit. Further details should be included in the electronic informed consent (eICF).

5.2 Pre-screening

The study team will identify and recruit potential subjects via social media platform advertising. Potential subjects will be directed to the study web page where they will complete an online pre-screening questionnaire assessing their eligibility to participate in the study. The information collected from the pre-screening questionnaire serves as the preliminary screening tool to isolate potentially eligible participants from ineligible subjects. Subjects who successfully pass the pre-screening questionnaire are deemed potentially eligible for participation and are directed to complete an online eICF. Potentially eligible subjects who execute the eICF will receive a copy of the signed eICF via email.

5.2.1 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria as per Section 4.2 and 4.3 will be collected via pre-screening survey and confirmed during the Screening and Baseline virtual visit with a trained & delegated study team member.

5.2.2 Demographics

The following demographic information will be collected: year of birth and age, sex at birth, race, ethnicity, height, weight, and smoking (including vaping) status.

5.2.3 Informed Consent

The eICF is a tool that assists in the consenting process by using multimedia components delivered by an electronic system. The eICF process for this study will be performed on the subject's mobile device, tablet or computer following successful completion of the study pre-screening questionnaire. Informed consent must be obtained before any study-specific activity is performed. Once the eICF has been signed and dated by the subject, the subject will be provided with a copy via email. An additional copy of the signed eICF will be saved as a Portable Document Format (PDF) in the virtual site file.

If, during a subject's participation in the study, the eICF undergoes any changes, each ongoing subject should receive a copy of this new information and be re-consented into the study. Each subject should be provided with a copy of the signed and dated amended consent form.

5.2.4 Medical History and Prior Medication/Treatment

Relevant medical and/or surgical history (in the previous 12 months) will be self-reported, 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 will be recorded as the Medical History/Current Medical Conditions.

Female subjects only:

- Female subjects who report being pregnant or confirm planning pregnancy during the study will be discontinued from participation in this study.
- Given the potential impact of pregnancy on study outcomes, female subjects of child-bearing potential will be reminded to inform the investigator site immediately if pregnancy is known or suspected.

Relevant medical and surgical history, including allergies or drug sensitivity can be documented by the investigator or designee in the medical history form.

Please refer to section 9 for further details on Adverse Event and Serious Adverse Event Monitoring and to section 8.3.6.2 for further details on concomitant medications.

The investigator and/or delegated study team member will review inclusion/exclusion criteria, medical history and prior medications to confirm subject eligibility to participate in the study.

5.2.5 Enrolled Subjects and Screen Failures

An enrolled subject is one who has agreed to participate in the clinical study following completion of the informed consent process and who has directly and successfully met eligibility criteria to proceed beyond the screening visit.

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized to a study group.

To ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include demography and screen failure details (e.g., withdrawal of consent, eligibility criteria, any protocol deviations and any adverse events).

Individuals who do not meet the criteria for participation in this study (screen failure) will not be re-screened.

5.3 Pre-screening Assessments

Prior to their scheduled Screening and Baseline virtual visit, subjects will be asked to complete the following:

- Medical & concomitant medication history
- Demographic information
- The MFI
    - Following MFI completion, the participant's MFI score will be automatically calculated via the Citrus platform to determine eligibility. A subject is considered eligible if their baseline score is ≥10 on the dimension of general fatigue of the MFI and a score ≥3 for at least ten of the 20 questions of the MFI.

Note: If the participant is not eligible based on responses to the above items, a member of the study team will notify and screen fail the participant.

5.4 Screening & Baseline: Virtual Visit 1

During the Screening and Baseline virtual visit, a trained member of the study team will verify the subject's identification (i.e. driver's license or government issued passport) on camera at the beginning of the visit. Should the subject elect not to show a form of identification or is unable to provide a valid identification at the beginning of the virtual visit, the visit may be rescheduled, or the subject may be considered a screen failure.

Following subject identification verification, the following visit procedures will be performed:

- Review self-reported medical and concomitant medication history
- Review inclusion/exclusion criteria
- Complete supplemental QoL questionnaire
- Provide instructions for the completion of the study questionnaire, daily diaries, and storage, preparation and administration of the study product
- Verify address for study product shipment
- Answer any questions the subject may have about the study

If the responses to all screening criteria are fulfilled, the subject will be considered enrolled. At enrollment, the following activities will occur:

- The subject will move forward to randomization into one of two study groups (on a 1:1 allocation) as follows: Group 1) Emergen-C Core Super Orange Powder or Group 2) Placebo.
    - Upon group allocation, subjects will be shipped the study product. Neither the subject or study team will be made aware which group arm the subject is allocated to.
    - Once the shipment is successfully received, the subject will confirm receipt via an online questionnaire directly entered into the EDC platform.
        - If unsuccessful (e.g. lost, damaged) study team will discuss with participant and arrange a new shipment if needed

Following the completion of the screening visit, and prior to Virtual Visit 2, subjects will be reminded each morning to consume the study product with 4-6 ounces of water at approximately the same time each day. Each evening, subjects will be prompted to complete an Electronic Diary (eDiary) consisting of one question to confirm the subject has consumed the study product.

5.5 Follow-up: Virtual Visits 2-4

Randomized subjects will participate in three follow-up visits conducted virtually with a trained study team member to review the following:

- Changes in concomitant medications and changes in health
- Subjects eDiary compliance & study product use
    - Subjects who are non-compliant with eDiary completion or study product use for greater than two consecutive days will receive a follow-up from a trained member of the study team re-educating them on study procedures.

- Review any adverse events or safety events and pregnancies which may have occurred since the last virtual visit. Participants will also be able to report any (S)AEs and pregnancies to the study team between virtual visits via dedicated trial phone number.

5.6 On-going Daily eDiaries

The subject will receive links via text and email with instructions for completion of the study daily diaries. The subject will input their responses directly into the EDC platform. The daily eDiary consists of one question to confirm the subject has consumed the study product.

If subjects fail to complete or state "no" to the study product consumption survey for greater than 48-hours, the study team will contact the subject to re-educate on the study procedures and compliance.

5.7 On-going Assessments: Week 4, Week 8 & Week 12

On the first day of the visit window of week 4, week 8, and week 12, the subject will receive links via text and email with instructions for completion of the MFI and Supplementary QoL questionnaire. The subject will input their responses directly into the EDC platform. The subject will receive reminders to complete the MFI and the Supplementary QoL questionnaire. If the subject does not complete the MFI and the Supplementary QoL questionnaire within the 48-hour timeframe, a trained member of the study team will contact them via text, phone, or email. If the subject has not completed the MFI by the time of their scheduled virtual visit, they will be instructed to complete the MFI during the visit.

End of Treatment Period

Subjects will have the option to discontinue treatment at their discretion. The reasons for discontinuing treatment will be captured by a trained study team member and every effort will be made to capture reasons for discontinuation (i.e. follow up calls, letters, texts, or e-mails to the subjects, etc. Subjects will be informed that the study will end after week 12 and will be asked to fill out an exit survey.

6 STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required assessments and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it infeasible to complete an assessment. When a protocol-required assessment cannot be performed, the investigator (or designee) will document the reason for the missed assessment as a protocol deviation and any corrective and preventative actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The Sponsor must be informed of any missed assessments.

6.1 Outcome Assessments

Assessments will be performed by delegated staff at the times, and in the order, defined in the Study Procedures section of this protocol.

The objective of the study is to evaluate the effectiveness of daily Emergen-C on QoL parameters. This includes self-reported outcomes from the Multidimensional Fatigue Inventory domains and supplemental QoL questions at baseline, week 4, week 8, and week 12.

Multidimensional Fatigue Inventory (MFI-20): The MFI (29) is a 20-item scale designed to evaluate five dimensions of fatigue: general fatigue (items 1, 5, 12, 16), physical fatigue (items 2, 8, 14, 20), reduced motivation (items 4, 9, 15, 18), reduced activity (items 3, 6, 10, 17), and mental fatigue (items 7, 11, 13, 19). Subjects will answer a series of questions indicating how they feel about each statement, lately. Items are scored 1–5, 1- indicating "yes, that is true" and 5- indicating "no, that is not true", with higher total scores representing a worse outcome. For scoring, 10 positively phrased items reverse scored (this concerns the following items: 2, 5, 9, 10, 13, 14, 16, 17, 18, 19) while 10 negatively phrased items are scored at face value (this concerns the following items: 1, 3, 4, 6, 7, 8, 11, 12, 15, 20). For each of the 5 scales (general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue) a total score is calculated by summation of the scores of the individual items. Domain scores can range from the minimum of 4 to the maximum of 20, the higher the score the worse the level of fatigue outcome.

Supplemental QoL questions: Six additional questions will be asked to evaluate the effectiveness of the intervention on target outcomes. Subjects will answer a series of questions indicating how they feel about each statement, lately. Questions are scored 1–5, 1- indicating "yes, that is true" and 5- indicating "no, that is not true", with higher total scores representing a worse outcome. Additional questions include:

- I feel more energized to look after my family and/or loved ones
- I feel more prepared for the future
- I feel resilient so I can be at my best each day
- I feel ready to cope with life's challenges
- I feel relaxed
- I feel able to unwind

Subjects will be asked to report their health in the previous 4 weeks using four additional questions:

- In the last 4 weeks, how many days did you feel rundown, if any?
- In the last 4 weeks, how many days did you have to cancel plans or work because you were not feeling 100%, if any?
- In the last 4 weeks, how many days did you have cold and cough symptoms (for example: runny nose, blocked nose, sneezing, cough, sore throat), if any?
- In the last 4 weeks, how many days were you in bed sick, if any?

Exit survey question: Subjects will be asked to complete an exit survey following their completion of the study asking one question:

- Would you use your assigned supplement again?

6.2 Safety and Other Assessments

The following safety assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Study Procedures section of this protocol.

6.2.1 Pregnancy Testing

For Haleon studies in which no drug is utilized or studies of single use marketed products that are classified as a non-medicinal product in the market where the testing is occurring and there is no pregnancy warning on labeling, a pregnancy test will not be required.

Female subjects will provide verbal confirmation of pregnancy status at Screening (Visit 1) and will be asked to inform study staff immediately should this change at any point during the study. Female subjects who are pregnant or planning pregnancy during the study (self-reported) will not participate further in the study.

7 STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and Haleon policy, study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. This includes a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

7.1 Study Product Supplies

Each subject will receive sufficient study product to cover usage during the treatment period of the study. The following study products will be supplied by the Sponsor's preferred vendor (Table 7-1). Study test product usage instructions are consistent with the commercially available pack instructions (excludes reference product). Subjects will not be required to return unused study products after treatment discontinuation or completion of week 12 study activities. However, subjects will be instructed to destroy unused study product after treatment discontinuation or completion of week 12 study activities.

Table 7-1 Investigational/Study Product Supplies

	Test Product	Reference Product
Product Name	**Emergen-C Core Super Orange Powder**	**Placebo**
Pack Design	**Large carton containing 3 small cartons of 30 sachets each**	**Large carton containing 3 small cartons of 30 sachets each**
Dispensing Details	**One labeled carton (containing 3 cartons, with 30 sachets per carton) shipped to**	**One labeled carton(containing 3 cartons, with 30 sachets per carton) shipped to subject following baseline visit**

	subject following baseline visit	
Haleon formula codes:	CCI [redacted]	CCI [redacted]
Dose	**As per label instructions: Subjects will consume one sachet stirred in 4-6 ounces of water once per day in the morning at approximately the same time each day**	**As per label instructions: Subjects will consume one sachet stirred in 4-6 ounces of water once per day in the morning at approximately the same time each day**
Route of Administration	**Oral**	**Oral**
Usage Instructions	**As per directions stated on the label**	**As per directions stated on the label**
Return Requirements	**All unused study products will be destroyed/disposed of.**	**All unused study products will be destroyed/disposed of.**

7.2 Product Supplies, Product Storage, Accountability, Returns and Destruction

All study products supplied are for use only in this clinical study and should not be used for any other purpose. Guidance will be provided to the Sponsor's preferred vendor for the receipt, storage and management of products for the duration of the trial by Haleon Clinical Supplies and with further instructions included with the shipping documentation.

CCI [redacted] preferred vendor should ensure that the room or area set aside for storage is able to maintain the correct temperature (room temperature) to meet the product label storage conditions, is sufficient to store all products and is secure and access controlled.

Any temperature excursions or discrepancies whilst study products are stored at site require the affected products to be quarantined and this must be communicated immediately to the Sponsor who will provide documentation to approve further usage. Use of any of the affected product(s) prior to sponsor approval will be considered a protocol deviation.

Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by designated investigator staff. Enrolled/randomized subjects will be informed on product usage and storage and what to do in the event of product loss when the products are first dispensed.

All study products will be accounted for using the investigational/study product accountability form/record. CCI [redacted] preferred vendor is responsible for study product accountability,

reconciliation, and record maintenance. Unused study products will not be returned or destroyed.

7.3 Blinding and Randomization

Qualifying subjects will be centrally randomized into one of two study groups using a randomization list provided by Haleon Clinical Supplies. Before the study is initiated, training and directions for the randomization will be provided to the investigator study team. Study products will be dispensed in sequential order as per the randomization schedule. CCI will submit a list of subject ID numbers and corresponding kit codes to the Vendor each day for study product shipment. Only subjects who meet the study inclusion criteria will be randomized to a study product.

This study is described as double-blind (i.e., the clinical examiner and study participants will be blinded to the study product each subject receives). Additionally, investigator staff involved in the clinical or safety assessments, study statistician(s), data management staff, other employees of the sponsor (including the sponsor's Clinical Research Scientist (CRS)) and vendors acting on behalf of the sponsor who may influence study outcomes, will also be blinded to treatment allocation.

To maintain the blind throughout the study:

- Subjects will see and use only one of the two study products during the study. They will be instructed not to discuss the appearance, usage, or perceived performance of their allocated study product with staff involved in clinical assessments or with other study subjects.
- The study product will be provided to the CCI preferred vendor in unmarked cartons masking their identity and obscure any branding on the commercial product with a study label affixed. Both study products (treatment and placebo) are packaged in individual, unmarked, identical foil sachets.
- The study product will be supplied in individual packs (cartons); each large carton will contain three smaller cartons, each containing 30 sachets of study product (90 sachets total). Each subject will receive one large carton, marked with a kit number containing only their randomized study product; product codes will not be used.

7.4 Breaking the Blind

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's product assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a subject's product assignment unless this could delay emergency treatment of the subject.

If a subject's study product assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

8 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

8.1 Sample Size Determination

The primary objective for this study is to evaluate the over-time effects of Emergen-C Core Super Orange Powder on QoL parameters, as measured by the MFI domain scores (*General Fatigue*, *Physical Fatigue*, *Reduced Activity*, *Reduced Motivation*, *Mental Fatigue*), compared to placebo, when taken daily over 12 weeks.

A total of 300 subjects will be randomized (approximately 150 per group) to ensure sufficient power for the primary analysis. Assuming a maximum drop-out rate of 20%, approximately 240 evaluable subjects in total (120 per group) complete the entire study.

The sample size calculation was performed using R software version 4.4.1.

8.2 Populations for Analysis

8.2.1 Definitions of Analysis Populations

The following four study populations will be used for statistical analysis:

- The modified Intention-To-Treat (mITT) population consists of all subjects who have been randomized, completed baseline visit (visit 1), completed at least one-post baseline MFI domain assessment and have taken at least one dose of their allocated randomized product. Group allocation will be based on the study product to which the subject was randomized. All subjects who receive a randomization number will be considered randomized. The mITT population will be used as the primary population for the assessment of efficacy.
- The Per-Protocol (PP) population includes all mITT subjects who have adhered to the allocated treatment regime and are not considered to have been affected by protocol deviations.
- The Safety population (SP) includes all randomized subjects who have taken at least one dose of their randomized study product. Analyses of this population will be based on the investigational product received.

8.2.2 Exclusions of Data from Analysis

Exclusion of any data/subject from the analyses will be agreed during a Blinded Data Review (BDR) Meeting prior to database lock. The reasons for exclusion of a subject from an analysis population or data from an analysis will be documented and listed, if applicable.

Any efficacy data agreed to have been potentially impacted by a protocol deviation will be excluded from the PP analysis. 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. A decision on whether a protocol deviation impacts any efficacy data and whether a PP analysis will be performed will be made as part of the BDR Meeting prior to database lock.

8.3 Statistical Analyses

Additional details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following finalization of the protocol and prior to study unblinding/analysis (as appropriate). This section is a summary of the planned statistical analyses of the primary and key secondary endpoints and a brief summary of how other collected data will be analyzed.

The mITT population will be used for all efficacy analyses.

All p-values presented will be two-sided and assessed at the 5% significance level. A sequential testing strategy will be used to adjust for the comparisons between the Emergen-C and placebo group at each assessment time point.

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.

Summary Statistics (mean, median, SE, SD, minimum, maximum) will be presented for each outcome variable at each assessment time point. Raw means (+/- SE) of the primary and secondary endpoints will be plotted by treatment group.

The results from each Mixed Model with Repeated Measures (MMRM) will be tabulated, presenting the least square mean change from baseline for each treatment group at each timepoint and the comparison between Emergen-C and Placebo, with two-sided p-values and 95% CIs.

8.3.1 Primary Endpoint Analysis(es)

The primary endpoint of this study is the Change from Baseline in QoL parameters as measured by the MFI domains at Week 12. The primary hypothesis test will be the comparison between Emergen-C and Placebo in the mITT population.

Change from Baseline will be calculated at Week 12 for all MFI domain scores:

- *General Fatigue* Domain score (sum of items 1,5,12,16)
- *Physical Fatigue* Domain score (sum of items 2,8,14,20)
- *Reduced Activity* Domain score (sum of items 3,6,10,17)
- *Reduced Motivation* Domain score (sum of items 4,9,15,18)
- *Mental Fatigue* Domain score (sum of items 7,11,13,19)

Change from Baseline will be calculated at the subject level first then the mean change from baseline will be calculated for each of the MFI domains across all subjects.

Change from Baseline for each of the MFI domains listed above will be analyzed using a MMRM with treatment, 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, 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% CIs. A Bonferroni-Holm correction will be applied to the p-values and CIs of the least square mean change between groups to account for multiple testing. Adjusted and non-adjusted p-values will be reported.

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 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 (+/- SE) for each MFI endpoint at each assessment timepoint will be plotted by treatment group.

8.3.2 Secondary Endpoint Analysis(es)

The secondary endpoints of each MFI domain at Week 4 and Week 8 will be 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, as described in section 8.2.

Similarly, the secondary endpoint for each of the individual MFI questions will be analyzed as described for the primary endpoint, but with baseline of the MFI domain score replaced 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 QoL questions will also be analyzed using the same MMRM model described above, but with baseline of the MFI domain score replaced with the Baseline of the respective QoL question for each timepoint (Week 4, Week 8 and Week 12).

8.3.3 Exploratory Analyses

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

- days feeling unwell
- days canceling plans

- days with cough and cold symptoms
- days sick in bed

Raw means (± SE) will be plotted for each assessment timepoint by treatment group. Analysis will be performed comparing treatment groups at each timepoint using a student's t-test. If data are found to be non-normal, a suitable non-parametric test will be used.

8.3.4 Safety Analysis(es)

The absolute and relative frequency of 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.

AE will be assessed by the investigator or medically qualified designee. AE review and coding will be in line with the Site and Safety Management Plan.

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, SAEs and any AEs leading to product or study discontinuation.

• Exposure to study product

8.3.5 Other Analysis(es)

A subgroup analysis will be conducted for the primary and secondary analysis as an exploratory outcome for:

- sex (male and female)
- age (≥18 to < 35 and ≥35 to ≤64 years)

8.3.6 Demographic and Baseline 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 variables (such as sex, race, ethnicity) will be summarized by the number and percentage of subjects with each relevant characteristic in each treatment group. Arithmetic mean, standard deviation, as well as median and 25%- and 75%-iles, minimum and maximum will be reported for continuous variables.

Outcome data collected repeatedly will be described for each measurement point in time.

8.3.7 Study Product Compliance and Use of Other Therapies

8.3.7.1 Study Product Compliance

Treatment compliance will be assessed daily during the 12-week treatment period. 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.

8.3.7.2 Prior and Concomitant Medications

Prior medication use will be assessed during the Screening visit. Concomitant medication use will be monitored at each study visit. Subjects will be able to report concomitant medications between visits. 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, including the frequency within each group, for the Safety population.

8.3.8 Handling of Dropouts and Missing Data

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, 2016; Baron, 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).

9 APPENDICES

9.1 Adverse Event (AE) and Serious AE (SAE)

Adverse events can be reported / recorded by any member of the trial team. The investigator and their authorized safety designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to study product, a study procedure or study participation, or that caused the subject to discontinue use of a study product or study participation.

All Adverse Events and Serious Adverse Events will be managed in line with the protocol and in line with the Site and Safety Management Plan.

9.1.1 Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study product including an acclimatisation product whether or not considered related to the study product, including an acclimatisation product **Note:** An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study product including an acclimatization product (or medical device).

Events <u>Meeting</u> the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry or urinalysis) or other safety assessments (e.g., electrocardiogram, radiological scans, vital sign measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study product administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- 'Lack of efficacy' or 'failure of expected pharmacological action' per se will not be reported as an AE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as an AE if they fulfill the definition of an AE.

Events <u>NOT</u> meeting the AE definition:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- A medical or surgical procedure (e.g., endoscopy, appendectomy) is not an AE. The condition that leads to the procedure is an AE (e.g., appendicitis). Planned medical or surgical procedures for pre existing illnesses are not an adverse event.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.1.2 Definition of a Serious Adverse Event

An SAE is a particular category of AE where the outcome is serious. If an event is not an AE per definition above, then it cannot be an SAE, even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease). A serious adverse event is any untoward medical occurrence at any dose that:

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolonged hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred, or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline more than would be expected under the normal progression of the disease not considered an AE.
- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Results in congenital anomaly/birth defect**
- **Other situations:**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but

may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Note: Classification of an AE as 'serious' is based on the outcome of the event and is a factor in determining reporting requirements.

Events exempt from immediate reporting as SAEs

Hospitalization for a pre-existing condition, including elective procedures planned prior to trial entry, which has not worsened, does not constitute an SAE.

9.1.3 Time Period and Frequency for Collecting AE and SAE Information

All AEs, and therefore all SAEs (except from those exempt from recording, as described in section 9.1.1 and section 9.1.2) will be collected from immediately after a subject is randomised within the trial and until 2 days following the last administration of study product (or the last study procedure).

Medical occurrences that began before randomisation will be recorded in the Medical History/Current Medical Conditions section of the Electronic Case Report Form (eCRF), not the AE section.

Details recorded by the subject that meet the definition of a serious AE must be discussed with the subjects and transcribed into the SAE section of the eCRF.

All SAEs will be recorded and reported to the sponsor or designee immediately, and under no circumstance should this exceed 24 hours. The investigator will submit updated SAE data to the sponsor within 24 hours of it being available.

9.1.4 Reporting Procedures

The investigator and study delegated designees are responsible for detecting, documenting and reporting events that meet the definition of an AE and remain responsible for following up AEs that are serious, considered related to study product, a study procedure or study participation, or that caused the subject to discontinue use of study product or study participation, until stabilization, resolution, trial completion or loss to follow up, whichever comes sooner.

The investigator and their authorized trial designees are to report all AEs at study visits and all AEs spontaneously reported by study subjects.

Study subjects will be questioned about AEs. Care will be taken not to introduce bias when questioning a subject about any changes in their health. Open-ended and non-leading verbal questioning should be used.

AEs spontaneously reported by study subjects and those elicited by asking subjects to respond to non-leading questions (such as 'how do you feel?') will be assessed, recorded in the eCRF and reported, as appropriate.

Each AE is to be assessed to determine if it meets the criteria for a SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

When an AE occurs, it is the responsibility of the investigator or their medically qualified designee to assess the severity of the event, which may require a review of additional documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event. The investigator or study staff will then record all relevant information relating to the event in the SAE section of the eCRF. In addition, all details relating to an SAE will be recorded electronically within Citrus using the SAE eCRF provided.

It is **not** acceptable for the investigator or their authorized safety designee to send photocopies of a subject's medical records to the sponsor in lieu of completion of the AE section of the eCRF/paper SAE form. There may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all subject identifiers, except for the subject number, will be redacted on the copies of the medical records prior to submission to the sponsor.

The investigator or their medically qualified designee will attempt to establish a diagnosis based on signs, symptoms and/or other available clinical information related to the event. The diagnosis will be documented as the AE/SAE, where known, and not the individual signs/symptoms (e.g., upper respiratory tract infection or seasonal allergy, not 'runny nose').

9.1.5 Reporting an AE

AEs will be reported by the investigator, their authorized trial designee or investigator staff in the AE section of the eCRF. These are collected throughout the study at each follow-up visit. Additionally, the subject will have the option to report any AEs to the study staff at any point during the study. Where an SAE is recorded the electronic SAE form should be utilized and reported within 24 hours of awareness. AEs/SAEs should be reported using concise medical terminology. Where the same data are collected, the AE section of the eCRF and the SAE eCRF must be completed in a consistent manner (e.g., the same AE term should be used for both).

9.1.6 Reporting an SAE

In addition to recording the details of each SAE in the AE section of the eCRF, an SAE form should be completed, as fully as possible. All SAE reporting will utilize the eCRF in Citrus

It is essential to record the following information for each SAE:

- Protocol and subject identifiers
- Subject demography
- Description of event with diagnosis, if available
- Investigator opinion of relationship to study product (or study procedure)
- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator and sponsor assessment of the SAE report:

- Date of onset of SAE
- Date SAE stopped, if relevant
- Study product start date

- Study product end date, if relevant
- Action taken in relation to study product
- Outcome, if known

The SAE form, completed as fully as possible, must be exported from Citrus, e-mailed to the sponsor's Case Management Group mailbox PPD , with the appropriate sponsor Study Manager in copy, with the study number and subject number in the subject line of the email **immediately after investigator staff learn of the event, and under no circumstances should this exceed 24 hours**. The investigator will submit any updated SAE data to the sponsor, **immediately once it becomes available, and under no circumstance should this exceed 24 hours of it being available**.

The initial report will be followed up with more information as relevant, or as requested by the sponsor's Study Manager. The sponsor's Study Manager will be responsible for forwarding the SAE form to other sponsor personnel as appropriate.

9.1.7 Evaluating AEs

Assessment of Intensity

The investigator or their medically qualified designee will make an assessment of intensity for each AE reported during the study and will assign it to one of the following categories:

- **Mild:** An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities
- **Severe:** An event that prevents normal everyday activities.

Note: An AE assessed as 'severe' should not be confused with an SAE. 'Severe' is a category utilized for rating the intensity of an event. Both non-serious AEs and SAEs can be assessed as severe, e.g., a headache may be severe (significantly interferes with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed in Section 9.1.2. An event is defined as 'serious' when it meets at least one of the pre-defined outcomes described in the definition of an SAE (Section 9.1.2), **not** when it is rated as 'severe'.

Assessment of Causality

For each AE (non-serious and serious), the investigator or their medically qualified designee **must** provide an assessment of causality in the AE section of the eCRF and on the SAE form (as appropriate, subject to classification of the AE). Causality is one of the criteria used to determine regulatory reporting requirements.

A 'reasonable possibility' of a relationship conveys there are facts (evidence) and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided in the AE/SAE report.

The investigator or their medically qualified designee will use clinical judgment to determine causality and will also consult the Investigator Brochure (IB), Safety Statement and/or Product Information, as appropriate, when making their assessment. Alternative causes, such as

underlying disease(s), concomitant therapy, other risk factors and the temporal relationship of the event to study product use will be considered and investigated.

Documentation of the (S)AE assessment will be recorded in trial database, including documenting the assessment of causality.Where applicable, the investigator or their medically qualified designee must document in the medical notes they have reviewed the AE/SAE and provided an assessment of causality.

There may be situations, when an SAE has occurred, where the investigator or their medically qualified designee has minimal information to include in the initial SAE report. **However, it is very important that the investigator or their medically qualified designee always makes an assessment of causality for every event prior to initial transmission of the SAE data to the sponsor.** The investigator may change their opinion of causality, in light of follow-up information, and send an SAE follow-up report with an updated causality assessment.

9.1.8 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator or their authorized safety designee is required to proactively follow up all ongoing serious and severe AE with each subject and provide further information on the subject's condition, as available.

All severe AEs (non-serious and serious) should be followed until resolution, until the condition stabilizes, until the event is otherwise explained or until the subject is lost to follow-up.

The investigator or their medically qualified designee is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated (or as requested by the sponsor) to elucidate as fully as possible the nature and/or causality of the AE/SAE. These may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

New or updated information will be recorded in the AE section of the eCRF and on the SAE form (as appropriate, subject to classification of the AE). The investigator or their authorized safety designee will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

The investigator and their authorized safety designees are not obligated to actively seek AEs or SAEs after the conclusion of study participation. However, if the investigator or their medically qualified designee learns of an SAE, including a death, at any time after a subject has been discharged from the study, and they consider the event to be reasonably related to study product or study participation, they must promptly notify the sponsor by emailing the information to the sponsor's Case Management Group mailbox PPD, with the appropriate sponsor Study Manager in copy.

The investigator or their authorized trial designee will submit any updated SAE data to the sponsor within the designated reporting time frames.

9.1.9 Withdrawal Due to an Adverse Event

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of an AE provided (Section 9.1.1) and recorded in the withdrawalAE section of the eCRF.

When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined in this protocol.

9.1.10 Regulatory Reporting Requirements for SAEs

The sponsor has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

The sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, the Institutional Review Board (IRB) and the investigator.

Investigator safety reports must be prepared for suspected Unexpected Serious Related Event (USRE) according to local regulatory requirements and sponsor policy, and forwarded to the investigator, as appropriate.

If the investigator receives an investigator safety report describing a SAE or other specific safety information (e.g., a summary or listing of SAEs) from the sponsor, they will review it, file it with other safety information (e.g., the IB) in the investigator site file and notify the REC, if appropriate, according to local requirements.

9.2 Pregnancy

9.2.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported while a female subject is participating in the study from the date/time of signing the informed consent until 5 days after the last administration of the study product.

9.2.2 Action to be Taken if Pregnancy Occurs

The investigator or their authorized trial designee will record pregnancy information on the appropriate eCRF and e-mail it to the Case Management Group mailbox PPD) within 24 hours, with the appropriate sponsor Study Manager in copy. Original completed pregnancy information forms will be retained in the investigator site file.

The female subject will not be followed to determine the outcome of the pregnancy. Any female subject who becomes pregnant while participating will be withdrawn.

9.3 Discontinuation of Study Product and Subject Discontinuation/Withdrawal

If a subject is discontinued early from the study product (Section 9.3.1) or discontinued or prematurely withdraws from the study (Section 9.3.2), the reason(s) for intervention discontinuation or withdrawal and the associated date must be documented in the relevant

section(s) of the eCRF. If a subject is discontinued early from the study product, the subject should stay in the study and complete the remaining assessments unless they need to be withdrawn (see Section 9.3.2).

9.3.1 Discontinuation of Study Product

A subject may be discontinued from the study product at any time whilst still in the study at the discretion of the investigator related to safety, subject consent or a potential worsening of the risk / benefit assessment from the subject of remaining on the intervention for the following reasons:

- Adverse Event
- Lack of efficacy from the intervention
- Subject request
- Subject to be withdrawn from the study (see Section 9.3.2)

9.3.2 Subject Discontinuation/Withdrawal

A subject may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures.

The following circumstances require discontinuation of study product and/or premature subject withdrawal:

- Protocol violation that may impact the subject's safety
- Withdrawal of informed consent
- Subject lost to follow-up
- Unblinding of the subject
- Pregnancy

If the subject withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9.3.3 Lost to Follow up

If a subject fails to attend required virtual visit, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls or emails or local equivalent methods) and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

A subject will be considered lost to follow up and withdrawn from the study if he or she repeatedly fails to attend scheduled virtual visits and is unable to be contacted by the study team.

If contact is made with the subject, the investigator should inquire about the reason for withdrawal and if appropriate request that the subject attend a final virtual visit and follow-up with the subject regarding any unresolved adverse events (AEs).

9.4 Data Management

As used in this protocol, the term eCRF is understood to refer to an electronic data record.

The source documents which contain the source of data recorded in the eCRF should be specified. The eCRF and/or eDiary can be used as a source document at the discretion of data management.

Each subject will be assigned and identified by a unique Screening Subject Number. Any reference made to an individual subject within the study must be done using their unique Screening Subject Number.

9.4.1 Case Report Form

An eCRF is an electronic document designed to record the protocol required information to be reported to the sponsor on each trial subject.

For each subject who has given informed consent the eCRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct. The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Management of clinical data will be performed in accordance with Third Party Biostatistics and Data Management (BDM) Vendor applicable standards and data cleaning procedures with oversight by Haleon to ensure integrity of the data, for example, to remove errors and inconsistencies in the data. To protect the privacy of subjects, no Personal Information (PI) (including the subject's name or initials or full birth date) is to be recorded in the CRF or as part of the query text. All CRF pages should be completed during a subject assessment when the CRF has been designated as the source. Data that is sourced elsewhere should be entered into the CRF in an agreed upon timeframe between the Investigator and Sponsor. Haleon will obtain and retain all CRFs and associated study data as applicable at the completion of the study.

9.4.2 Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance.

Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

Adverse events will be coded (in line with the Site and Safety Management Plan) and concomitant medications terms (if applicable) using the CCI dictionary.

Programmed edit checks will be generated automatically, as the data are being entered into the system. Reports and listings on the CRF data will also be run, in addition to the queries already

programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The 3rd Party BDM Vendor will raise queries as needed on safety data to code the terms (AEs and Drugs or concomitant medication) appropriately.

The study monitor will perform ongoing review the of the CRFs in accordance with the monitoring plan, to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

9.4.3 Data Queries

Any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. The study monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction.

Due to the low risk associated with the study intervention, there will be no data monitoring committee for the study. Monitoring will occur as documented on the study risk assessment and monitoring plan.

9.5 Processing Patient Reported Outcomes and Data Collection from Internet of Medical Things

Electronic Patient reported outcome (ePRO) that are measured by Internet of Medical Things (IoMT) devices (i.e., wearables, patches, sensors, and mobile data collection units such as smartphones and tablets) will be transferred in the protocol-specified aggregated and/or raw form electronically to Haleon or Third-party DM vendor.

All ePRO source data should be reviewed by the study staff and the study monitor to ensure accurate transcription of data and that any potential AEs or concomitant medications reported on these documents are discussed with the subject and transcribed accurately to the eCRF and/or DMS. ePROs that are classed as source data will be retained by the investigator and true/certified copies may be sent to a designated vendor or Haleon as required. Any AEs or concomitant medications collected as ePRO will be reviewed and transcribed to the eCRF by the site.

To protect the privacy of subjects, no Personal Information (PI) (including the subject's name or initials or birth date) is to be recorded on any PRO/ePRO/IoMT Devices Data that will be forwarded to Haleon or Third-Party Vendor.

9.6 Regulatory and Ethical Considerations

9.6.1 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent document, safety statement (including any updates) and other relevant documents, e.g. recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of

IRB/EC approvals should be forwarded to Haleon prior to the initiation of the study, and also when subsequent amendments to the protocol are made.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Haleon in writing immediately after the implementation.

9.6.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and legal and regulatory requirements, as well as the ethical principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2016), guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

9.6.3 Subject Information

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to Haleon and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Haleon in order to de-identify study subjects.

The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Haleon will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

9.7 Records Retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location. The duration of archiving will be as per local regulatory requirements.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must notify Haleon of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

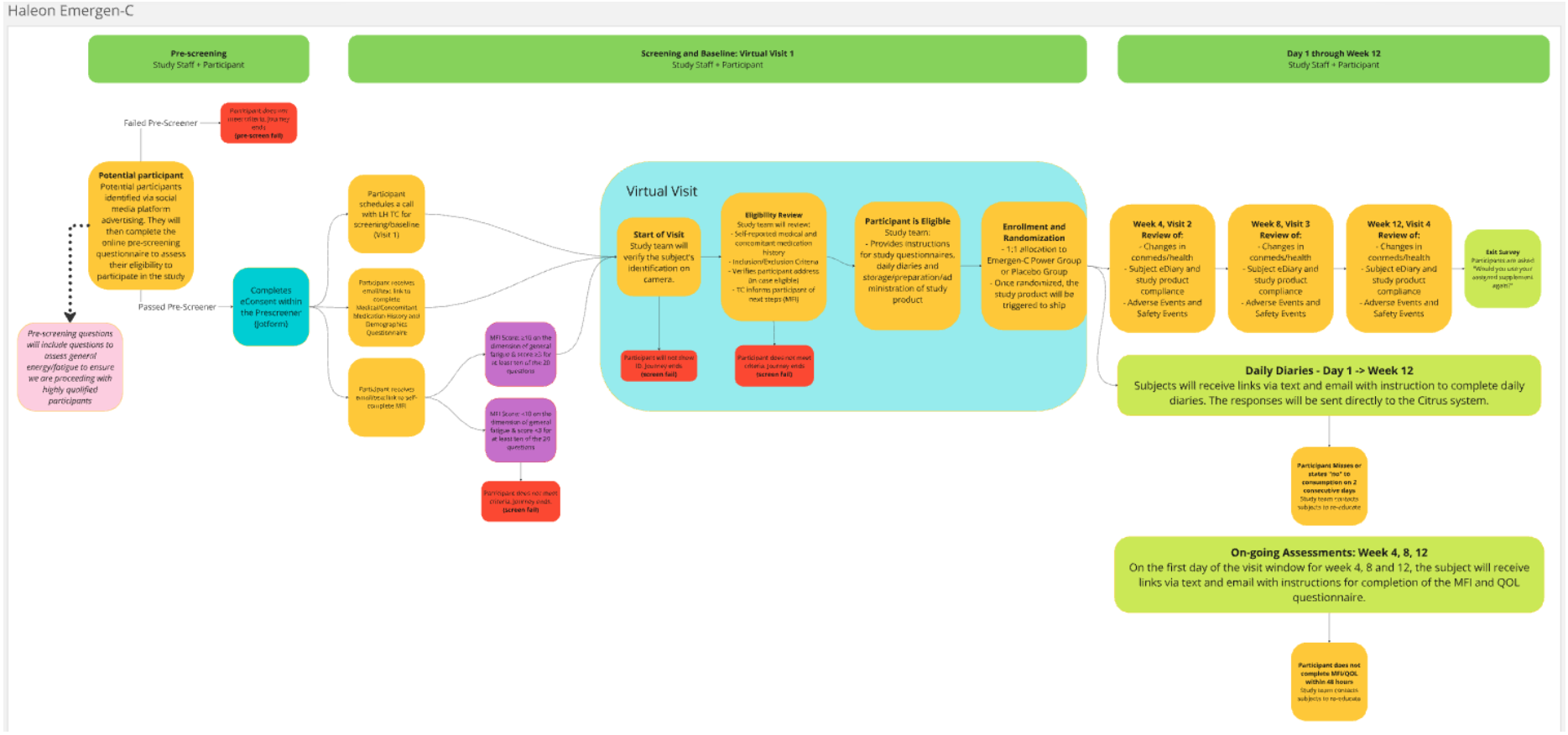
9.8 Disclosure and Publication Policy

Study information from this protocol may be posted on publicly available clinical trial registers before enrollment of subjects begins in accordance with applicable Haleon policies.

Haleon intends to make anonymized subject-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with sponsor policy and as per the country specific requirements for disclosure.

9.9 Schedule of Activities Schematic



9.10 Study Questionnaires

9.10.1 Multidimensional Fatigue Index (MFI-20)

Question:	Response:						
1. I feel fit	yes, that is true	1	2	3	4	5	no, that is not true
2. Physically I feel only able to do a little	yes, that is true	1	2	3	4	5	no, that is not true
3. I feel very active	yes, that is true	1	2	3	4	5	no, that is not true
4. I feel like doing all sorts of nice things	yes, that is true	1	2	3	4	5	no, that is not true
5. I feel tired	yes, that is true	1	2	3	4	5	no, that is not true
6. I think I do a lot in a day	yes, that is true	1	2	3	4	5	no, that is not true
7. When I am doing something, I can keep my thoughts on it	yes, that is true	1	2	3	4	5	no, that is not true
8. Physically I can take on a lot	yes, that is true	1	2	3	4	5	no, that is not true
9. I dread having to do things	yes, that is true	1	2	3	4	5	no, that is not true
10. I think I do very little in a day	yes, that is true	1	2	3	4	5	no, that is not true
11. I can concentrate well	yes, that is true	1	2	3	4	5	no, that is not true
12. I am rested	yes, that is true	1	2	3	4	5	no, that is not true
13. It takes a lot of effort to concentrate on things	yes, that is true	1	2	3	4	5	no, that is not true
14. Physically I feel I am in a bad condition	yes, that is true	1	2	3	4	5	no, that is not true
15. I have a lot of plans	yes, that is true	1	2	3	4	5	no, that is not true
16. I tire easily	yes, that is true	1	2	3	4	5	no, that is not true
17. I get little done	yes, that is true	1	2	3	4	5	no, that is not true
18. I don't feel like doing anything	yes, that is true	1	2	3	4	5	no, that is not true
19. My thoughts easily wander	yes, that is true	1	2	3	4	5	no, that is not true
20. Physically I feel I am in an excellent condition	yes, that is true	1	2	3	4	5	no, that is not true

9.10.2 Additional QoL Questions

I feel more energized to look after my family and/or loved ones	yes, that is true	1	2	3	4	5	no, that is not true
I feel more prepared for the future	yes, that is true	1	2	3	4	5	no, that is not true
I feel resilient so I can be at my best each day	yes, that is true	1	2	3	4	5	no, that is not true
I feel ready to cope with life's challenges	yes, that is true	1	2	3	4	5	no, that is not true
I feel relaxed	yes, that is true	1	2	3	4	5	no, that is not true
I feel able to unwind	yes, that is true	1	2	3	4	5	no, that is not true
In the last 4 weeks, how many days of work did you miss, if any?	yes, that is true	1	2	3	4	5	no, that is not true
In the last 4 weeks, how many days with cold and flu symptoms did you have, if any?	yes, that is true	1	2	3	4	5	no, that is not true
In the last 4 weeks, how many days did you feel rundown, if any?	yes, that is true	1	2	3	4	5	no, that is not true
In the last 4 weeks, how many days did you have to cancel plans or work because you were not feeling 100%, if any?	yes, that is true	1	2	3	4	5	no, that is not true
In the last 4 weeks, how many days did you have cold and cough symptoms (for example: runny nose, blocked nose, sneezing, cough, sore throat), if any?	yes, that is true	1	2	3	4	5	no, that is not true
In the last 4 weeks, how many days were you in bed sick, if any?	yes, that is true	1	2	3	4	5	no, that is not true

End of Study question:

- Would you use your assigned supplement again?

10 ABBREVIATIONS

The following is a list of abbreviations that may be used in the protocol.

Table 10-1 Abbreviations

Abbreviation	Term
AE	Adverse Event
BDR	Blinded Data Review
CRS	Clinical Research Scientist

Abbreviation	Term
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
eICF	Electronic Informed Consent Form
ePRO	Electronic Patient Reported Outcome
EDC	Electronic Data Capture
e.g.	exempli gratia (for example)
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	Identification
IRB	Institutional Review Board
IoMT	Internet of Medical Things
ITT	Intention-To-Treat
MAOI	Monoamine Oxidase Inhibitors
mITT	Modified Intention-to-Treat
MCID	Minimal Clinically Important Difference
MFI	Multidimensional Fatigue Index
mg	milligrams
MMRM	Mixed Model with Repeated Measures
N/A	Not Applicable
PDF	Portable Document Format
PP	Per Protocol
QoL	Quality of Life
RWE	Real World Evidence
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SP	Safety Population
SUSAR	Suspected Unexpected Serious Adverse Event
UK	United Kingdom
US	United States
Wi-Fi	Wireless Fidelity
Yr	Years

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