4. STUDY SUMMARY

Study Title	A Pivotal, Randomized, Open-Label, 3-Period Crossover Study to Assess the Efficacy and Safety of AM-301 during House Dust Mite Challenge in an Environmental Exposure Chamber in Study participants with Perennial Allergic Rhinitis
Protocol Number	Sponsor Study Number: AM-301-CL-21-02 Cliantha Research Study Number: C2D01121
Study Phase	Pivotal Confirmatory Clinical Investigation
Study Objectives	**Primary Objective** To compare the efficacy of AM-301 Device between treated and non-treated subjects in the treatment of perennial allergic rhinitis (PAR) when evaluated in House Dust Mite (HDM) allergic study participants in an Environmental Exposure Chamber (EEC). **Secondary Objective** To compare the efficacy of AM-301 device between single and double applications per nostril of Altamira AM-301 Device in the treatment of perennial allergic rhinitis (PAR) when evaluated in House Dust Mite (HDM) allergic study participants in an Environmental Exposure Chamber (EEC).
Study Endpoints	**Primary Efficacy Endpoint:** Changes from baseline in TNSS at each post-dose assessment time points (0 to 3 hours) at Visit 3, Visit 4 and Visit 5 **Secondary Efficacy Endpoints:** • Difference of TNSS at individual timepoints during house dust mite challenge in the EEC (0-180 min) between single and double application of AM-301 and no treatment. • Change from baseline in individual NSS at Visit 3, Visit 4 and Visit 5 • Patient reported Global rating for efficacy at single application and double application of AM-301 during EEC treatment visits. • Investigator reported Global rating for efficacy for single and double application of AM-301 during EEC treatment visits. **Safety endpoints:** • Occurrence and severity of Adverse Events (AEs) and Serious Adverse Events (SAEs). • Patient reported Global rating for tolerability at single application and double application of AM-301 during EEC treatment visits. Investigator reported Global rating for tolerability for single and double application of AM-301 during EEC treatment visits.
Study Design	Randomized, open label, 3-Period crossover trial. The clinical trial will consist of 5 visits, followed by a follow-up telephone call. The total period of the trial will be approximately 65 days. The 5 visits will be as follows: • Visit 1- Screening visit • Visit 2- EEC Screening Visit • Visit 3- Treatment Visit

	• Visit 4- Treatment Visit • Visit 5- Treatment Visit • Follow-up telephone call
Study Products and Study Sequence	Study Product: AM-301 Nasal Spray Treatment groups will be as follows: A: One Spray of AM-301 per nostril B: Two Sprays of AM-301 per nostril (with different spray angles) C: No treatment The study will consist of 6 study sequences: • Sequence 1 (n = 6): ABC • Sequence 2 (n = 6): BCA • Sequence 3 (n = 6): CAB • Sequence 4 (n = 6): ACB • Sequence 5 (n = 6): BAC • Sequence 6 (n = 6): CBA
Study population	Approximately 36 males and non-pregnant females, 18-65 years of age inclusive, with a History of Perennial Allergic Rhinitis (PAR) due to house dust mites.
Route of Administration	Intranasal
Confinement	Study participants will remain confined to the clinic for approximately 4-5 hours during each screening and treatment EEC visits.
Study Conduct	The clinical trial will consist of 5 clinic visits; (1 medical screening, 1 EEC screening visit 3 EEC treatment visits). **Medical Screening Visit 1 (Day-28 to -1)** At Visit 1, eligible study participants will first sign the informed consent document, complete all screening procedures, including inclusion and exclusion criteria and safety labs, and move on to Visit 2 if eligible for EEC screening. **EEC Screening Visit 2 (Day 1)** At Visit 2, eligible study participants will have a nasal exam performed by the Investigator. Study participants will then enter the EEC for a total of 3 hours. Study participants will record their symptoms every 20 ± 5 minutes throughout the 3-hour EEC session. **Treatment Visit 3 (Day 8 + 2), Visit 4 (Day 15 + 2) and Visit 5 (Day 22+ 2)** Eligible study participants will return for Visit 3 after at least 7 days after visit 2. Study Participants will be randomized at Visit 3. Subsequently study participants will return to the clinic for Visit 4 at least 7 days after Visit 3 and for Visit 5 at least 7 days after Visit 4. Treatment will occur on site performed by trained clinical staff. Study participants will enter the EEC on these visits following administration, but no later than 10 minutes after

	treatment administration and will record their symptoms every 20 minutes throughout the 3-hour EEC session. Following the assessments at Visit 5, this will conclude the study. AE's will also be recorded throughout each visit . **Follow-Up Telephone Call** Follow-up Telephone call will be done after approximately 7 + 2 days of completion of Visit 5. The following assessment will be conducted: • Subjects will be asked for any occurrence of adverse events after last treatment administration. • Subjects will be asked if they have taken any concomitant medications since last treatment administration.
Inclusion Criteria	1. Study participants must be willing and able to give their signed and dated written informed consent to participate in the study prior to commencing any study-related activities 2. Male and female study participants aged 18-65 years at the time of Informed consent and medical screening will be included in the study. Women will be considered for inclusion if they are • Not pregnant, as confirmed by pregnancy test at visit 1, not nursing and not planning to become pregnant over the duration of the study. • Of non-child bearing potential (i.e. physiologically incapable of becoming pregnant, including any female who is post-menopausal, surgically sterile with documented proof of hysterectomy or tubal ligation or bilateral oophorectomy or meets clinical criteria for menopause and has been amenorrhoeic for more than 1 year prior to the screening visit). • WOCBP must use effective methods of birth control starting at least 1 month prior to the Screening Visit 1 and until 72 hours after the last study procedure, such as total abstinence, hormonal or non-hormonal intrauterine device, a double-barrier method (Condom and diaphragm/cervical with spermicide (foam, cream, gel, sponge)), oral, transdermal, injected or implanted hormonal contraceptive. A sterile sexual partner is not considered an adequate form of birth control. 3. Body mass index between 18.0 and 32.0 kg/m^2 inclusive. 4. History of perennial allergic rhinitis to house dust mite for more than 1 year. 5. Positive Skin Prick Test (SPT) for Dermatophagoides pteronyssinus (*der p*) allergen at screening or within 12 months prior to the screening visit. Test will not be repeated if they have been performed at Cliantha Research in previous 12 months. 6. Spirometry will be performed at Screening. Study participants must have an acceptable spirometry assessment showing FEV1 that is ≥80% of the predicted GLI-2012 value and a Tiffeneau ratio (FEV1/FVC ratio [FEV1%]) of ≥0.7 performed as per American Thoracic Society (ATS) standards to be eligible for the study. 7. Adequate level of rhinitis symptoms in a house dust mite challenge, defined as a change in TNSS of at least 4 units over pre-EEC TNSS on at least two time points within the 3-hour screening house dust mite challenge (Visit 2).

	8. Total Nasal Symptom Score (TNSS) of ≤ 4 prior to entering the house dust mite chamber at screening EEC Visit 2. 9. Smokers need to be able to refrain from smoking six hours before the allergen challenge during all EEC visits 10. Agree to abide by the study restrictions and return for the required assessments and must be willing to comply with study procedures and study protocol.
Exclusion Criteria	1. Any clinically relevant abnormal findings in physical examination, clinical chemistry, hematology, urinalysis, vital signs, lung function at screening visit, which, in the opinion of the investigator, may either put the subject at risk because of participation in the study or may influence the results of the study, or the subject's ability to participate in the study. 2. Use of any medication considered to have an influence on the outcome of the study during the EEC session, at the discretion of the Investigator and/or designee. 3. Recent nasal ulcers, mucosal erosion, nasal surgery, or nasal trauma, that might interfere with study results as determined by the Investigator and/or designee. 4. Past or present concomitant medical conditions, which as judged by the investigator, may affect the outcome of this study. These diseases include, but are not limited to, cardiovascular disease, malignancy, hepatic disease, renal disease, hematological disease, neurological disease, endocrine disease or pulmonary disease (including but not confined to chronic bronchitis, emphysema, tuberculosis, bronchiectasis or cystic fibrosis). 5. Allergen-specific Immunotherapy (SIT) within 2 years prior to the study. 6. Any upper respiratory tract infection (including rhinitis and sinusitis) in the last 14 days before entering the study Visit 1. 7. Asthmatics will be excluded from the study. 8. Conditions or factors, which would make the subject unlikely to be able to stay in the EEC for 3 hours. 9. Any medical condition or concomitant medication that makes the use of adrenalin less effective (e.g. use of local and systemic beta-blockers, ACE inhibitors). 10. Known sensitivity to the constituents of AM-301 like Propylene glycol or Mannitol. 11. Treatment with antipsychotic medications with antihistaminic effect (e.g. chlorpromazine, levomepromazine, clozapine, olanzapine, tioridazine). 12. Participation in another clinical trial 30 days prior to enrollment. 13. History of drug or alcohol abuse within the last two years. 14. Risk of non-compliance with study procedures. 15. Suspected inability to understand the protocol requirements, instructions and study-related restrictions, the nature, scope, and possible consequences of the study. 16. History of an acute infection four weeks prior to Visit 1. 17. Study participants with severe septum deviation or other structural nasal abnormalities that prevent the intranasal administration of a medical device.

	18. Subject has a positive result for SARS-CoV-2 and/ or has clinical signs and symptoms consistent with COVID-19 infection, e.g., fever, dry cough, dyspnea, sore throat, fatigue, muscle or body aches and gastrointestinal symptoms or confirmed infection by appropriate SARS-CoV-2PCR test within the 2 weeks prior to visit 1. 19. Study participants who have taken COVID-19 Vaccine 3 days or less prior to a visit. 20. Study participants that have a relationship dependency with the Sponsor or study site staff.
Statistical Analysis	For applicable endpoints, the treatment comparison between treated and non-treated will be performed using a mixed-effects Analysis of Covariance Model (ANCOVA) for a crossover study for 3 periods. The model will include Treatment, Period (Visit) and Sequence as fixed effects, baseline (pre-dose) measurement as a covariate. Subject nested within treatment sequence will be fitted as a random effect. LS means and SEs by treatment arm will be extracted from the model and presented. Further, contrasts between LS means will be extracted for (i) (1-spray+2-sprays)/2 vs no treatment (ii) 1-spray vs no treatment and (iii) 2-sprays vs no treatment. The 95% CI and 2-sided p-values will be provided for each of these contrasts. Appropriate statistical analysis will be performed to analyze the global rating scales for efficacy and tolerability. Safety Population: All study participants who are randomized will be included in the Safety population. Intent to Treat (ITT) Population: All study participants in the Safety Population who provide at least one TNSS assessment will be included in ITT population. Per Protocol (PP) Population: PP Population will include all study participants in ITT who completed the study and do not have any major protocol violations. The analyses of all efficacy endpoints will be carried out using the ITT population. Supportive analyses will also be provided for the primary endpoint using the PP population.
Safety Analysis	Safety analysis will include descriptive analysis and listings according to received treatment.
Sample Size Determination	It is hypothesized that the Total Nasal Symptom Score (TNSS) over 180 min post treatment with no treatment is 2.3 units as compared to 1.0 and 1.6 units for, respectively, 2-sprays and 1-spray of AM-301. Assuming the SD of the within subject change is 2 units, N=30 randomized subjects will provide 87.4% power at the 2-sided 5% alpha level to test the hypothesis that the TNSS score averaged across 1-spray and 2-sprays is superior to no treatment. Sufficient numbers of volunteers will be screened to randomize approximately 36 study participants to have 30 completed study participants.