CLINICAL PROTOCOL COVER PAGE

Protocol Title: A Phase II, randomized, double-blind, controlled, single-centre 21-day study to investigate the efficacy of AllerPops to reduce nasal symptoms in adult volunteers with seasonal/year-long nasal allergies.

Protocol Number: 21-SAHSE-01

Protocol Date: February 14, 2022

Version: 4

Study Design: Phase II, randomized, controlled

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Protocol Revisions:

Version #	Description of Changes	Date	Signature

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1. List of Abbreviations

ADA	Anti-Drug Antibodies
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
BMI	Body Mass Index
BPM	Beats per minute
BUN	Blood urea nitrogen
CBC	Complete Blood Count
CRF	Case Report Form
CTMS	Clinical Trial Management Software
Cl	Chloride
Cr	Creatinine
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
ET	Early Termination
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GGT	Gamma glutamyl transpeptidase/transferase
h **or** hr	Hour
HCT	Hematocrit
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ID	Identification
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
K	Potassium
Kg	kilogram
m	Meter
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
Na	Sodium
NCS	Not clinically significant
OTC	Over the counter
PD	Protocol Deviation
PI	Principal Investigator
PV	Protocol Violation
RBC	Red Blood Cell
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
WBC	White Blood Cell
EDA	Exploratory Data Analysis

2. Protocol Synopsis

Title: A randomized, double-blind, controlled, single-centre, 21-day study to investigate the efficacy of AllerPops to reduce nasal symptoms in adult volunteers with seasonal/year-long nasal allergies.

Phase: Phase II

Duration: Up to 30 days between Screening (V1) and Baseline (V2), and a 21-day intervention period, with dosing occurring every other day for a minimum of 3 doses, and thereafter until the participant is satisfied with the relief of the nasal allergy symptoms. The suitable season for the trial will be determined based on the seasonal variation measures.

Primary Objectives: To assess the effectiveness of AllerPops on relieving nasal symptoms compared to the control group in volunteers with seasonal/year-long allergies during the first 7 days of the 21-day intervention period.

Secondary Objective:

1. To evaluate the safety of AllerPops administration in volunteers with seasonal/year-long allergies during a 21-day intervention period.
2. To assess the duration of effectiveness of AllerPops in relieving nasal symptoms compared to the control group in volunteers with seasonal/year-long allergies during a 21-day intervention period (exploratory).
3. To evaluate the effect of the AllerPops administration on the oral microbial presentation/microbiota using Amplicon Metagenomics Sequencing test through saliva samples during a 21-day intervention period (exploratory).
4. To evaluate the effect of the AllerPops administration on the IgE (total) blood level during a 21-day intervention period (exploratory).

Study Population: Seventy-two participants with seasonal/year-long nasal allergies.

2.1. Inclusion Criteria

Participants must meet all of the following criteria to be considered eligible for admission to the study.

1. Participants will be clinically diagnosed with persistent or intermittent allergic rhinitis, according to the Allergic Rhinitis and Its Impact on Asthma (ARIA) classification. (The guidelines of Allergic Rhinitis and its Impact on Asthma (ARIA) group, classified it to intermittent (less than 4 days per week and for less than 4 weeks) and persistent (more than 4 days per week or lasting more than 4 weeks regardless of the number of days per week).
2. Male or female seasonal/year-long nasal allergy sufferers (as assessed by a questionnaire at screening) between the ages of 18 and 70.

3. Females who are not of childbearing potential (post-menopausal defined as those with amenorrhea for at least 2 years). Females of childbearing potential should be either sexually inactive (abstinent) for 60 days prior to the first dose of the study, throughout the study and for 30 days after completion of the study, or be using one of the following acceptable methods of birth control:
    i. Surgically sterile (bilateral tubal-ligation, hysterectomy, bilateral oophorectomy) for at least 90 days prior to the first dose of the study.
    ii. IUD in place for at least 60 days prior to the first dose of the study, throughout the study and for 30 days after completion of the study.
    iii. Barrier methods (condom, diaphragm) with spermicide for at least 60 days prior to the first dose of the study, throughout the study and for 30 days after study completion.
    iv. Hormonal contraceptives for at least 90 days prior to the first dose of the study, throughout the study, and for 30 days after study completion.

*Changes to the method of birth control while participating in the study will be judged by the PI for acceptability.

4. Written informed consent obtained and signed by participant.
5. BMI between 18.5 and 29.9 kg/m^2, with a stable weight over the last 3 months. (A stable weight is defined as <5% of total body weight change in the last 3 months).
6. Agrees not to use any over the counter, prescription, health supplement or dietary supplement from at least 14 days prior to screening until the end of the study.
7. Agrees to maintain current dietary habits, level of physical activity, occupational and living environment for the trial duration.
8. Does not regularly consume more than 2 standard* alcoholic beverages a day as assessed through verbal confirmation at screening, and agrees not to consume >2 standard* alcoholic beverages per day for the trial duration.
9. Non-smoker within 12 months prior to dosing as assessed by verbal confirmation.
10. Stable medical conditions that do not require medication use routinely and do not affect or involve the immune systems as determined by medical history, physical examination, clinical chemistry performed at screening, and as assessed by the Principal Investigator.
11. Agrees not to use nasal steroid spray from at least 14 days prior to screening until the end of the study.
12. Agrees not to use neti-pot and oil-pulling for at least 7 days prior to screening until the end of the study.
13. .
14. Have access to a microwave.

** A standard alcoholic beverage is defined as 12 ounces of beer, 5 ounces, of wine, or 1.5 ounces of liquor*

2.2.Exclusion Criteria

Participants meeting any of the following criteria will not be eligible for admission to the study:

1. Participants who are pregnant/lactating or planning to become pregnant during the course of the clinical trial.
2. Participants who have any sings of active or recurrent upper airway infection (bacterial/viral).
3. Participants who have a known sensitivity or allergy to any of the study products, or ingredients.
4. Participation in another research study within 30 days prior to enrollment in this clinical trial.
5. Participants who are not able to tolerate venipuncture and/or have poor venous access.
6. Participants dependent on decongestants (nasal or oral) or receiving allergen-specific immunotherapy.
7. Participants who have been diagnosed with other clinical forms of rhinitis such as infectious rhinitis, rhinitis of pregnancy, food and alcohol-induced rhinitis, atrophic rhinitis, vasomotor rhinitis, rhinosinusitis and age-related rhinitis.
8. Participants who have receive previous acupuncture treatment or alternative medicine for AR in the last three months or planned in the next two years.
9. Participants who have received allergy desensitization therapy (current, during the past two years, or planned in the next two years).
10. Participants who have had any major surgery within 1 year of enrollment into the clinical trial or have any anticipated major surgeries intended to occur during the clinical trial.
11. Participants who have received a blood transfusion within 8 weeks of enrollment in the clinical trial.
12. Participants who have donated blood or plasma to a blood bank or clinical study within 8 weeks of enrollment and during the study except venipuncture as part of clinical trial.
13. Participant has known severe medical conditions, such as cardiovascular, liver or renal dysfunction, diabetes mellitus, cancers, cerebrovascular diseases, blood system diseases which in the opinion of the Principal Investigator, may preclude safe study participation, or interfere with study objectives.
14. Participants who are immunocompromised or have been diagnosed HIV/AIDS, Hepatitis B, or untreated Hepatitis C.
15. Participant has a history of alcohol or drug addiction treatment within the last 2 years prior to inclusion in the study, or any current addiction on alcohol or drugs.
16. Participants with Grade II or III septum deviation and/or presence of nasal polyps or other conditions that lead to nasal obstruction.
17. Participant has any other medical, social or other condition that, in the opinion of the Principal Investigator, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.
18. Participants with allergic asthma and/or moderate to severe atopic dermatitis.
19. History of anaphylactic reactions.

20. Participants with any risk of developing dental cavity or on-going oral health issue, as assessed during their regular dentist visit in past 6 months.
21. Participants who brush more than twice a day and/or mouthwash more than once a day and/or floss more than once a day.

2.3. Schedule of Assessments

Assessment	Visit 1 Screening Day -30 to Day 0	Visit 2 Baseline Day 1	Visit 3 Follow-Up Day 7	Visit 4 Follow-Up Day 14	Visit 5 End of Study Day 21
Informed Consent	X				
Physical Exam	X				
Medical History and Concomitant Medications	X				
Temperature, blood pressure, heart rate measurements taken	X	X	X		X
Questionnaires administered	X	X	X	X	X
Peak Nasal Inspiratory Flow (PNIF) Assessment		X	X	X	X
Urine Sample Collected (for females of childbearing potential)	X	X	X		X
Blood Draw – study endpoint related		X	X		X
Blood Draw - safety	X				X
Saliva Sample – Amplicon Metagenomics Sequencing		X	X		X
Dispense Study Product		X			
Dispense Study Diary		X			
Calculate Compliance			X		
Collect Unused Study Product (if applicable)					X
Collect Study Diary			X	X	X
Adverse Event Assessment		X	X	X	X
Concomitant Medication Review		X	X	X	X
Study Exit Assessments					X

3. Background

Allergic rhinitis (AR) was described in 1929 as a process which included three cardinal symptoms: sneezing, nasal obstruction, and mucus discharge [1]. AR is clinically defined as a symptomatic disorder of the nose induced by an IgE-mediated inflammation after allergen exposure of the membranes lining the nose. AR is a widely prevalent condition in Canada (20-

25%) [2] and other countries; it is often accompanied with significant physical sequelae and recurrent or persistent morbidities. Increasing literature in animals and humans has implicated changes in the gut microbiome with the development of allergic disease [3]–[7], which were shown to be associated with reduced early microbial exposure [6], [8], [9]. Changes of the nasal [10]–[15] and oral microbiota [16]–[18] were found as well.

Some investigations have shown that the oral administration of probiotics and prebiotics may benefit allergic rhinitis patients [19]–[22]. The local nasal administration of Lactococcus lactis NZ9000 can affect the local and systemic immune responses against *Streptococcus pneumonia* [23]. Probiotics seem a promising therapeutic approach for allergic airway diseases, however, clinical benefit of probiotic therapy depends upon numerous factors, such as type of bacterium, dosing regimen, delivery method and other underlying host factors, e.g. the age and diet of the host [22]. Among mechanisms of action underlying modulation of immune responses by microbial species, are reduction of permeability of gut barrier and systemic penetration of antigens [22], [24], generation of pro- and anti-inflammatory cytokines in the gut [25]–[27], and modulation of proliferation of immune cells [22], [28], [29].

AllerPops is Natural Health Product in a lozenge dosage form indicated for the alleviating (seasonal) AR. Immune-mediated disorders such as allergic rhinitis is being linked to reduced early microbial exposure [6], [8], [9], dysbiosis of the gut [6], [7], the nasal [10]–[12] and oral microbiota [16]–[18]. The medicinal ingredient was chosen based on its capability to provide balanced nutritional support to the oral microbiota, and thereby restore its presentation and the normal function. The active ingredient, L-Arginine, 5.04%, is used in the formula with the purpose of reducing the nasal symptoms of allergy.

There will be 2 groups of participants in the study (investigational and control). For the investigational group; the method of use of the lozenge product will include two steps: 1) mechanical cleaning of the mouth, followed by 2) slow consumption of the investigational product with the target of its natural dissolution in the mouth after 60 minutes. The purpose of the first step is to remove the biofilm from the teeth and tongue and to provide an unoccluded surface for targeted bacteria to grow.The purpose of the second step is proposed to provide nutrition to the oral bacteria and thereby to restore their balance.

For the control group, the same investigational product will be administered, however the procedure for use will be modified as follows: There will be no mouth cleaning before the product consumption (No step 1 as mentioned above). The product will be swallowed instead of dissolved in the mouth, in order to reduce its presence in the mouth as much as possible. The purpose of this control group is to support the effect of use of the entire two-step method as compared to the investigational group.

The active ingredient, L-Arginine is known to Health Canada. L-Arginine is listed in the NHPID, and allowed for use in NHPs under proposed here conditions of use. Safety of the of current ingredient combination, while allowed for use separately, will also be tested under proposed conditions of use.

The Rationale for Performing Research:

Increase in immune-mediated conditions [30]–[32](Allergic rhinitis is one of them) and the few medical solutions available (each of which is associated with side effects) prompted this research and clinical study. The medicinal ingredient, L-Arginine, in the formulation of AllerPops is a well-known Natural Health Product Ingredient with history of human use.

4. Study Objectives

Objectives:

Primary Objective: To assess the effectiveness of AllerPops on relieving nasal symptoms compared to the control group in volunteers with seasonal and perennial (or intermittent and persistent) allergic rhinitis during the first 7 days of the 21-day intervention period.

Secondary Objectives:

1. To evaluate the safety of AllerPops administration in volunteers with seasonal/year-long allergies during a 21-day intervention period.
2. To assess the duration of effectiveness of AllerPops in relieving nasal symptoms compared to the control group in volunteers with seasonal/year-long allergies during a 21-day intervention period (exploratory).

3. To evaluate the effect of the AllerPops administration on the oral microbial presentation/microbiota using Amplicon Metagenomics Sequencing test through saliva samples during a 21-day intervention period (exploratory).
4. To evaluate the effect of the AllerPops administration on the IgE (total) blood level during a 21-day intervention period (exploratory).

Endpoints:

Primary Endpoint: The reduction of nasal allergic symptoms during the first 7 days of the 21-day intervention period (once every other day – D1, D3, D5). The reduction of symptoms will be measured using the following assessments.

- Total Nasal Symptoms Score (TNSS) Questionnaire: This assessment will be conducted at the V1, V2, and V3.
- Peak Nasal Inspiratory Flow (PNIF): Measures nasal flow for assessing nasal airway patency. This assessment will be conducted at the baseline D1 and D7.

Secondary Endpoint(s):

1. To evaluate the safety of the AllerPops product during a 21-day intervention period. The safety evaluation will be measured based on the following assessments:
    a. Safety will be assessed by collecting vital signs, the emergence of adverse events, and clinical chemistry (CBC and a comprehensive safety panel) and PI assessment.
2. The exploratory study of the effect of AllerPops in relieving nasal symptoms compared to the control group during a 21-day intervention period. The reduction of symptoms will be measured based on the following assessments:
    a. Total Nasal Symptoms Score (TNSS) questionnaire: This will be assessed at D14 (V4) and D21 (V5).
    b. Peak Nasal Inspiratory Flow (PNIF) measurement: This will be assessed at D14 and D21.
3. The exploratory study of the effect of AllerPops in oral microbial presentation/microbiota through Amplicon Metagenomics Sequencing test which is a rRNA gene sequencing method in saliva. The evaluation will be measured at D1, D7 and D21.
4. The exploratory study of the effect of AllerPops on the IgE (total) blood level through blood samples during a 21-day intervention period. The evaluation will be measured at D1, D7 and D21.

5. Selection of Study Population

5.1. Inclusion Criteria

Participants must meet all of the following criteria to be considered eligible for admission to the study.

1. Participants will be clinically diagnosed with persistent or intermittent allergic rhinitis, according to the Allergic Rhinitis and Its Impact on Asthma (ARIA) classification. The guidelines of Allergic Rhinitis and its Impact on Asthma (ARIA) group, classify intermittent as less than 4 days per week and for less than 4 weeks and persistent as more than 4 days per week or lasting more than 4 weeks regardless of the number of days per week).
2. Male or female seasonal/year-long nasal allergy sufferers (as assessed by a questionnaire at screening) between the ages of 18 and 70.
3. Females who are not of childbearing potential (post-menopausal defined as those with amenorrhea for at least 2 years). Females of childbearing potential should be either sexually inactive (abstinent) for 60 days prior to the first dose of the study, throughout the study and for 30 days after completion of the study, or be using one of the following acceptable methods of birth control:
    v. Surgically sterile (bilateral tubal-ligation, hysterectomy, bilateral oophorectomy) for at least 90 days prior to the first dose of the study.
    vi. IUD in place for at least 60 days prior to the first dose of the study, throughout the study and for 30 days after completion of the study.
    vii. Barrier methods (condom, diaphragm) with spermicide for at least 60 days prior to the first dose of the study, throughout the study and for 30 days after study completion.
    viii. Hormonal contraceptives for at least 90 days prior to the first dose of the study, throughout the study, and for 30 days after study completion.

*Changes to the method of birth control while participating in the study will be judged by the PI for acceptability.

4. Written informed consent obtained and signed by participant.
5. BMI between 18.5 and 29.9 kg/m^2, with a stable weight over the last 3 months. (A stable weight is defined as <5% of total body weight change in the last 3 months).
6. Agrees not to use any over the counter, prescription, health supplement or dietary supplement from at least 14 days prior to screening until the end of the study.
7. Agrees to maintain current dietary habits, level of physical activity, occupational and living environment for the trial duration.
8. Does not regularly consume more than 2 standard* alcoholic beverages a day as assessed through verbal confirmation at screening, and agrees not to consume >2 standard* alcoholic beverages per day for the trial duration.
9. Non-smoker within 12 months prior to dosing as assessed by verbal confirmation.

10. Stable medical conditions that do not require medication use routinely and do not affect or involve the immune systems as determined by medical history, physical examination, clinical chemistry performed at screening, and as assessed by the Principal Investigator.
11. Agrees not to use nasal steroid spray from at least 14 days prior to screening until the end of the study.
12. Agrees not to use neti-pot and oil-pulling for at least 7 days prior to screening until the end of the study.
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14. Have access to a microwave.

** A standard alcoholic beverage is defined as 12 ounces of beer, 5 ounces, of wine, or 1.5 ounces of liquor*

5.2 Exclusion Criteria

Participants meeting any of the following criteria will not be eligible for admission to the study:

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4. Participation in another research study within 30 days prior to enrollment in this clinical trial.
5. Participants who are not able to tolerate venipuncture and/or have poor venous access.
6. Participants dependent on decongestants (nasal or oral) or receiving allergen-specific immunotherapy.
7. Participants who have been diagnosed with other clinical forms of rhinitis such as infectious rhinitis, rhinitis of pregnancy, food and alcohol-induced rhinitis, atrophic rhinitis, vasomotor rhinitis, rhinosinusitis and age-related rhinitis.
8. Participants who have receive previous acupuncture treatment or alternative medicine for AR in the last three months or planned in the next two years.
9. Participants who have received allergy desensitization therapy (current, during the past two years, or planned in the next two years).
10. Participants who have had any major surgery within 1 year of enrollment into the clinical trial or have any anticipated major surgeries intended to occur during the clinical trial.
11. Participants who have received a blood transfusion within 8 weeks of enrollment in the clinical trial.
12. Participants who have donated blood or plasma to a blood bank or clinical study within 8 weeks of enrollment and during the study except venipuncture as part of clinical trial.
13. Participant has known severe medical conditions, such as cardiovascular, liver or renal dysfunction, diabetes mellitus, cancers, cerebrovascular diseases, blood system diseases

which in the opinion of the Principal Investigator, may preclude safe study participation, or interfere with study objectives.

14. Participants who are immunocompromised or have been diagnosed HIV/AIDS, Hepatitis B, or untreated Hepatitis C.
15. Participant has a history of alcohol or drug addiction treatment within the last 2 years prior to inclusion in the study, or any current addiction on alcohol or drugs.
16. Participants with Grade II or III septum deviation and/or presence of nasal polyps or other conditions that lead to nasal obstruction.
17. Participant has any other medical, social or other condition that, in the opinion of the Principal Investigator, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.
18. Participants with allergic asthma and/or moderate to severe atopic dermatitis.
19. History of anaphylactic reactions.
20. Participants with any risk of developing dental cavity or on-going oral health issue, as assessed during their regular dentist visit in past 6 months.
21. Participants who brush more than twice a day and/or mouthwash more than once a day and/or floss more than once a day.

5.3 Concomitant Medications

Apart from the dispensed IP(s), any medication taken by the participant throughout the study period will be regarded as concomitant treatment. During the study, participants shall be instructed not to take medications unless absolutely necessary. If the use of any concomitant treatment becomes necessary during the study, the treatment will be recorded, including the name of the drug or treatment, indication for use, dosage, route, date, and time of treatment.

5.4 Early Withdrawal

Removal of Study Participants:

The removal of a study participant will be based on the Clinical, and Protocol Violation conditions outlined below. If possible, any evaluations or assessments planned for the end of the study will be completed at an Early Termination (ET) Visit. Criteria for participant removal at the PI's discretion are:

Removal by Principal Investigator
The removal of a study participant by the principal investigator will be based on the Clinical and Protocol Violation conditions outlined below. If possible, any evaluations or assessments planned for the end of the study will be completed at an Early Termination (ET) Visit. Criteria for participant removal at the PI's discretion are:

Clinical
A participant may be withdrawn from the study if, in the opinion of the PI, it is not in the best interest of the participant to continue. Participants who experience an adverse event (AE) or

severe adverse event (SAE) will be assessed by the PI and determine if removal from the study is necessary. Participants experiencing a SAE will be follow up by PI until resolution of SAE. Any female who becomes pregnant during the course of the study will be removed and followed-up with accordingly.

Protocol Violation
Protocol violations may be a result of the above inclusion/exclusion criteria. Violations will be assessed by the PI on a case-by-case basis with removal from the study, if necessary. Participants can be withdrawn from the study at the discretion of the Sponsor. Participants who are deemed to be a protocol violation will not be followed up on.

6. Investigational Product

6.1 Investigational Product Details

Unit dose: 1 lozenge (8g)

Package size: 1 box containing 8 lozenges

Ingredients: sucrose (cane sugar), L-arginine, honey, trehalose, lactose, inulin, D-mannose, corn syrup, coconut oil, calcium gluconate, calcium lactate, carrageenan, cocoa powder, sodium chloride (salt), cinnamon, vanilla extract.

6.2 Manufacturing and Storage

AllerPops is manufactured at:

QINGDAO XIZHITANG FOOD CO., LTD.

No. 998 Wangsha Road

Chengyang District

Qingdao, Shandong, China

The product will be shipped by the Sponsor to the CRO prior to trial commencement. The CRO will be responsible for storing, maintaining, and dispensing the product accordingly. The product will be stored at room temperature in a limited-access location. Temperature of the storage location will be checked and recorded as per the site's SOPs.

6.3 Labelling

The IP will be labelled according to Health Canada and ICH-GCP E6(R2) guidelines and will contain the following information in both official languages (English and French):

- a statement indicating that it is an investigational product to be used only by a qualified investigator
- the brand name or code of the study product(s)
- the expiry date
- the storage conditions
- the lot number

- the name and address of the manufacturer and the sponsor
- the protocol code or identification

Written instructions on how to use the investigational product will be provided to the participant as part of the Informed Consent Form.

6.4 Directions

IMPORTANT: Must be fasting for at least 4 hours before taking the study product.

Directions for the Investigational Group:

1. Brush teeth with tap water (no toothpaste).
2. Scrub tongue with disposable tongue scraper provided. (***Caution:*** *reaching too far may cause a gag reflex.)*
3. Gargle and swish hot (optimal 120°F) water for 10-20 seconds. Spit out and repeat gargling over the next 5 minutes. The tongue should be red and without any biofilm. If it is not, repeat *Step 2*, and gargle once more.
4. Self-administer one lozenge. Let the lozenge slowly melt in the mouth. Do not chew or swallow whole. This may take up to 60 minutes. Discard if it is not fully dissolved after 60 minutes. Wait at least 30 minutes before eating your next meal.
5. Repeat *Step 1* to *Step 5* every other day for a minimum of 3 doses.
6. After the 3rd dose, you may repeat *Step 1* to *Step 5* every other day until you are satisfied with the symptom relief up to and including Day 13. Do not take the product on Day 14 onwards and return all remaining product at Visit 4.

Directions for the Control Group:

1. A box containing 8 units of the Investigational Product will be dispensed. This box will only be dispensed once, at visit 2.
2. Microwave: heat the product in 5 second increments until soft. (Caution: more than 10 seconds of microwaving the product may cause it to burn).
3. Cut: cut the product into smaller pieces those are the size of your usual medication/supplement.
4. Swallow: Participant will be instructed to swallow each of the small pieces over time with plenty of warm water. The participant will also be allowed to have a few sips of water to moisten the mouth and throat prior to swallowing the control product, if they feel it is necessary. Wait at least 30 minutes before eating your next meal. For next 2 doses, you must repeat *Step 2* to *Step 4* once every other day (day 3 and day 5).
5. After the 3rd dose, you may choose to use additional doses until you are satisfied with the symptom relief. If you choose to continue using the product, you must repeat *Step 2* to *Step 6* once every other day up to (and including) day 13. Maximum dose expected during day 1 to 13 is 7. Do not take the product on day 14 onwards and return all remaining product at visit 4.

6.5 Randomization

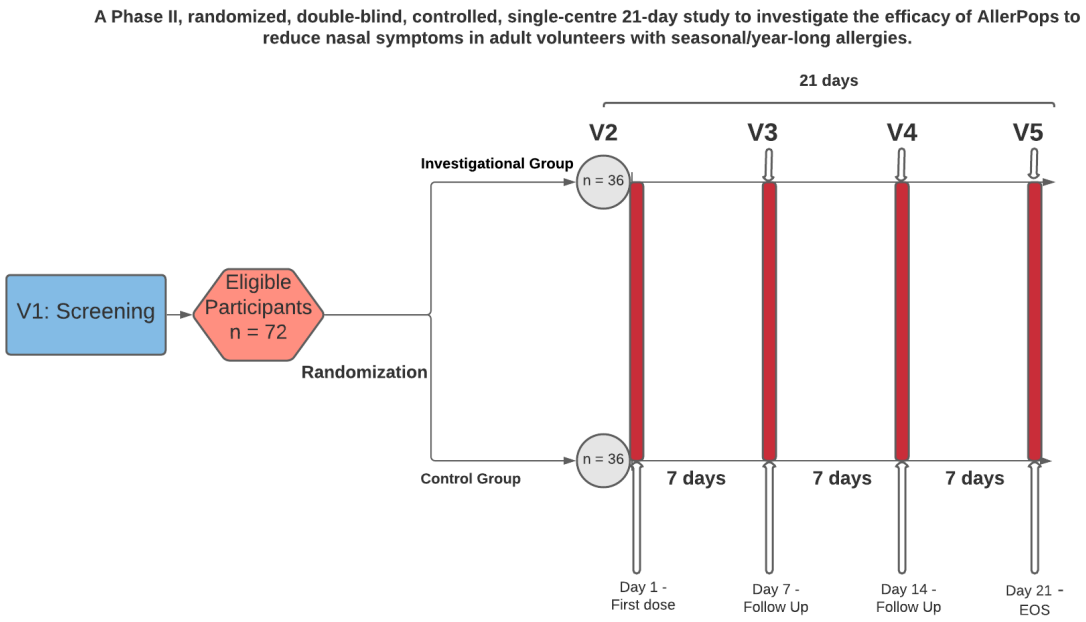
After eligibility for participants has been confirmed, they will be allocated to a study arm (Investigational or control). Participants will then be randomized accordingly to ensure an equal and unbiased distribution of products. The master randomization list will only be accessible to the designated unblinded personnel at the site until the database is locked. Participants will be given an envelope containing a detailed dosing instruction sheet. They will be instructed to take this home and open it, read and understand the procedure, and contact the site if they have any questions. The contact information for the site will be that of the designated unblinded personnel – these individuals will be able to answer any questions the participants may have about their assigned dosing instructions. Participants will be asked to not disclose information about their assigned dosing instructions to any study staff except the unblinded personnel whose contact information is contained in the detailed dosing instruction sheet.

6.6 Blinding and Unblinding

Blinding of study products will be maintained by appropriately delegated study staff. Designated unblinded personnel will randomize the groups using block randomization ensuring an equal distribution in each group. All site staff (excluding designated unblinded personnel) will remain blinded throughout the study until the data-lock and study-closeout stage.

Since both groups will be receiving identical products (with different instructions of use for each group), emergency unblinding will not be applicable to this trial.

7. Study Design (Flow chart)



8. Planned Study Visits

Pre-Screening Telephone Call:

Potential participants who will be contacted to participate in this study will be pre-screened over the phone. They will be asked a series of questions about their health and lifestyle. As part of that telephone pre-screening the following questions will be asked regarding their allergy symptoms:

1- How do you score your nasal congestion (0-5, with 5 being the worst)?
2- How do you score your Nasal Discharge or sneezing (0-5, with 5 being the worst)?
3- How do you score your watery or itchy eyes (0-5, with 5 being the worst)?
4- How many times do you brush your teeth a day (0-3, 0,1,2,3 or more)?
5- How many times do you use mouthwash a day (0-2, 0,1,2 or more)?
6- How many times do you floss your teeth a day (0-2, 0,1,2 or more)?

Scoring Standards: Total score ≥ 7 in question 1-3 and Total score ≤ 4 in question 4-6 will be booked for Screening (V1). Potential participants with a total score of < 7 in question 1-3 and/or total score > 4 in question 4-6 will not pass the telephone pre-screening and will not be booked for Visit 1.

Visit 1 – Screening

Participants will not be required to fast prior to this visit. The delegated study staff will present the ICF, and review its contents with the participant. The study staff will answer any questions the participant may have.

The Informed Consent Form (ICF) will be provided to the participant. After a sufficient period of reflection, the written and informed consent of the participant will be sought. Each page of the ICF will be initialed and the last page will be signed by the participant. Once signed and attested to by the PI or delegate, a copy of the signed original ICF will be provided to the participant.

After informed consent has been obtained, the PI and/or delegated research site staff will collect demographic information, complete a thorough medical history which will include the review of existing medical records to confirm inclusion/exclusion criteria. Biometric measurements (body temperature, SSH blood pressure, heart rate), anthropometric measurements (height, weight, calculated BMI) will be taken and a short questionnaire to assess allergy symptoms will be conducted. If none of the collected information excludes participation, screening clinical chemistry assessments will be conducted.

The screening information will be reviewed by the PI and/or delegate to determine if the participant is to be scheduled for a physical examination* and a final eligibility assessment.

*Physical exam will be done before dosing. This may be scheduled on another day.

Participants that have met all of the inclusion criteria and none of the exclusion criteria will proceed to the next scheduled visit, and TNSS questionnaire will be administered.

For females of childbearing potential, a urine sample will be collected for a urine pregnancy test.

Blood samples to be collected will be analyzed for the following:

- CBC [Includes: White Blood Cell Count (WBC), Red Blood Cell Count (RBC), Hemoglobin (HB), Hematocrit (HCT), MCV, MCH, MCHC, Platelet Count]
- Aspartate aminotransferase (AST)
- Sodium
- Potassium
- Chloride
- Serum creatinine
- Alanine Amino Transferase (ALT)
- Alkaline Phosphatase (ALP)
- Bilirubin Total
- Gamma Glutamyl Transpeptidase (GGT)

Visit 2 – Baseline – Day 1

These assessments may not be completed in the order shown below.
Participants:

1. Must be at least 8 hours fasting (no food, only water) prior to visit.
2. Will have any changes to health reviewed by delegated study staff.
3. For females of childbearing potential, a urine sample will be collected for a urine pregnancy test.
4. Will have the following measurements taken: temperature, blood pressure, heart rate.

5. Will have the following saliva test:
    - Amplicon Metagenomics Sequencing
6. Will complete the following assessments:
    - Total nasal symptoms score (TNSS) questionnaire (appendix 2).
    - Peak nasal inspiratory flow (PNIF) measurement.
7. Will have the following blood tests:
    - CBC (WBC, RBC, Hb, HCT, MCV, MCH, MCHC, Platelet Count)
    - Aspartate aminotransferase (AST)
    - Alanine aminotransferase (ALT)
    - Bilirubin
    - Gamma-glutamyl transferase (GGT)
    - Alkaline phosphatase (ALP)
    - Serum creatinine
    - Potassium
    - Chloride
    - Sodium
    - IgE (total)
8. Be provided with a paper/electronic diary – IP dosing, adverse events, concomitant medication.
9. Be provided with the IP (and oral hygiene kit if applicable) and instructions on dosing.
10. Be provided with dates/times of subsequent visit(s).
11. Review of all information for the visit by the PI and/or delegate prior to the next study visit to determine continued safe participation.

The participant will be given a paper/electronic daily diary in order to record the use of concomitant medications, IP dosing, symptoms, and any adverse events (such as fatigue, fever or headache) that may have occurred. The diary will be collected and/or reviewed at the research site at each visit as indicated on the Schedule of Assessments.

The participant should take the IP after this visit at home. The participant should take AllerPops at a maximum frequency of once every other day until the next study visit (Day 7). The participant should not take the product the morning of the next visit. The designated maximum dose until the next visit on day 7, is 3 doses.

Visit 3 – Follow-Up – Day 7 ± 1

These assessments may not be completed in the order shown below.
Participants:

1. Must be at least 8 hours fasting (no food, only water) prior to visit.
2. Will have any changes to health reviewed by delegated study staff.
3. Study diary will be collected and/or reviewed by delegated study staff for completion, and any AEs and/or concomitant medications.
4. For females of childbearing potential, a urine sample will be collected for a urine pregnancy test.

5. Will have the following measurements taken: temperature, blood pressure, heart rate.
6. Will have the following saliva test:
    - Amplicon Metagenomics Sequencing
7. Will complete the following assessments:
    - Total nasal symptoms score (TNSS) questionnaire
    - Peak nasal inspiratory flow (PNIF) measurement
8. Will have the following blood tests:
    - CBC (WBC, RBC, Hb, HCT, MCV, MCH, MCHC, Platelet Count)
    - Aspartate aminotransferase (AST)
    - Alanine aminotransferase (ALT)
    - Bilirubin
    - Gamma-glutamyl transferase (GGT)
    - Alkaline phosphatase (ALP)
    - Serum creatinine
    - Potassium
    - Chloride
    - Sodium
    - IgE (total)
9. Be reminded to complete daily diary.
10. Review of all information for the visit by the PI and/or delegate prior to the next study visit to determine continued safe participation.

After completion of treatment dose, the participants are allowed for extra 4 maintenance doses, at a maximum frequency of once every other day (on day 7, 9, 11, and 13). Participant will not take the product on day 14 and onwards, and must return all remaining product at visit 4. Between day 7 and day 13, the participants may take AllerPops with any recurrence of nasal allergy symptoms or until the participant is satisfied with the relief of the nasal allergy symptoms, as long as the minimal interval of alternate day dosing is not violated. The participant will continue to fill out a daily diary to indicate the time of dosing, symptoms, AEs (such as fatigue, fever or headache), and concomitant medications, if applicable.

Visit 4 – Follow-Up – Day 14 ± 2

These assessments may not be completed in the order shown below.
Participants:

1. Do not need to fast prior to this visit.
2. Will have any changes to health reviewed by delegated study staff.
3. Study diary will be collected and/or reviewed by delegated study staff for completion, and any AEs and/or concomitant medications.
4. Will have the following measurements taken: temperature, blood pressure, heart rate.
5. Will complete the following assessments:
    - Total nasal symptoms score (TNSS) questionnaire
    - Peak nasal inspiratory flow (PNIF) measurement
6. Be reminded to complete daily diary.

The participant will continue to fill out a daily diary to indicate symptoms, AEs (such as fatigue, fever or headache), and concomitant medications, if applicable.

After this visit, the participant will not continue taking the IP. Any remaining IP will be collected from the participant at this visit.

Visit 5 – End of Study – Day 21 ± 2

These assessments may not be completed in the order shown below.
Participants:

1. Must be at least 8 hours fasting (no food, only water) prior to visit.
2. Will have any changes to health reviewed by delegated study staff.
3. Study diary will be collected and reviewed by delegated study staff for completion, and any AEs and/or concomitant medications.
4. For females of childbearing potential, a urine sample will be collected for a urine pregnancy test.
5. Will have the following measurements taken: temperature, blood pressure, heart rate.
6. Will have the following saliva test:
    - Amplicon Metagenomics Sequencing
7. Will complete the following assessments:
    - Total nasal symptoms score (TNSS) questionnaire
    - Peak nasal inspiratory flow (PNIF) measurement
8. Will have the following blood tests:
    - CBC (WBC, RBC, Hb, HCT, MCV, MCH, MCHC, Platelet Count)
    - Aspartate aminotransferase (AST)
    - Alanine aminotransferase (ALT)
    - Bilirubin
    - Gamma-glutamyl transferase (GGT)
    - Alkaline phosphatase (ALP)
    - Serum creatinine
    - Potassium
    - Chloride
    - Sodium
    - IgE (total)
9. Review of all information for the visit by the PI and/or delegate to determine further action, if necessary.

The results of the clinical chemistry will be assessed by the PI. The clinical chemistry parameters must be within the reference value ranges and/or deemed by the PI as not clinically significant. Otherwise, the participant will be contacted by the PI or delegated site staff to further assess and determine an appropriate course of action.

9. Clinical Assessments and Procedures

9.1. Height and Weight

Height and weight measurements will be performed as per the site's SOPs. Participants will be weighed on a calibrated scale at specified visits.

9.2. Biometric Measurements

Blood pressure, heart rate, and temperature will be measured at each visit. All measurements will be done according to the site's applicable SOP. Calibrated equipment will be used at every visit. Manual measurements may be taken for particular parameters where required by the PI and/or delegate.

9.3. Urine Sample Collection

A urine pregnancy test will be done for females of childbearing potential at Visit 1. If any pregnancies arise the participant will be screen-failed and therefore not be enrolled in the study.

9.4. Blood Sample Collection

Blood draws will be done for participants at all visits. Blood will be drawn by delegated site personnel from the antecubital site into the appropriate vacutainers as per the schedule of assessments, study visit details, and in accordance with the site's SOPs. The samples will be stored and/or sent for analysis as indicated in the Laboratory Manual. The total volume of blood to be collected (for safety parameters) from each participant over the course of the trial is 240 millilitres (approximately 16 tablespoons) and approximately 48 mL from each participant at each visit.

9.5. Questionnaires

- Total Nasal Symptoms Score (TNSS) Questionnaire: a method developed to assess allergic rhinitis symptoms, based on the administration of a questionnaire [33]. According to this method, allergic rhinitis symptoms are scored from 0 to 3 (4 grades of severity), and the differences between groups will be statistically assessed.

9.6. Peak Nasal Inspiratory Flow (PNIF) measurement

The assessment of allergic rhinitis [34] . Using this method (PNIF manual), the nasal volume and flow for assessing nasal airway patency will be measured.

9.7. Amplicon Metagenomics Sequencing Collection

This rRNA gene sequencing method would allow for the assessment of the effect of the treatment on the microbial diversity in saliva. Previous evidence has been given to suggest that allergic rhinitis may be associated with dysbiosis of the oral microbiota [16], [17], [18]. Changes in the parameters of microbiota will be analyzed.

9.8. Compliance

The participant will receive counselling and reminders pertaining to IP compliance and protocol requirements from delegated research site personnel.

Each participant will be required to complete a daily study diary to record the daily intake of the IP, concomitant medications, and record the occurrence of any adverse events. The participant will be required to return the IP to the research site for the IP compliance calculation using the following formula:

(%) as [(doses taken/doses intended) x 100]

In the event the IP is returned to the study site compliance outside of 80-120% will be treated as a protocol deviation.

This compliance calculation will only apply to Visit 3.

9.9. Laboratory Analysis

All laboratory samples will be collected, processed, and stored until shipment or destruction by delegated personnel.

9.9.1. Endpoint-Related Samples

The following endpoints will be collected for each visit during the trial life cycle:

- V1-screening: Vital signs (Body temperature, blood pressure, and heart rate) will be measured and Blood Clinical Chemistry samples will be collected. Total Nasal Symptoms Score (TNSS) will be administered. A physical examination will be completed.
- V2-Baseline (D1): Total Nasal Symptoms Score (TNSS), Peak Nasal Inspiratory Flow (PNIF) values, Saliva sample collection for Amplicon Metagenomics Sequencing test, Vital signs (Body temperature, blood pressure, and heart rate) will be measured and Blood Clinical Chemistry samples will be collected.
- V3- Follow up (D7): Total Nasal Symptoms Score (TNSS), Peak Nasal Inspiratory Flow (PNIF) values, Saliva sample collection for Amplicon Metagenomics Sequencing test, Vital signs (Body temperature, blood pressure, and heart rate) will be measured and Blood Clinical Chemistry samples will be collected.
- V4- Follow up: Total Nasal Symptoms Score (TNSS), Peak Nasal Inspiratory Flow (PNIF) values, and Vital signs (Body temperature, blood pressure, and heart rate) will be measured.
- V5- End of study (D21): Total Nasal Symptoms Score (TNSS), Peak Nasal Inspiratory Flow (PNIF) values, Saliva sample collection for Amplicon Metagenomics Sequencing test, Vital signs (Body temperature, blood pressure, and heart rate) will be measured and Blood Clinical Chemistry samples will be collected.

9.9.2. Clinical Chemistry

Clinical chemistry parameters will be analyzed by a local analytical laboratory. For each laboratory parameter, results will be assessed by the PI. All in-study out-of-range and clinically significant laboratory results will be identified on the lab report by the analytical laboratory and/or PI and documented as adverse events, as applicable.

9.10. Termination of the Trial

The trial may be terminated at any time by the Sponsor, PI, or applicable regulatory authority (Health Canada and/or IRB). If the trial is terminated prematurely, the PI, participants, and the regulatory authorities must all be notified of the termination promptly. Upon termination of the trial whether premature, or due to completion, site-closeout activities will be initiated including regulatory closeout to the appropriate authorities.

10. Safety Instructions and Guidance

10.1. Adverse Events

Definition:

An unexpected event (i.e., medical occurrence, sign, or symptom) that happens during the study period with an investigational product. Adverse event (AE) may be mild, moderate, or severe, and may be caused by something other than the drug or therapy being given. Adverse events must be followed-up to resolution or when the condition is deemed stable by the PI.

10.2. Collecting, Recording, and Reporting of AEs

Collection:

The PI of delegated study staff must record all adverse events in an AE form with information about:

- Details of adverse event
- Date of onset (time can be recorded, if applicable)
- Intensity (mild, moderate, severe)
- Causal relationship to trial involvement (probable, possible, unlikely, not related)
- Other actions taken
- Date and time of outcome
- Outcome

Reporting:

The following timelines apply to the reporting of AEs/SAEs as applicable:

- Within 24 hours of the PI becoming aware of the event if it results in death of a participant

- Within 2 weeks (10 business days) after becoming aware of the event if:
  - It is an AE which is related to the conduct of the study;
  - It is an AE that is expected (listed in the ICF as a potential side effect) but is occurring more frequently than expected;
  - It is an unexpected AE/SAE that is related to the conduct of the study but is not life-threatening
- Annually (together with the Study Status Report) if:
  - It is an expected AE (listed in the ICF as a potential side effect);
  - It is an unexpected AE that is unlikely to be related to the conduct of the study and is not life-threatening.

Severity Assessment

All clinical events will be graded as mild, moderate, or severe according to the following scale:

Mild - The adverse event does not interfere in a significant manner with the subject's normal functioning level.

Moderate -The adverse event produces some impairment of functioning but is not hazardous to the subject's health.

Severe -The adverse event produces significant impairment of functioning and may be potentially hazardous to the subject's health.

Causality Assessment:

Certain – An adverse event that cannot be explained by disease or any other drugs.

Probably/Likely – An adverse event that follows a known, expected or suspected response pattern of the drug and is unlikely to be explained by any other factors or another etiology.

Possible – An adverse event that follows a known, expected or suspected response pattern of the drug but could readily have been produced by a number of other factors or explained by another etiology.

Unlikely – An adverse event that does not follow a known, expected, or suspected response pattern of the drug and could readily have been produced by a number of other factors or explained by another etiology.

Conditional/Unclassified – An adverse event that requires more data for proper assessment or there is additional data under examination.

Un-assessable/Unclassifiable – An adverse event that cannot be judged because information is insufficient or contradictory.

10.3. Serious Adverse Events

Definition:

A Serious Adverse Event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization;
- Results in persistent or significant disability/incapacity or;
- Is a medical event that may jeopardize the patient/participant and may require medical or surgical intervention.

Reaction Reporting:

(1) During the course of a clinical trial, the sponsor shall notify the Minister of Health of any serious adverse reaction and any serious unexpected adverse reaction to the natural health product that has occurred inside Canada as follows:

(a) if it is neither fatal nor life threatening, within 15 days after the day on which the sponsor becomes aware of the information; and

(b) if it is fatal or life threatening, within seven days after the day on which the sponsor becomes aware of the information.

(2) The sponsor shall, within eight days after the day on which the Minister is notified under paragraph (1)(b), provide the Minister with a complete report in respect of that information that includes an assessment of the importance and implication of any findings made.

10.4. Laboratory Test Abnormalities

Occurrences of adverse events (serious and non-serious) will be assessed by the PI and/or delegate. For this purpose, a blood sample will be collected along with a clinical examination (to measure and assess vital signs), an interview of the participant for changes in health or concomitant medications, and a review of the participant's daily diary will be carried out to assess the occurrence of adverse events.

10.5. Treatment and Follow-Up of Laboratory Abnormalities

All events will be treated in accordance with GCP to resolution or until stabilized as deemed by the PI and/or delegate

11. Statistical Evaluation

11.1. Determination of Sample Size

Seventy-two participants will be participating in the study. The sample size was chosen based on the G*Power calculator in order to detect an effect of 0.6 (Medium effect size) considering 80% power in t tests. Parametric statistical techniques including, but not limited to t tests -

Means: Difference between two independent means (two groups) will be performed on data sets which meet all requirements for normality and variance. The application of non-parametric techniques might be used for relevant data sets. Should any of the statistical methods proposed prove unsuitable during the final analysis, more appropriate methods will be used, and any changes will be documented in the clinical study report, including the rationale for use. These include the transformation of the data (for example to a logarithmic scale) in order to satisfy model assumptions, if applicable. A p-value of < 0.05 will indicate statistical significance for all tests. An exploratory data analysis (EDA) will be performed for the exploratory study part to analyze and investigate data sets and summarize the main characteristics, employing data visualization methods.

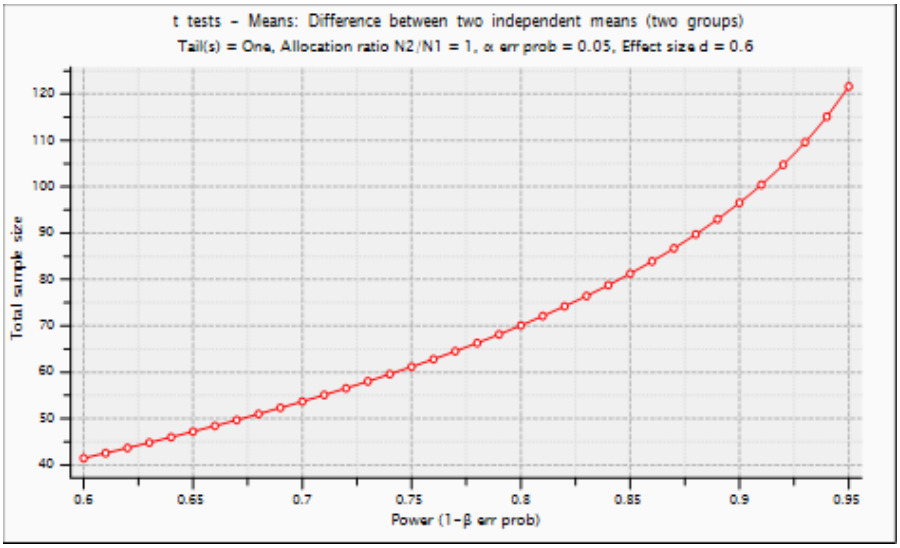


Figure 1:Analysis: A priori: Compute required sample size.

11.2. Study Population

Intention-to-treat (ITT) analysis will be considered in this study. ITT analysis includes every subject who is randomized according to randomized treatment assignment. The ITT analysis includes all randomized patients in the groups to which they were randomly assigned, regardless of their adherence with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol. ITT analysis reflects the practical clinical scenario because it admits noncompliance and protocol deviations. ITT analysis maintains prognostic balance generated from the original random treatment allocation and it gives an unbiased estimate of treatment effect.

11.3. Analysis Plan

11.3.1. Primary Variables

- The Total Nasal Symptoms Score (TNSS) change from the screening (V1), baseline by comparing D1(V2) and D7(V3) for each group and the differences between groups (investigational and control) will be statistically assessed.
- Peak Nasal Inspiratory Flow (PNIF) values change from the baseline by comparing D1 and D7 for each group and the differences between groups (investigational and control) will be statistically assessed.

11.3.2. Secondary Variables

1. Safety of the AllerPops product during a 21-day intervention period. Safety will be assessed by collecting vital signs, the emergence of adverse events, clinical chemistry (CBC and a comprehensive safety panel) and PI assessment.
2. The change of nasal symptoms will be measured based on the following variables during a 21-day intervention period:
    - The Total Nasal Symptoms Score (TNSS) score change will be assessed by comparing control group and investigational group.
    - Peak Nasal Inspiratory Flow (PNIF) values change will be assessed by comparing control group and investigational group.
3. Amplicon Metagenomics Sequencing values change during a 21-day intervention period will be assessed by comparing control group and investigational group.
4. IgE (total) blood level change during a 21-day intervention period will be assessed by comparing control group and investigational group.

11.3.3. Data Analysis

A descriptive statistics study will be performed for the primary variables. Continuous variables will be presented with the average and standard deviation or median range, as appropriate, and categorical variables will be presented as proportions. Parametric or non-parametric independent or related samples tests will be used, according to whether the distribution of the data in each variable is normal or not. A p-value < 0.05 is considered statistically significant. An EDA will be performed for the secondary variables (except safety) to analyze and investigate data sets and summarize their main characteristics, employing data visualization methods.

11.3.4. Safety Analysis

The safety evaluation will include assessment of AEs, vital signs, clinical laboratory safety tests, and physical examination findings.

For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges, if applicable. Frequencies and percentages will be presented by

gender and BMI group for participants who had a shift to low and for participants who had a shift to high from baseline to any post-dosing assessment, if applicable.

The number and percentage of participants with normal and abnormal physical examination results will be presented for evaluations at baseline, each indicated visit and final visit, if applicable. Individual and summary clinical laboratory data will be presented in tabular form with mean, median, standard deviation, and range (minimum and maximum) as appropriate.

12. Protocol Deviations

Protocol Deviation (PD) forms must be filed for any deviation from this protocol. PDs which place participants at increased risk of harm, or affect data integrity may be considered Protocol Violations (PVs) and must be reported to the appropriate regulatory authorities no later than 2 weeks (10 business days) from the time of identification. PDs will be filed in the applicable participant chart, and in the Trial Master File upon study closeout. PDs will be filed and signed by delegated study staff and reviewed and signed by the PI. The PI will determine if the PD is reportable to the IRB based on an assessment of the participant's safety and/or the effects on the integrity of the study data.

13. Protocol Amendments

Any changes to the protocol must be tracked and documented in the form of an amendment after it has been reviewed by the appropriate regulatory bodies. The reasons for change must be documented in writing and provided to the regulatory bodies and included in the Trial Master File (TMF). These changes will be subject to regulatory approval prior to implementation. All amendments will be documented in the study report.

14. Data Collection and Storage

The PI and/or delegated site staff agree to maintain accurate CRFs and source documentation. Source documents are the originals of any documents which will be used by the site that allow verification of the existence of the participant and substantiate the integrity of the data collected during the trial.

dicentra will supply either paper or electronic CRFs for each participant. CRFs will be completed only by persons delegated by the PI. Corrections will be made so as not to obliterate original data and will be identified and dated by the person who made the correction. The PI will allow designated representatives and regulatory bodies to have direct access to the source documents to verify the data reported in the CRFs.

All study records will be retained by the site for a period of 25 years after study completion.

An independent, third-party clinical trial management system (CTMS) software vendor may be used at the site for laboratory report data and participant-associated document storage. All activities and actions performed on the vendor platform will be tracked and will product an electronic audit-trial in accordance to regulatory standards.

Paper documents will be used in the event that the CTMS system is not used due to any unforeseen or incidental circumstance causing disruption to data collection. All paper documentation will be subject to ICH-GCP E6(R2) and applicable guidelines.

All site-specific documentation generation and management, including documents shared with the Sponsor prior to the start of the study follow internal SOPs for version control and approval for implementation. All procedural SOPs, reports and source documents that will be shared with the Sponsor during and after the study, including those that require changes during the course of the study, will be reviewed and approved by the appropriate site staff in accordance with site approval processes and SOPs.

15. Ethical Considerations

15.1. IRB Approval

All necessary forms, advertisements, and subject-facing study documents will be compiled into a submission to an Institutional Review Board (IRB) for approval prior to the conduct of the study. No conduct of the trial will commence until written approval has been obtained from the IRB. dicentra must adhere to the requirements of the IRB and notify them of any study document changes, protocol amendments, and reportable protocol deviations/violations. Study termination must be reported to the IRB, and renewal of study approval must be obtained annually (or as per IRB's stipulations).

15.2. Informed Consent Form

Informed consent will be obtained from participants by delegated study staff. The staff will explain the study and review each page of the consent document. Participants will then be asked to review the consent document, initial each page, and sign the appropriate section(s). The Informed Consent Form (ICF) will contain pertinent study details, a statement indicating the participant is free to withdraw from the study at any point and for any reason, contact information of the IRB (to report ethical concerns), local and applicable regulations surrounding disclosure of personal and health information of the participants, compensation information, and a section explaining the potential risk(s) of participating in the study.

15.3. Risks and Procedures to Minimize Risk

Potential risks are disclosed to the study participants in the ICF prior to their participation in the study. The potential risks associated with the study include venipuncture and associated risks. The risks of venipuncture (at the site) include:

- Pain
- Bruising
- Infection

All venipuncture will be performed by certified phlebotomists and all applicable procedures will be carried out to minimize risk of infection.

The major active ingredient in the product, L-Arginine (402.81mg per dosage unit), does not affect endocrine, hepatic or renal function and can be safely used in adults. However, the individual with or at risk or cancer are excluded due to possible increased risk of adverse event occurrence.

The potential risks associated with the study product include development of low-grade fever, feeling tiredness or low-energy, and mild headache. Emergence of adverse events will be assessed at each visit.

16. Quality Assurance and Quality Control

16.1. Auditing

All material used in this clinical trial will be subject to quality control. This study will be conducted in accordance with ICH-GCP E6(R2) and all applicable Regulations and local laws. Quality assurance audits may be performed by the Sponsor or any health authority during the course of the study or after its completion.

The PI and site agree to comply with the Sponsor and regulatory requirements for auditing the study. This includes access to the source documents for source data verification.

16.2. Monitoring

Prior to the start of the study, the Sponsor representatives, site personnel, and any third-party vendor representatives will hold at least one meeting to go over the details of the study design and plans for study execution. During the study, the Sponsor may arrange the visit of appointed site monitors to ensure that the execution of the study plan by the site meets the Sponsor's expectations and follows the study protocol objective. The site's delegated staff will monitor the conduct of the study and documentation throughout the course of the trial.

16.3. Data Management

16.3.1. Source Data and Source Documents

As defined by the International Conference on Harmonization (ICH), source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

All source data and source documents will be stored and archived according to local regulatory requirements. For this study, source data and documents include, but are not limited to:

- Signed and dated Informed Consent Form (ICF);
- Name, gender, date of birth and other personal information/demographic information;
- Participant ID;
- Date and time of each visit;

- All clinical measurements and laboratory results;
- Status of participant throughout the study;
- Paper-based or electronic daily diary (to record any concomitant medications, pre-emergent adverse events, changes in health, dosing time, and adverse events);
- Reason for discontinuation/withdrawal, if applicable.

16.3.2. Case Report Forms (CRFs)

Case report forms will be created following protocol finalization and approval to capture study data. These forms may be in the form of paper, or may be electronic (e-CRFs). An eCRF system, provided by an independent third-party vendor, may be used to capture data. Prior to deployment of the study, the eCRF system will be validated and specified to address source documentation, in accordance with Sponsor and regulatory requirements.

16.3.3. Data Storage and Access

In case of eCRF, data will be entered into the CTMS system, checked for discrepancies and queried for any issues in accordance to site-approved SOPs. The database housing the eCRF input will be hosted by the eCRF vendor and paper CRFs will be used as the backup plan, if deemed necessary and applicable. Official corrections and/or modifications during the trial will be automatically tracked by an audit trail detailing the date, time, and personnel involved/approving the modification of the eCRF. All vendor data access and entry can only be performed by authorized users, using a unique user login and password. The Sponsor and dicentra will permit trial-related monitoring, audits, IRB review, and regulatory inspections, providing direct (read-only) access to source data/documents. Paper CRFs will be monitored for completion, queried through internal review by delegated site staff, identified items resolved and documented where applicable, and any required data from source documents will be entered into the final database prior to locking.

16.4. Data Quality Assurance

Data cleaning will be performed to check for completeness and consistency of data using both programmed and manual edit checks. Discrepancies in data will be resolved through querying, delegation and resolution in accordance to site SOPs. Actions changing original data collection will be recorded using an electronic audit trail or done manually for paper CRFs according to ICH-GCP E6(R2).

16.5. Confidentiality of Participant Data

The PI and/or delegated site staff will ensure that the confidentiality of the participant's data will be preserved to the extent permitted by law. In any documents collected after enrollment into the study, the participants will only be identified by their participant ID; the ID consists of the participant's initials and an assigned number related to the sequence of received ICFs for the study. Documents that house participant information, such as signed ICFs and personal information/demographic forms will be maintained and store by delegated site staff under strict access.

17. References

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Appendix 1: Questionnaires TNSS Questionnaire

21-AAHSE-01 – SSH Corp.

Visit #:

Participant ID: __ __ __ - __ __ __ (ABC ###) Date of Visit: __ __ __/__ __/__ __ __ __ (MMM DD YYYY)

Total Nasal Symptom Score

Please answer all questions to the best of your ability. This information will assist us in understanding and treating symptoms.

Please rate the following rhinitis symptom for the last week:

1. Nasal obstruction

No Symptoms	0
Mild – awareness but not troubled	1
Moderate – troublesome but not interfering with normal daily activities or sleep	2
Severe – interfering with normal daily activities or sleep	3

2. Itching/Sneezing

No Symptoms	0
Mild – awareness but not troubled	1
Moderate – troublesome but not interfering with normal daily activities or sleep	2
Severe – interfering with normal daily activities or sleep	3

3. Secretion/runny nose

No Symptoms	0
Mild – awareness but not troubled	1
Moderate – troublesome but not interfering with normal daily activities or sleep	2
Severe – interfering with normal daily activities or sleep	3

Total Score: _____
9