1. TITLE PAGE

CLINICAL STUDY REPORT

A Randomized, Double-Blind, Multi-Center Study to Evaluate the Efficacy and Safety of Ethyl Lauroyl Arginate Hydrochloride (LAEH) Formulation Versus a Matching Placebo Formulation Administered as a Nasal Spray to Reduce Viral Load From Nasal Area of Subjects with Coronavirus Disease 2019 (COVID-19)

Investigational Product	:	Covixyl-V LAEH® (Ethyl lauroyl arginate hydrochloride, 0.1% concentration)
Indication	:	Coronavirus Disease 2019
Study Design	:	Double-Blind, Placebo Controlled, Multi-Center, Randomized Study
Name of the Sponsor	:	Salvacion USA Inc., 210 Sylvan Avenue Suite 24 Englewood Cliffs, NJ, 07632, USA
Protocol Identification Number	:	SLV-CV19-SPRAY
Protocol Version	:	Version 1.1 (Amendment 1), dated 28 September 2021
Development Phase of the Study	:	Phase I
Study Initiation Date	:	29 May 2021
Study Completion Date	:	04 Oct 2021
Principal Investigator	:	(1) Dr. Altagracia Adalgiza Victoria, MD; 2300 W 84 St Suite 303, Hialeah, FL 33016 USA (2) Dr. Jorge P. Amaya, MD; 8485 Bird Road, Suite 303, Miami FL 33155
Name of the Sponsor Signatory	:	Dr. Abdul Gaffar, MD
Date of the report	:	Will be mentioned once report is final

This study was conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements including the archiving of essential documents.

Confidential Information

2. SYNOPSIS

Name of Sponsor: Salvacion USA Inc.	
Name of the Finished Product: Covixyl-V (Ethyl lauroyl arginate hydrochloride [LAEH], 0.1% concentration)	
Name of the Active Ingredient: Ethyl lauroyl arginate hydrochloride (0.1% concentration)	
Title of Study: A Randomized, Double-Blind, Multi-Center Study to Evaluate the Efficacy and Safety of Ethyl Lauroyl Arginate Hydrochloride (LAEH) Formulation Versus a Matching Placebo Formulation Administered as a Nasal Spray to Reduce Viral Load From Nasal Area of Subjects with Coronavirus Disease 2019 (COVID-19).	
Investigators: (1) Dr. Altagracia Adalgiza Victoria, MD; 2300 W 84 St Suite 303, Hialeah, FL 33016 USA (2) Dr. Jorge P. Amaya, MD; 8485 Bird Road, Suite 303, Miami FL 33155.	
Study centers: 2	
Study period: 8 months **Date of first enrolment:** 02 Aug 2021 **Date of last completion:** 04 Oct 2021	**Phase of Development:** Phase I
Objectives: Primary: To evaluate efficacy of LAEH nasal spray on SAR-COVID-2 viral load in nasal areas. Secondary:	

1. To evaluate the efficacy of LAEH on the viral load in terms of proportion of COVID-19 infection free subjects between the two arms.

2. To evaluate the safety of LAEH versus a matching placebo administered as a nasal spray.

Methodology:

This was a multi-center, randomized, double-blind, placebo-controlled clinical study carried out to evaluate and compare the safety and efficacy of Ethyl Lauroyl Arginate Hydrochloride (LAEH) nasal spray against a matching placebo nasal spray, administered to reduce viral load from the nasal area of subjects with Coronavirus Disease 2019.

Subjects were enrolled after obtaining written informed consent and were screened for eligibility for the study based on inclusion/exclusion criteria. Subjects were screened with the help of Reverse transcription polymerase chain reaction (RT-PCR) test for confirmation of COVID-19. Only those Subjects who had laboratory-confirmed diagnosis of COVID-19 at the time of screening (Day -3 to 0) using RT-PCR method and who met all eligibility criteria were enrolled. Along with viral load values from RT-PCR test, cycle threshold (CT) value was also included in the laboratory reports.

Thirty (30) subjects with Coronavirus Disease 2019 were randomized into this study with LAEH nasal spray and placebo nasal spray. Subjects were randomized in a 1:1 fashion to either receive twice daily LAEH formulation or matching placebo.

Subjects were instructed to use the assigned treatment through nasal spray (2 to 3 puffs in each nostril at a time) twice a day from Day 1 to Day 5 and only once in the morning on Day 6. Prior to use of nasal spray, subjects were instructed to refrain from eating, drinking, or using any nasal gavage at least 30 minutes. It was informed to the subjects that the daily second treatment should be taken approximately 6 hours apart from the first treatment. The site personnel explained the effective use of the nasal spray in a step-by-step manner and documented the same training in the source documents. The subjects were instructed to record his/her initials and date and time he/she administered the assigned treatment on a daily basis in the subject diary. On Day 6/end of study (EOS), all the subjects took the first treatment (11^{th} dose) at home around 8:00 am and then visited their respective site as instructed. Then the site performed the viral load enumeration

using RT PCR test (including CT value) within 3 and 6 hours post last dose (at end of 11th treatment).

Group A assessed about 15 subjects with COVID-19 who received LAEH nasal spray for 6 days.

Group B assessed about 15 subjects with COVID-19 who received placebo nasal spray for 6 days.

The site called each subject daily and collected information on Adverse events (AEs) (if any), concomitant medications, and treatment compliance and completion of subject diary. Adverse events (AEs) were collected after signing of informed consent till end of study.

The frequency of assessment was at screening/baseline and on Day 6.

Reverse transcription polymerase chain reaction (RT-PCR) testing was performed for confirmation of positive COVID-19 test, and enumerating viral load (including CT value). Vital signs such as Blood Pressure (BP), Heart Rate (HR), Respiratory Rate (RR), Oxygen Saturation (SpO2), body temperature was noted and nasal and physical examination was performed.

Safety and tolerability of LAEH nasal spray were assessed by evaluating of AEs, SAEs, vital signs, discontinuation due to AEs, laboratory testing and nasal and physical examinations.

Number of Subjects (Planned and Analyzed):

Total 30 subjects were enrolled in the study as planned. Total 30 subjects were analyzed in the study at 2 sites across United States (US).

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

A subject was included in the study when he/she met below inclusion criteria:

1. Ability to provide written informed consent or, by his or her legal/authorized representatives when the subject is not capable of giving consent, prior to initiation of any study procedures
2. Male or female of ≥18 years and ≤65 years of age (inclusive) at time of enrollment
3. Subjects with laboratory-confirmed diagnosis of COVID-19 at the time of screening (Day -3 to 0) using RT PCR method.

4. Subject with mild COVID-19 symptoms (e.g., fever, cough, sore throat, headache, muscle pain, nasal congestion, rhinorrhea, loss of smell and taste) but who did not have shortness of breath or dyspnea
5. Subjects who did not require hospitalization
6. Subjects with SpO2 levels ≥ 95%
7. Viral load by RT-PCR between 3.3 × 106 copies/mL to 6.6 × 106 copies/mL
8. Female subject who was not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile
9. Female subject of childbearing potential who had negative urine pregnancy test.

Exclusion Criteria

Subjects were not included in the study when he/she met any of the below exclusion criteria

1. Allergy to LAEH or any of the excipients of the formulation
2. History of allergies or flu within 30 days prior to the day of enrollment
3. Sensitivity to nostril skin or irritation or bleeding history within 30 days prior to the day of enrollment
4. Females who were breast-feeding, lactating, pregnant or intending to become pregnant
5. COVID-19 subjects with moderate, severe or critical illness or requiring intensive care or mechanical ventilation
6. History of severe respiratory disease and requirement for long-term oxygen therapy
7. Had received antibiotic/s, antiviral drug, and hormonal drugs within 30 days prior to the day of enrollment
8. Any condition or disease detected during the medical interview/physical examination that would render the subject unsuitable for the study, place the subject at undue risk or interfere with the ability of the subject to complete the study in the opinion of the Investigator
9. Had received or had a plan to receive a SARS-CoV-2 vaccine during the study period
10. Participation in any interventional drug or medical device trials within 30 days prior to the day of enrollment.

Test Product, Dose and Mode of Administration, Batch Number:

Commented [KP1]: Kindly provide these details for test as well as reference therapy.

Covixyl-V (Nasal Spray) - Ethyl lauroyl arginate hydrochloride (0.1% concentration) formulation administered through nasal spray (2 to 3 puffs in each nostril at a time) twice a day for 6 days (On Day 6, only morning treatment was administered).

Other information: Store at room temperature. Keep away from direct sunlight and heat source.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Vehicle (matching placebo) formulation administered through nasal spray (2 to 3 puffs in each nostril at a time) twice a day for 6 days (On Day 6, only morning treatment was administered).

Other information: Store at room temperature. Keep away from direct sunlight and heat source.

Duration of Treatment:

The duration of the use of study product was 6 days. Subjects were instructed to administer treatment using nasal spray with the assigned formulation (LAEH or matching placebo) twice a day for 6 days (On Day 6, only morning treatment was administered).

Criteria for Evaluation:

Primary Efficacy Endpoint:

- Comparison of change in viral load from baseline between the two treatment arms

Secondary Efficacy Endpoint:

- Proportion of COVID-19 infection free subjects between the two treatment arms

Safety Endpoint (Secondary):

All safety endpoints were summarized and compared using descriptive statistics between two treatment arms.

- Number of subjects with AE
- Number of subjects with serious adverse event (SAE)
- Change in vital signs
- Change in nasal examination from baseline

Statistical Methods:

Statistical Analysis

The continuous data was summarized using the number of observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum value (min), and maximum value (max).

The number of observations (n) was presented with no decimal place, mean and median was presented up to one decimal place from the original value, SD up to two decimal places from the original value and (min, max) as an original value.

The categorical variables were summarized using the frequency count (n) and percentage (%) for each possible value. The frequencies were presented up to 0 decimal places, percentage up to 1 decimal place.

Analysis Data Sets:

The statistical analysis was performed using mITT (Modified Intent-to-treat), PP (Per protocol) and safety analysis population.

Modified Intent-to-Treat Analysis Population (mITT): All subjects who were randomized, took at least one dose of study medication, and had at least one post baseline evaluation.

Per Protocol population (PP): The PP population included all mITT subjects who remained in the study and had no major protocol violations and received at least 80% of the doses.

Safety Population: All randomized subjects who took at least one dose of study medication.

Analysis of Efficacy Endpoint

Primary Efficacy Endpoint Analysis

- Comparison of change in viral load in RT-PCR Test from baseline at Day 6 between the two treatment arms.

The viral load at Day 1 (Baseline), Day 6 within 3hrs post last dose and Day 6 within 6hrs post last dose was summarized using descriptive statistics by treatment group by mITT and PP population. Change from baseline was calculated from Day 6 within 3hrs post last dose and Day 6 within 6hrs post last dose and summarized using descriptive statistics by treatment group by mITT and PP population. Mean change in viral load was compared using Analysis of Covariance (ANCOVA) where Change from baseline (CFB) at Day 6 was considered as dependent variable, the treatments were considered as independent variable and baseline viral load as covariate, to find the statistically significant difference between the treatment for mITT population and PP population.

Secondary Efficacy Endpoint Analysis

- Proportion of COVID-19 infection free subjects between the two treatment arms.

Outcome of the RT-PCR test for viral load was presented as positive or negative values for each enrolled subject who was tested. Proportion of infection free subjects for which the result of the RT-PCR Test for viral load was negative was presented with frequency count (n) and percentage (%) by treatment group at baseline and Day 6 within 3hrs post last dose and Day 6 within 6hrs post last dose.

Chi square test for independence was used to find the statistical significance between the treatment groups at each visit for mITT as well as PP population.

Analysis of Safety Endpoints

Safety and tolerability of LAEH was assessed through a review and evaluation of AEs, SAEs, discontinuation due to AEs, laboratory testing, vital signs, nasal and physical examinations. Adverse events were coded according to MedDRA and grouped by preferred term (PT) and system organ class (SOC).

Subject counts (n) and percentages (%) were presented for all the subjects by treatment group in safety population and were sorted descending by total and then alphabetically. If a subject had more than one episode of an AE, subject was counted only once in specific system organ class (SOC) and once for each specific preferred term (PT).

Summarization for AEs by subjects is provided for following categories:

- All Adverse Events
- AE's By SOC And PT
- Serious AEs by SOC and PT
- Study Drug Related AEs by SOC and PT
- AEs leading to death by SOC and PT
- AEs leading to permanent discontinuation by SOC and PT
- AE's By SOC, PT And Severity
- Study Drug Related AEs by SOC and PT and Severity

Summary - Conclusions: (This section will be summarized when main CSR contents finalized)

Efficacy Results

XXXXX

Safety Results

XXXXX

Conclusion:

XXXXX

Date of Report

Date of the report will be mentioned once the report is final.

3. TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

No table of figures entries found.

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
	This section will be completed once report is final

5. ETHICS

5.1 Institutional Ethics Committee (IEC)

Prior approval of the Institutional Review Ethics Committee of the protocol, submission of any protocol amendments, consent process, the case report form (CRF), and all study-related documents were mandatory. Written informed consent was mandatory for each subject before participation in the study. Subject's participation was strictly voluntary. The Investigator had to notify the IEC of any serious deviations from the protocol, or anything, which might involve added risk to subjects.

5.2 Ethical Conduct of the Study

The Investigator ensured that the study was conducted in compliance with the principles of the fourth in guidelines of the World Medical Association Declaration of Helsinki, International Council for Harmonisation - Good Clinical Practice guidelines, and applicable regulatory requirement(s):

- Food and Drug Administration Regulations (21 CFR Parts 11, 50, 54, 56, 312, and 812).
- The Health Insurance Portability and Accountability Act as appropriate.

5.3 Subject Information and Informed consent

A written informed consent in compliance with regulatory authority regulations was obtained from each subject before entering the study or performing any unusual or non-routine procedure that involves risk to the subject. An informed consent form (ICF) was provided. If any study center-specific modifications to study-related procedures were proposed or made by the study center, the ICF was to be updated and reviewed before IEC submission. The consent document including forms were translated in regional languages, as per the languages stated by the Investigator and/or IEC. All the consent forms were submitted by the Investigator to IEC for review and approval before the start of the study. When the ICF was revised during the course of the study, all active participating subjects had to sign the revised ICF.

Before recruitment and enrolment, each prospective subject was provided explanation of the study and were allowed to read the ICF. Once the Investigator assured that the subject understood the

implications of participating in the study, the subject was asked to give consent to participate in the study by signing the ICF.

Where the subject and his/her legally acceptable representative (LAR) was unable to read/ write, an impartial witness was required who was present during the entire informed consent discussion had to sign the consent form.

Informed consent was obtained in accordance with US regulations (§ 21 CFR Part 50), Council for Harmonisation - Good Clinical Practice guidelines as well as country specific national regulations and/or local laws.

Further, it was understood that consent is a matter solely within the realm of Investigator subject relationship and not subject to the influence by the Sponsor or CRO.

Re-consenting Process

Re-consenting might require for various reasons including but not limited to cases:

- When significant new information obtained to light that affect the safety of the subjects and/or might have influenced the subject's original decision to take part.
- Where protocol amendments were required the ICF to be revised e.g., Changes in study procedures, entry criteria, subject numbers etc.
- If the sponsor had decided to modify the ICF.

The Investigator had to retain the signed original ICF(s) and handover a copy of the signed original form to the subject.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study was administered and monitored by a CRO (Global Clinical Trials Inc). The Medical Monitor was available to provide appropriate medical expertise on study-related medical questions. Global Clinical Trials Inc was responsible for the timely reporting of the SAEs.

6.1 Investigative Site(s)

Site	Principle Investigator Name	Site Name and Address
1	Dr. Altagracia Adalgiza Victoria, MD	2300 W 84 St Suite 303, Hialeah, FL 33016 USA
2	Dr. Jorge P. Amaya, MD	8485 Bird Road, Suite 303, Miami FL 33155

6.2 Study Dates

Study initiation date	29 May 2021
First subject first visit date	02 Aug 2021
Last subject last visit date	04 Oct 2021
Database lock date	17 Nov 2021
Final clinical study report date	Will be updated once report is final

6.3 Sponsor information

Salvacion USA Inc., 210 Sylvan Avenue Suite 24, Englewood Cliffs, NJ, 07632, USA.

6.4 Coordinating Investigator and Medical Monitor

Dr. Abdul Gaffar MD, [609.647.1088, agaffar@verizon.com].

6.5 Contract Research Organization

Global Clinical Trials, LLC, 256 Bunn Drive, Suite 6, Princeton, NJ 08540.

6.6 Study Statistician

Statiza Statistical Services, 209, South Bopal Trade Centre (SBTC), Near Aryan Gloria, Gala Gymkhana Road, South Bopal, Ahmedabad-380058, Gujarat, India.

Commented [KP2]: To Alina:
Kindly recheck if there is no medical Monitor for this study, as the protocol in section 8.2.1 mentions that "The Investigator should contact the Medical Monitor via phone immediately before unblinding a subject unless it is not possible to do so without risk to the subject."

According to a https://ccrps.org/clinical-research-blog/medical-monitor-responsibilities-in-a-clinical-trial website,
A medical monitor (MM) is a physician and spokesperson of a drug sponsor responsible for examining the safety aspects of a clinical trial. Medical monitors provide physician-level opinions for a company on multiple trials/sites whereas a physician principal investigator only conducts their site-specific trials. Medical monitors consult on protocol design, patient safety concerns, deciding if a specific adverse event requires unblinding, mediating between sponsor and trial sites (like CRAs), reviewing if a "adverse event" i.e. patient symptom is coded/reported properly, and much more. In the light of E6-GCP definition of medical monitoring, a medical monitor is a person responsible for supervising the process of clinical trial, ensuring that protocols, standard operating procedures SOP's, Good manufacturing practices (GCP) and regulatory requirements are according to the standard.
The alternative terminologies of a medical monitor are Clinical research associate(CRA) , site manager, Senior CRA and Clinical trial assistant (CTA) , in which CRA is most frequently used(Shah, 2012) .

Commented [AM3R2]: There was no MM delegated. We can indicate Dr. Gaffar as a Sponsor representative for any medical issues discussion. Your suggestions?

Commented [KP4R2]: I agree and added Dr. Gaffar's name and contact details from Protocol. However, please confirm whether Dr. Abdul Gaffar is a Medical Doctor.

6.7 Clinical Supply Management

Salvacion USA Inc., 210 Sylvan Avenue Suite 24, Englewood Cliffs, NJ, 07632, USA.

6.8 Central Laboratory

Not Applicable.

6.9 Clinical Study Report Writing

Innvocept Global Solutions Private Limited (IGSPL), B-7/1 Kothari Compound-27 Acres, Nr Tiku-ji-ni wadi Resort Chitalsar, Manapada, Thane (W) Mumbai - 400 607, Maharashtra, India.

Commented [KP5]: To Alina:
Kindly mention the name of the organization who is dealing with/managing the logistics of the study product to the clinical sites. If it is GCT, GCT name can be mentioned here.

Commented [AM6R5]: Need to confirm with R.Hwang

7. INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease (COVID-19) broke out in December 2019 and has quickly become a global pandemic with serious health and social consequences (Koopmans M, 2020). As of May 2, 2021, more than 151 million confirmed cases have been reported around the world and about close to one-fifth are from the U.S. Globally, more than 3,186,128 people have died due to COVID-19 and 570,537 in the U.S. alone (Johns Hopkins, 2021).

The virus can infect respiratory systems through entry in nasal area. While vaccines have been developed, means are required to arrest or reduce transmission of virus through nasal. Effective antiviral therapies, especially in the early stage of infection, are vitally important to halt viral proliferation long enough for the immune system to respond to the virus and limit cellular damage inflicted by viral invasion as well as to minimize genetic mutations caused by the high replication frequency of the virus, which might lead to therapeutic resistance.

N^{α}-Lauroyl-L-arginine ethyl ester monohydrochloride, hereinafter LAE (Lauric Arginate for labelling purposes under FDA approval), is a derivative of lauric acid, L-arginine and ethanol. The main characteristics of this molecule are a wide range of antimicrobial properties derived from its surfactant chemical structure that additionally yields certain tensioactive properties. The antimicrobial properties of LAE are due to its action on the cytoplasmic membranes of the microorganisms in such a manner that their metabolic processes are altered and their normal cycle is inhibited but without cellular lysis.

LAE shows chemical stability at pH range between 3 and 7 and maintains its antimicrobial activity in this interval; this offers a significant advantage compared to other products currently available in the market. LAE is hydrolyzed in the human body by chemical and metabolic pathways breaking the molecule into natural compounds common in human diet; this feature gives LAE a remarkable degree of safety. This non-toxicity is demonstrated by numerous toxicological studies carried out over the past years. On 1st September 2005, FDA issued the No Objection Letter regarding that LAE is Generally Recognized as Safe (GRAS) for use as antimicrobial in several food categories at levels up to 200 ppm. Besides, USDA approved its use in meat and poultry products.

In the human intestine and in the plasma, LAE is rapidly metabolized to N^{α}-lauroyl-Larginine (LAS) which is subsequently metabolized to arginine and finally to endogenous compounds. LAE does not produce mutagenic or clastogenic effects and concerning to the LAE effect onto the reproductive and developmental effects, the NOAEL was fixed at 15000 ppm for the reproductive performance and development of F1 and F2 (LMA-041, 2003 and LMA-042, 2004).

The lethal dose in both oral and dermal acute toxicity experiments is greater than 2000 mg/kg bw, the highest dose tested. Subchronic toxicity studies established a NOAEL of 15000 ppm (1143 and 1286 mg/kg bw/day for males and females, respectively) (LMA-031, 2000). The NOAEL fixed for chronic studies was 6000 ppm (307 and 393 mg/kg bw/day for males and females, respectively) (LMA-050). LAE and its hydrolysis products have been sufficiently characterized to assure that human consumption of LAE used as a preservative in foods and human exposure to LAE used as a preservative in cosmetics are safe.

In conclusion, the toxicological profile of lauric arginate looks favorable for its use as a preservative with no risk to consumer health.

Human metabolic studies of LAE were undertaken after the toxicity studies confirmed that the product is safe. The first human experiment was an in vitro study that was helpful to obtain information about the metabolism of LAE after ingestion including the potential points of degradation (intestines, liver and plasma) and it's pharmacokinetic (LMA, 2003). Under all three of the in vitro conditions tested, LAE was rapidly degraded to LAS and subsequently to arginine.

In a second human study, LAE was administered to six volunteers divided into two dose groups. All of the subjects were given clinical examination and samples of blood were extracted for analysis. The clinical examination consisted of identifying any possible adverse physiological effect of LAE after its administration in a single oral dose. The blood work was focused on determining the pharmacokinetic of LAE through determination of the concentrations of LAE and its by-products. Two volunteers received an oral dose of 2.5 mg/kg bw (LMA-047, 2004). Four volunteers received an oral dose of 1.5 mg LAE/kg bw (LMA-049, 2004). Results from the study has shown that LAE was metabolized so quickly that it could not be detected in the blood samples, even those taken immediately following administration. In addition, there were no clinically significant abnormalities in any of the laboratory data for either of the two oral doses. Finally,

LAE has no immunological action in either inducing or suppressing normal immunological functions of the body. LAE's mode of action is local and not systemic.

Ethyl Lauroyl Arginate Hydrochloride (LAEH) is monohydrochloride salt of LAE, and hereinafter referred as LAEH formulation.

COVID-19 infections are worldwide. While effective treatments are being developed, the current emphasis is on prevention utilizing facial masks, applying hand sanitizers and social distancing. Masks alone cannot protect against transmission of infections through aerosol and droplets. Therefore, effective antiseptics that can be used in nasopharynx or oral routes is needed to reduce and prevent transmission. Salvacion USA Inc., announced that Covixyl-V, antiseptic, demonstrated virucidal activity against SAR-CoV-2, the virus that causes COVID -19. It is a proprietary combination of two FDA approved ingredients developed to inactivate SAR-CoV-2 for nasal and oral administration. The proprietary combination proved to be effective in inactivating the viruses up to 100%. The combination is effective at low concentrations, applicable for nasal sprays and/ or oral rinse to inactivate the virus.

A study conducted by Shrivastava and et al., showed natural course of symptoms of the viral COVID-19 infection. Viral load increased from Day 1 to Day 7, however after Day 7, it started to decrease (Shrivastava R, 2021). Also, COVID-19 infected patients normally show respiratory symptoms during first 4-6 days due to viral growth, inflammation and nasal mucosal damage and start stabilizing after 6 days (Singhal T, 2020). Additionally, in vivo study conducted in Syrian Hamsters at BIOQUAL, Inc., showed similar pattern to human COVID-19 virus progression. Therefore our five days planned treatment period should be within disease progression pattern (Study No.: SALV-20-1A and SALV-20-02, 2021).

The aim of this study was to evaluate the efficacy of nasal spray containing LAEH formulation versus a matching placebo formulation administered as a nasal spray to reduce SAR COVID-2 viral levels in nasal area of COVID-19 positive patients.

The trial was not intended to be reported to FDA because the product is lawfully marketed in the United States (US).

8. STUDY OBJECTIVES

Primary:

To evaluate efficacy of LAEH nasal spray on SAR-COVID-2 viral load in nasal areas.

Secondary:

1. To evaluate the efficacy of LAEH on the viral load in terms of proportion of COVID-19 infection free subjects between the two arms.

2. To evaluate the safety of LAEH versus a matching placebo administered as a nasal spray.

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan:

This was a multi-center, randomized (1:1), placebo-controlled, double-blind clinical study carried out to evaluate and compare the safety and efficacy of Ethyl Lauroyl Arginate Hydrochloride (LAEH) nasal spray against a matching placebo nasal spray, administered to reduce viral load from the nasal area of subjects with Coronavirus Disease 2019. Pretreatment and post treatment viral load enumeration (including CT values) using Reverse Transcription Polymerase Chain Reaction (RT-PCR) was performed to assess the effect (LAEH formulations or matching placebo) after 6 days of nasal spray administration.

Total Thirty (30) subjects with Coronavirus Disease 2019 were randomized into this study with LAEH nasal spray and placebo nasal spray. Subjects were randomized in a 1:1 fashion to either receive twice daily LAEH formulation or matching placebo.

Group A assessed about 15 subjects with COVID-19 who received LAEH nasal spray for 6 days.

Group B assessed about 15 subjects with COVID-19 who received placebo nasal spray for 6 days.

The frequency of assessment was at screening/baseline and on Day 6.

9.2 Discussion of Study Design, Including the Choice of Control Groups

This was a multi-center, randomized (1:1), placebo-controlled, double-blind clinical study carried out to evaluate and compare the safety and efficacy of Ethyl Lauroyl Arginate Hydrochloride (LAEH) nasal spray against a matching placebo nasal spray, administered to reduce viral load from the nasal area of subjects with Coronavirus Disease 2019.

This phase I clinical study was designed to conduct in United States (US) at 2 clinical research centers during year 2021.

Subjects were enrolled after obtaining written informed consent and were screened for eligibility for the study based on inclusion/exclusion criteria. Subjects were screened with the help of Reverse transcription polymerase chain reaction (RT-PCR) test for confirmation of COVID-19. Prior to nasal swabbing at screening, subjects were instructed to refrain from eating, drinking, or using any nasal gavage or nasal spray at least 30 minutes. A nasal mid-turbinate specimen for COVID-19 testing was collected initially from all enrolled subjects as per the protocol of Center for Disease

Control and Prevention (https://www.cdc.gov/coronavirus/2019-ncov/testing/How-To-Collect-NMT-Specimen-for-COVID-19.pdf) for enumerating viral load using RT-PCR. Only those subjects who had laboratory-confirmed diagnosis of COVID-19 at the time of screening (Day -3 to 0) using RT-PCR method and who met all eligibility criteria were enrolled. Along with viral load value from RT-PCR, cycle threshold (CT) value was also included in the laboratory reports. Subjects were randomized in a 1:1 fashion to either receive twice daily LAEH formulation or matching placebo.

Subjects were instructed to use the assigned treatment through nasal spray (2 to 3 puffs in each nostril at a time) twice a day from Day 1 to Day 5 and only once in the morning on Day 6/end of study (EOS). Prior to use of nasal spray, subjects were instructed to refrain from eating, drinking, or using any nasal gavage at least 30 minutes. It was informed to the subjects that the daily second treatment should be taken approximately 6 hours apart from the first treatment. The site personnel explained the effective use of the nasal spray in a step-by-step manner and documented the same training in the source documents.

Investigators informed all the subjects to follow below instructions prior to each use of nasal spray:

- Washing of hands thoroughly with soap and water
- Blowing of nose to clear nostrils before using nasal spray (if needed)
- While keeping the bottle upright, shaking and then removing cap to spray into the air until a mist to comes out
- Keeping head upright
- Careful placement of the spray nozzle inside the nostril and not too deep in the nose
- Spraying 2-3 puffs into one nostril and repeating the same into the other nostril
- Putting protective cap back after use
- Avoiding blowing of nose shortly after taking a dose of the medication
- Avoiding contact with the eyes
- Stopping the usage of spray if experienced any allergic reaction, swelling or irritation and then calling the investigator
- Keeping away the nasal spray from direct sunlight and heat source
- Storage at room temperature

The subjects were also instructed to record his/her initials and date and time he/she administered the assigned treatment on a daily basis in the subject diary. On Day 6/EOS, all the subjects took the first treatment (11^{th} dose) at home around 8:00 am and then visited their respective site as

instructed. Then the site performed the viral load enumeration using RT PCR (including CT value) within 3 and 6 hours post last dose (at end of 11th treatment).

The GCP, ICH (Declaration of Helsinki) and local regulations were strictly followed throughout the study. Basic demographic data including medical history (including ENT history), and details on any concomitant medications was recorded. Reverse transcription polymerase chain reaction (RT-PCR) testing was performed for confirmation of positive COVID-19 test, and enumerating viral load (including CT value). Vital signs such as Blood Pressure (BP), Heart Rate (HR), Respiratory Rate (RR), Oxygen Saturation (SpO2), body temperature was noted and nasal and physical examination was performed.

Subjects fulfilling inclusion/exclusion criteria received respective doses of LAEH nasal spray (test) or placebo nasal spray. The site called each subject daily and collected information on Adverse events (AEs) (if any), concomitant medications, and treatment compliance and completion of subject diary. Adverse events (AEs) were collected after signing of informed consent till end of study.

Safety and tolerability of LAEH nasal spray were assessed by evaluating of AEs, SAEs, vital signs, discontinuation due to AEs, laboratory testing and nasal and physical examinations.

Subjects were randomized to one of the two groups according to the randomization scheme on Day 1/Baseline in the ratio of 1:1.

Group A: about 15 subjects received LAEH nasal spray (2 to 3 puffs in each nostril at a time) twice a day from Day 1 to Day 5 and only once in the morning on Day 6/EOS.

Group B: about 15 subjects received Placebo nasal spray (2 to 3 puffs in each nostril at a time) twice a day from Day 1 to Day 5 and only once in the morning on Day 6/EOS.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

A subject was included in the study when he/she met below inclusion criteria:

1. Ability to provide written informed consent or, by his or her legal/authorized representatives when the subject is not capable of giving consent, prior to initiation of any study procedures
2. Male or female of ≥18 years and ≤65 years of age (inclusive) at time of enrollment

3. Subjects with laboratory-confirmed diagnosis of COVID-19 at the time of screening (Day -3 to 0) using RT-PCR method.
4. Subject with mild COVID-19 symptoms (e.g., fever, cough, sore throat, headache, muscle pain, nasal congestion, rhinorrhea, loss of smell and taste) but who did not have shortness of breath or dyspnea
5. Subjects who did not require hospitalization
6. Subjects with SpO2 levels ≥ 95%
7. Viral load by RT-PCR between 3.3×10^6 copies/mL to 6.6×10^6 copies/mL
8. Female subject who was not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile
9. Female subject of childbearing potential who had negative urine pregnancy test.

9.3.2 Exclusion Criteria

Subjects were not included in the study when he/she met any of the below exclusion criteria:

1. Allergy to LAEH or any of the excipients of the formulation
2. History of allergies or flu within 30 days prior to the day of enrollment
3. Sensitivity to nostril skin or irritation or bleeding history within 30 days prior to the day of enrollment
4. Females who were breast-feeding, lactating, pregnant or intending to become pregnant
5. COVID-19 subjects with moderate, severe or critical illness or requiring intensive care or mechanical ventilation
6. History of severe respiratory disease and requirement for long-term oxygen therapy
7. Had received antibiotic/s, antiviral drug, and hormonal drugs within 30 days prior to the day of enrollment
8. Any condition or disease detected during the medical interview/physical examination that would render the subject unsuitable for the study, place the subject at undue risk or interfere with the ability of the subject to complete the study in the opinion of the Investigator
9. Had received or had a plan to receive a SARS-CoV-2 vaccine during the study period
10. Participation in any interventional drug or medical device trials within 30 days prior to the day of enrollment.

9.3.3 Removal of Subjects from Therapy or Assessment

Subjects could withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the study center. Every effort was made to keep subjects in the study. When available, a reason for not completing the study was recorded in the

case report form (CRF). A subject may be withdrawn from the study at any time for any of the following reasons:

- Due to any AE.
- As per Investigator discretion in the best interests of the subject.
- Withdrawal of consent
- In case of study termination due to the safety reasons
- Due to protocol violation

9.4 Treatment

9.4.1 Treatment Administered

LAEH

LAEH nasal spray (2 to 3 puffs in each nostril at a time) was self-administered twice a day from Day 1 to Day 5 and only once in the morning on Day 6/EOS.

Placebo

Placebo nasal spray (2 to 3 puffs in each nostril at a time) was self-administered twice a day from Day 1 to Day 5 and only once in the morning on Day 6/EOS.

9.4.2 Identity of Investigational Product

LAEH

Investigational product	Formulation	Strength		Batch number
LAEH	Nasal spray	Ethyl lauroyl arginate hydrochloride	0.1Wt% concentration	
		Glycerin	10 Wt%	
		Xylitol	5 Wt%	
		1, 2 hexanediol	2 Wt%	
		PVP	1 Wt%	
		PEG- 40 hydrogenated castor oil	0.8 Wt%	
		Sodium citrate	0.06 Wt%	
		Phenoxyethanol	0.05 Wt%	
		Lavender	0.04 Wt%	
		Copper gluconate	0.005 Wt%	
		Citric acid	0.001 Wt%	
		Sodium hydroxide	0.0001 Wt%	
		Aqua	80.944 Wt%	

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1.1.Section 8.1 Description of Study Product
Kindly confirm if this is fine.

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Placebo

Placebo	Formulation	Strength		Batch number
Placebo	Nasal spray	Glycerin	10 Wt%	
		Xylitol	5 Wt%	
		1, 2 hexanediol	2 Wt%	
		PVP	1 Wt%	
		PEG- 40 hydrogenated castor oil	0.8 Wt%	
		Sodium citrate	0.06 Wt%	
		Phenoxyethanol	0.05 Wt%	
		Lavender	0.04 Wt%	

Placebo	Formulation	Strength		Batch number
		Copper gluconate	0.005 Wt%	
		Citric acid	0.001 Wt%	
		Sodium hydroxide	0.0001 Wt%	
		Aqua	80.944 Wt%	

9.4.3 Method of Assigning Subjects to Treatment Groups

After obtaining written informed consent, subjects received a subject identifier number. Subject was screened according to the inclusion and exclusion criteria. Subjects who complied with all criteria were enrolled into the study.

Randomization of the subjects to one of the two treatment groups was performed based on the pre-defined randomization list. ~~by XXX.~~ The study was conducted with two groups as LAEH (Group A) and placebo (Group B). Each group had 15 evaluable subjects. The study was of double-blinded nature hence neither the investigator or study staff were aware of LAEH/placebo assignment to the subject. The principal investigator at the study site was allowed to break blind of individual subject in case of a SAE/in case of emergency.

Commented [KP9]: Current study LAEH Nasal spray uses randomization method for allotment of study product or placebo; however, the details of randomization procedure are not mentioned in the protocol.
Kindly provide the details about the randomization procedure followed during the conduct of this study.

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Commented [KP11R9]: Can you please clarify whether the randomization was done centrally at study level or was it done at respective site level (Did each site have a randomization list to refer?)

9.4.4 Selection of Doses in the Study

LAEH has been extensively studied for toxicity, metabolism, and effectiveness studies in vitro and in vivo. Its Anti-microbial effects are well documented and regulatory approvals have been granted by both the EU and the US FDA for the use of this chemical as a safe and effective ingredient for use in preserving a variety of food and consumer products. The extensive metabolism data in humans indicated LAEH breaks down in body to two, body ingredients; arginine and lauric acids. The toxicological and metabolic studies demonstrated that LAEH has no metabolic, pharmacologic, or immunologic action against human body. It is listed as GRAS ingredient by FDA and safe to use in food and other over the counter products in the EU, UK, and Germany.

On 1st September 2005, FDA issued the Non-Objection Letter regarding that lauric arginate is GRAS for use as an antimicrobial in the above food categories at levels up to 200 ppm of ethyl Nα-lauroyl-L-arginate hydrochloride. The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic infection to critical illness. Among patients who are symptomatic, the median incubation period is approximately 4 to 5 days, and 97.5% have symptoms within 11.5 days after

infection. A major challenge to containing the spread of SARS-CoV-2 is that asymptomatic and presymptomatic people are infectious. Patients may be infectious 1 to 3 days before symptom onset, and up to 40 to 50% of cases may be attributable to transmission from asymptomatic or presymptomatic people. Just before and soon after symptom onset, patients have high nasopharyngeal viral levels, which then fall over a period of 1 to 2 weeks (Gandhi RT, 2020).

Considering early stage of viral infection, 5 days treatment of LAEH formulation would benefit the subjects to reduce the transmission from mild to moderate stage of the COVID-19 at initial stage of the infection.

Hence, each subject administered LAEH nasal spray or placebo nasal spray, twice daily (2 to 3 puffs in each nostril at a time) from Day 1 to Day 5 and only once in the morning on Day 6/EOS.

9.4.5 Selection and Timing of Dose for Each Subject

Subjects were provided sufficient medication/placebo at the time of visit, provided instructions about the effective use of the nasal spray in a step-by-step manner on drug administration at home and were requested to comply with the instruction given by the Investigator or the designated study team. It was informed to the subjects that the daily second treatment should be taken approximately 6 hours apart from the first treatment. Nasal spray (2 to 3 puffs in each nostril at a time) was administered twice daily from Day 1 to Day 5 and only once in the morning on Day 6/EOS. Subject were encouraged to record their dosing on a daily basis, starting from the Day 1 till completion of study period on Day 6 in a subject diary.

9.4.6 Blinding

The study was of double-blinded manner. Hence, neither the Investigator, study staff and the subjects were informed which drug (LAEH or placebo) the subjects received. Only the Principal Investigator at the study site was allowed to break blind of individual subject in case of emergency/SAE reported during the study which required the product information dispensed to the subject. The Principal Investigator followed the unblinding procedures as per the Protocol or per the SOPs at the site or of the CRO.

9.4.7 Prior and Concomitant Therapy

Any prior or concomitant medication required by the subject was prescribed at the discretion of Investigator and/or the attending clinician for concomitant illness. All the treatments which were prescribed to subject including over the counter (OTC) medications, vitamins, herbal and other medications include but not limited to antibiotics, antiviral drug, hormonal drugs, antipyretic and analgesic drugs for all indications [ENT and other] taken 28 days prior to the Screening/Baseline visit and/or throughout the course of the study apart from study treatments were recorded in concomitant medication form in the source document and CRF with generic name and/or trade name of the medication, start and end dates of treatment, route of dose along with associated medical condition.

9.4.8 Treatment Compliance

Subjects were provided with a paper/electronic diary (as applicable) to record after each dosing indicating compliance to the dosing per the study requirement. The site called the subject daily and checked for treatment compliance and completion of subject diary. Subjects were counseled regarding proper treatment adherence/compliance, and re-trained if needed in the proper use of the nasal spray device at the specified visits by phone calls.

9.5 Efficacy and Safety Endpoints

9.5.1 Efficacy and Safety Measurements Assessed

9.5.1.1 Study Procedures

Before performing any study procedures, the Investigator or designee explained the nature of the study to the potentially interested subjects in detail and if he/she voluntarily agreed to participate in the study, they were given an opportunity to ask any questions before signing. Once all queries were resolved and once subjects voluntarily agreed to participate in the study and they signed an Informed Consent Form (ICF). After meeting the eligibility criteria, subjects were enrolled into the study and were assigned a unique identification number to maintain confidentiality; their study records were not be identified by names. The study was conducted in accordance with the protocol. The details of study assessments per visit is explained in the schedule of assessment Table 1. . The Investigator also signed the ICF and provided a copy to the participating subjects.

Table 1: Schedule of Assessments

Assessment	Screening / Baseline	Treatment Period					
Day	**-3 to 0**	**D1/P1**	**D2/P2**	**D3/P3**	**D4/P4**	**D5/P5**	**D6/EOS Visit**
Informed consent	X						
Demographics	X						
Medical history (including ENT history)	X						
Urine pregnancy test[a]	X						
Height and weight	X						
Vital signs (HR, RR, BP, temperature, SpO2) and nasal examination	X						X
Inclusion/exclusion criteria assessment	X						
RT-PCR test results for viral loads[b]	X						X[c]
Randomization[d]	X						
Study product and material distribution[e]	X						
Treatment through nasal spray[f]		X	X	X	X	X	X[g]
Concomitant medication review	X	<<< ongoing >>>					
Adverse event record[h]	X	<<< ongoing >>>					
Subject diary record[i]		X	X	X	X	X	X
Treatment and subject diary compliance[j]		X	X	X	X	X	X

BP=Blood Pressure; D=Day; ENT= Ear, Nose, Throat; EOS=End of Study; HR=Heart Rate; P= Phone Call; RR= Respiratory Rate; RT-PCR= Reverse Transcription Polymerase Chain Reaction; SpO2= Oxygen Saturation.

[a] Female participant of childbearing potential only

[b] Subjects were asked to refrain from eating, drinking, or using any nasal gavage at least 30 minutes prior to use of nasal spray. Nasal swabs were collected initially for enumerating viral load using RT-PCR (including CT value) at baseline (Day -3 to 0) by swabbing for 30 seconds from each nostril.

[c] After 6 days (at the end of 11 treatments, i.e. post morning treatment on Day 6), subjects visited the site and nasal swab was taken within 3 and 6 hours post 11th treatment for viral load enumeration using RT-PCR (including CT value).

[d] Based on RT-PCR test report, and other eligibility criteria; subjects were randomized in a 1:1 fashion to either receive twice daily LAEH formulation or matching placebo through nasal spray twice a day for 5 days and only once in the morning on Day 6.
[e] Materials (Subject Diary and Treatment Instructions) were provided to subjects.
[f] Subjects were administered assigned treatment (LAEH or matching placebo) through nasal spray twice a day from Day 1 to Day 5 and only once in the morning on Day 6 (11 treatments). Subjects were asked to refrain from eating, drinking, or using any nasal gavage at least 30 minutes prior to treatment. Nasal swabs were collected for enumerating viral load using RT-PCR at baseline by swabbing for 30 seconds from each nostril. Site was responsible to provide the training to the subject and document the training in the source documents.
[g] On Day 6/EOS, the subject took the first treatment (administered through nasal spray by themselves at home around 8:00 am) and recorded the same in the subject diary and then visited to the site.
[h] The site called the subject daily and collected AE information (adverse event [AE]; Serious Adverse Event [SAE])
[i] Subjects recorded in the subject diary his/her initials and date and time he/she administered the assigned treatment on a daily basis. The site called and confirmed the compliance for treatment administration and completion of subject diary with the subject daily.
[j] The site called the subject daily and checked for treatment compliance and completion of subject diary.

9.5.1.2 Adverse Events

Adverse Events:

An AE is defined as any untoward medical occurrence associated with the use of a medicinal product in humans, whether or not considered to have a causal relationship to this treatment. An AE can, therefore, be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events meeting the definition of an AE included:

- 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 that occur during the reporting periods, even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction (e.g. drug-drug interaction)

Events that did not meet the definition of an AE included:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that led to the procedure was reported as an AE if it meets the criteria of an AE
- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital)
- 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.

If there was evidence of an AE through report or observation, the Investigator or designee evaluated this further and recorded the following information:

- Time of onset and resolution
- Severity
- Seriousness

- Causality/relation to study product
- Action taken regarding study product
- Action taken regarding AE
- Outcome

Serious Adverse Events

If an event met any of the following criteria, it was considered an SAE:

- Death
- Life threatening (in the opinion of the Investigator, the subject is at immediate risk of death from the event [substantial risk of dying at the time of the adverse event])
- In-patient hospitalization into intensive care or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (a substantial disruption of a person's ability to conduct normal life functions)
- Congenital anomaly or birth defect
- Important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above.

Adverse Drug Reaction

All noxious and unintended responses to an investigational product related to any dose of the investigational product should be considered adverse drug reactions (ADRs). The phrase "responses to an investigational product" means that a causal relationship between an investigational product and an AE is at least a reasonable possibility. All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to an investigational product was designated as ADRs. All AEs, with the causal relationship to the study drug reported as "possible", "probable" or "definite" were considered ADRs.

9.5.1.3 Recording of Adverse Events

All AEs occurring at any time during the study period, from the time of consent, were recorded on the AE page in the eCRF, as well as in the subject's clinic, office or hospital chart using standard medical terminology.

Any medical condition that was present at the initial visit, which remains unchanged or improved, should not be recorded as an AE. If there was a worsening of a medical condition that was present at screen baseline, then this was considered a new AE and recorded.

For each AE, the Investigator provided information on severity, start and stop dates, relationship to study drug, action taken with study drug, any other action taken, and outcome of the event. AE resulting from concurrent illnesses, reactions to concurrent medications, or progression of disease states was also recorded.

If several signs, symptoms or diagnostic abnormalities clearly related to a medically defined diagnosis or syndrome, the diagnosis were reported on the AE page of the eCRF. All clearly related signs, symptoms and abnormal diagnostic procedures were grouped together as a single diagnosis. Any new/worsening abnormalities noted on physical examination was recorded as an AE. The date of onset and resolution of each AE were recorded. For single AE, the date(s) and time frame(s) were recorded. For recurrent AEs, the date of onset of the first AE, and date of last occurrence of the AE was recorded, with a description of the frequency occurrence for the time period. If an AE was considered serious, both the AE page of the eCRF and the Serious Adverse Event form were completed.

9.5.1.4 Severity

The Investigator assigned a severity rating to each AE. The severity of AE was assessed as per the "Common Terminology Criteria for Adverse Events" (CTCAE) version 4.03, 2010. For AEs not defined under CTCAE, the following criteria was used for assessing the severity:

- Grade 1- Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 - Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)*.
- Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 - Life-threatening consequences; urgent intervention indicated.
- Grade 5 - Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

9.5.1.5 Drug-Event Relationship/Causality

For all AEs, sufficient information was obtained by the Investigator to determine the causality. The Investigator was responsible for assessing relationship of AEs to test product in accordance with the following definitions:

Category	**Causality**	**Description**
DEFINITE	Causal relationship is certain	For example: the temporal relationship between test product exposure and the adverse event (AE) onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated; the event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.
PROBABLE	High degree of certainty for causal relationship	High degree of certainty for causal relationship. For example: the temporal relationship between test product exposure and AE onset/course is reasonable, there is a clinically compatible response to de-challenge (re-challenge is not required), and other causes have been eliminated or are unlikely.
POSSIBLE	Causal relationship is uncertain	Causal relationship is uncertain. For example: the temporal relationship between test product exposure and the AE

Category	Causality	Description
		onset/course is reasonable or unknown, de-challenge information is either unknown or equivocal; could also be explained by disease or other drugs.
UNRELATED/ NOT RELATED	No possible relationship	The temporal relationship between drug exposure and the AE onset/course is unreasonable or incompatible, or a causal relationship to test product is impossible.

For SAEs, if the relationship to the test product(s) was considered to be not related, an alternative suspected etiology was provided when possible (e.g., concomitant medications, inter-current events, study-related procedure).

9.5.1.6 Event Outcome

For all adverse events, the investigator had to pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it met the criteria for classification as a SAE requiring immediate notification to Sponsor or its designated representative and regulatory agency. The outcome at the time of last observation was classified as:

RECOVERED/RESOLVED where the subject was recuperated and was free of any pathological conditions resulting from the prior disease or injury.

RECOVERED WITH SEQUELAE where the subject was recuperated but retained pathological conditions resulting from the prior disease or injury.

NOT RECOVERED/NOT RESOLVED (i.e., ongoing) where the subject did not recuperate from the condition or injury and the event was still considered ongoing

RECOVERING where the subject was begun to recuperate from the condition or injury, but the event was considered ongoing at a reduced intensity

FATAL the condition or injury resulted in the subject's death. The investigator must identify the principal cause of death and assign fatal outcome to that event. Other concurrent ongoing AE/SAEs present at the time of death would remain Not recovered/Not resolved.

UNKNOWN can be selected if none of the other situations apply or were known. Follow-up was conducted to obtain one of the preceding outcomes.

9.5.2 Appropriateness of Measurement

At screening prior to nasal swabbing for RT-PCR, all the subjects were asked to refrain from eating, drinking, or using any nasal gavage or nasal spray at least 30 minutes. A nasal mid-turbinate specimen for COVID-19 testing was collected initially from all enrolled subjects as per the protocol of Center for Disease Control and Prevention (https://www.cdc.gov/coronavirus/2019-ncov/testing/How-To-Collect-NMT-Specimen-for-COVID-19.pdf) for enumerating viral load using RT-PCR test. Screening measures were conducted prior to enrollment constitute standard tests designed to thoroughly examine the potential subject to assess any medical issues. Subjects were screened to determine whether an individual satisfied all eligibility criteria. Only those subjects who had laboratory-confirmed diagnosis of COVID-19 at the time of screening (Day -3 to 0) using RT-PCR method and who met all eligibility criteria were enrolled.

Efficacy measures were established measures of the symptoms known to be reliable and valid. All outcome measures were investigated by Principal Investigator for an objective endpoint for evaluation of clinical outcome. All outcome measures were conducted at screening/baseline, and on Day 6.

The measures of safety used in this study were routine clinical procedures. Vital parameters (blood pressure, heart rate, respiratory rate, SpO2 and body temperature) were measured at screening/baseline and end of the study (Day 6). Safety measures were conducted by the investigators from signing of informed consent till end the study for an individual subject. Safety measure included AEs, SAEs, nasal and physical examination as well as frequent measurement of vital parameters, and laboratory parameters.

The efficacy and safety assessments performed in this study are widely used and generally recognized as reliable, accurate, and relevant.

The study assessments and procedures were as per standard treatment protocols established by participating study centers and COVID-19 disease management guidelines from the Government of USA.

9.5.3 Study Endpoints

9.5.3.1 Primary Efficacy Endpoint

- Comparison of change in viral load from baseline between the two treatment arms

9.5.3.2 Secondary Efficacy Endpoints

- Proportion of COVID-19 infection free subjects between the two treatment arms

9.6 Data Quality Assurance

The Sponsor/CRO had the right to conduct a quality assurance audit of the site records. The study was open for internal and external audit, as required to ensure compliance with Good Clinical Practices and all applicable regulatory requirements. In the event of an audit or inspection, the Investigator (and institution) had to agree to grant the auditor(s) complete access to all the study-related documents and to provide ample time to discuss any relevant issues.

9.7 Statistical Methods Planned and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

9.7.1.1 Statistical Methods:

All statistical analyses were performed using SAS® Version 9.4 [SAS Institute Inc., USA]. The denominator for percentages was based on the number of patients appropriate for the purpose of the analysis.

Descriptive statistics for continuous data

The continuous data was summarized using the number of observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum value (min), and maximum value (max).

The number of observations (n) was presented with no decimal place, mean and median was presented up to one decimal place from the original value, SD up to two decimal places from the original value and (min, max) as an original value.

Descriptive statistics for categorical data

The categorical variables were summarized using the frequency count (n) and percentage (%) for each possible value. The frequencies were presented up to 0 decimal places, percentage up to 1 decimal place.

Listings

Subject-wise data listings was provided for captured data

9.7.1.2 Statistical Analysis

The statistical analysis was performed using mITT (Modified Intent-to-treat), PP (Per protocol) and safety analysis population

9.7.1.2.1 Analysis Data Sets

Modified Intent-to-Treat Analysis Population (mITT): All subjects who were randomized, took at least one dose of study medication, and had at least one post baseline evaluation.

Per Protocol population (PP): The PP population included all mITT subjects who remained in the study and had no major protocol violations and received at least 80% of the doses.

Safety Population (SP): All randomized subjects who took at least one dose of study medication.

- Safety analysis was performed on safety population.
- Efficacy analysis was performed on mITT and PP populations.
- The results in the PP population were considered definitive with those in the mITT population considered supportive.

9.7.1.3 Analysis of Primary Endpoint

- Comparison of change in viral load in RT-PCR Test from baseline at Day 6 between the two treatment arms

The viral load at Day 1 (Baseline), Day 6 within 3hrs post last dose and Day 6 within 6hrs post last dose was summarized using descriptive statistics by treatment group by mITT and PP population. Change from baseline was calculated from Day 6 within 3hrs post last dose and Day 6 within 6hrs post last dose and summarized using descriptive statistics by treatment group by

mITT and PP population. Mean change in viral load was compared using Analysis of Covariance (ANCOVA) where Change from baseline (CFB) at Day 6 was considered as dependent variable, the treatments were considered as independent variable and baseline viral load as covariate, to find the statistically significant difference between the treatment for mITT population and PP population.

9.7.1.4 Analysis of Secondary Endpoints

- Proportion of COVID-19 infection free subjects between the two treatment arms

Outcome of the RT-PCR test for viral load was presented as positive or negative values for each enrolled subject who was tested. Proportion of infection free subjects for which the result of the RT-PCR Test for viral load was negative was presented with frequency count (n) and percentage (%) by treatment group at baseline and Day 6 within 3hrs post last dose and Day 6 within 6hrs post last dose.

Chi square test for independence was used to find the statistical significance between the treatment groups at each visit for mITT as well as PP population.

9.7.1.5 Analysis of Safety Endpoints

Safety and tolerability of LAEH was assessed through a review and evaluation of AEs, SAEs, discontinuation due to AEs, laboratory testing, vital signs, nasal and physical examinations.

Analysis of Adverse Events

Adverse events were coded according to MedDRA and grouped by preferred term (PT) and system organ class (SOC).

Subject counts (n) and percentages (%) were presented for all the subjects by treatment group in safety population and were sorted descending by total and then alphabetically. If a subject had more than one episode of an AE, subject was counted only once in specific system organ class (SOC) and once for each specific preferred term (PT).

Summarization for AEs by subjects is provided for following categories:

- All Adverse Events
- AE's By SOC And PT

- Serious AEs by SOC and PT
- Study Drug Related AEs by SOC and PT
- AEs leading to death by SOC and PT
- AEs leading to permanent discontinuation by SOC and PT
- AE's By SOC, PT And Severity
- Study Drug Related AEs by SOC and PT and Severity

9.7.2 Determination of Sample Size

No formal sample size calculation was performed. A total of 30 patients were enrolled and considered as sufficient sample size to compare the estimates of tests treatment with reference treatment. Sample size determination was based on Singapore human clinical trial (Seneviratne CJ, 2021), which evaluated the effectiveness of mouth rinses on viral load in saliva. The data observed to obtain 2 log difference in initial and post treatment PCR viral load. Based on the standard deviation of the study of mean difference at 95% and standard deviation of mean ranging from 0.2-0.4, the sample size was estimated as follows for 2 log difference in viral PCR counts:

N= z^2xp(1-p)/sd

Thus, N=1.96x0,5/0.2=5

In this study, 15 subjects were enrolled per treatment to see 2 log difference. Therefore, it should be sufficient to detect differences in nasal viral load.

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Changes

The original protocol Version 1.0 dated 27 May 2021 was amended to include administrative changes. Final version of the Protocol: Version 1.1 dated 28 September 2021.

9.8.2 Statistical Changes

There were no statistical changes in the planned analysis. (To be confirmed by statistician. If any deviation/change from planned analysis, please provide the details)

10. STUDY SUBJECTS

10.1 Disposition of Subjects

Xxxxxxxx.

Table 2: Summary of Subject Disposition – All Subjects

	Covixyl-V (N = xx) n (%)	**Placebo (N = xx) n (%)**	**Total (N = xx) n (%)**
Number of subjects screened [1]			xx
Number of screen failures [2]			xx
Number of randomized subjects.	xx	xx	xx
Number of subjects in Safety population	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of subjects in mITT population	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of subjects in PP population	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of subjects who completed the study	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of subjects withdrawal/ discontinuations	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reasons for subject withdrawal/discontinuation			
Screen failure	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow- up	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject withdrew consent	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subject withdrawn by Principal Investigator	xx (xx.x)	xx (xx.x)	xx (xx.x)
AE / SAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pregnancy	xx (xx.x)	xx (xx.x)	xx (xx.x)
Others (specify)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N = number of subjects in the specified treatment group; n = number of subjects in specified category.
Note 1: Percentages are based on number of subjects in the specified treatment in Safety population.
Note 2: [1] Subjects who provided informed consent
Note 3: [2] Counts taken from eligibility conducted on screening visit
Reference listing XXXX

10.2 Protocol Deviations

Xxxxxxxx.

Table 3: Summary of Protocol Deviations /Violations – Safety Population

Protocol Deviation Type	**Covixyl-V (N = xx) n (%)**	**Placebo (N = xx) n (%)**	**Total (N = xx) n (%)**

Subjects having at least one protocol deviation/violation [1]	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at least one major protocol deviation [2]	xx (xx.x)	xx (xx.x)	xx (xx.x)
Xxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)
Xxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)
Xxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)
Xxxx	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N = number of subjects in specified treatment group; n = number of subjects in specified category.
Note1: Percentages are based on the number of subjects in the specified treatment group
Note2: [1] = Percentages for the subjects with at least one protocol deviation is based on the number of subjects in respective treatment group in safety population.
Note3: [2] = Percentages of particular protocol deviation is based on number of subjects with at least one major protocol deviation of that respective flag in respective treatment group.
Reference listing XXXX

11. EFFICACY EVALUATION

11.1 Demographic and other Baseline characteristics

11.1.1 Study Demographics

Xxxxx.

Table 4: Demographic Characteristics and Anthropometry Results – Safety Population

Characteristic (Unit)	Statistics	Covixyl-V (N = xx)	Placebo (N = xx)	Total (N = xx)
Gender				
Male	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Female	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Age (Years)	n	xx	xx	xx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Weight (kg)	n	xx	xx	xx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Height (cms)	n	xx	xx	xx
	Mean (SD)	xx.x(xx.xx)	xx.x(xx.xx)	xx.x(xx.xx)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Ethnicity				
Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race				
American Indian or Alaska Native	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black or African American	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian or Other Pacific Islander	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Reported	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other, Specify	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N = number of subjects in specified treatment group; n = number of subjects in specified category
Note 1: Percentages are based on the number of subjects in the specified treatment group.
Reference listing XXXX

11.1.2 Medical History

Xxxxx.

Table 5: Medical History – Safety Population

System Organ Class **Preferred Term**	**Covixyl-V** **(N = xx)** **n (%)**	**Placebo** **(N = xx)** **n (%)**	**Total** **(N = xx)** **n (%)**
Subjects having at least one medical history	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 3	xx (xx.x)	xx (xx.x)	xx (xx.x)

System Organ Class 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N = number of subjects in specified treatment group; n = number of subjects in specified category
Note 1: System organ class and preferred terms are coded using the standards of MedDRA.
Note 2: Percentages are based on number of subjects in specified treatment group in Safety population.
Reference listing XXXX

11.1.3 Prior or Concomitant Medications

Xxxxx

Table 6: Prior/Concomitant Medications –Safety Population

ATC Drug Class **Generic Drug Name**	**Statistics**	**Covixyl-V** **(N = xx)**	**Placebo** **(N = xx)**	**Total** **(N = xx)**
Number of Subjects with at least One Prior/Concomitant Medication	n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC Drug Class 1	n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Generic Drug Name 1		xx (xx.x)	xx (xx.x)	xx (xx.x)
Generic Drug Name 2		xx (xx.x)	xx (xx.x)	xx (xx.x)

ATC Drug Class 2	n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Generic Drug Name 1		xx (xx.x)	xx (xx.x)	xx (xx.x)
Generic Drug Name 2		xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N = number of subjects in specified treatment; n = number of subjects in specified category
Note 1: Percentages are based on number of subjects in specified treatment group in Safety population.
Note 2: ATC level 2 text and generic names are coded using the standards of WHODD
Reference listing XXXX

11.2 Measurement of Treatment Compliance

Xxxxx.

Table 7: Summary of Treatment Exposure and Compliance– Safety Population

	Visit	**Statistics**	**Covixyl-V (N = xx)**	**Placebo (N = xx)**	**Total (N = xx)**
Treatment Exposure (Days)		N	xxx	xxx	xxx
		Mean (SD)	xx.xx(xx.xxx)	xx.xx(xx.xxx)	xx.xx(xx.xxx)
		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx
Number of patients having treatment Compliance	Day 1	n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Day 2	n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N = number of subjects in specified treatment group; n = Number of subjects in specified category.
Reference listing XXXX

11.3 Efficacy Results and Tabulations of Individual Subject Data

Xxxxx.

11.3.1 Analysis of Efficacy (Primary and Secondary Endpoints)

11.4.1.1 Primary Efficacy Endpoint

11.3.1.1.1 Comparison of change in viral load from baseline between the two treatment arms

Xxxxx

Table 8: Change in Viral Load from RTPCR Test – mITT Population

	Visit	Statistics	Covixyl-V (N = xx)	Placebo (N = xx)	p value
Viral Load (x 10^6 copies/mL)	Day 1	n	xx	xx	x.xxxx#
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	
		Min, Max	xx, xx	xx, xx	
	Day 6 (with in 3 hr)	n	xx	xx	x.xxxx#
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	
		Min, Max	xx, xx	xx, xx	
	CFB at Day 6 (with in 3hr)	n	xx	xx	x.xxxx*
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	
		Min, Max	xx, xx	xx, xx	
		Mean Diff (95% CI)*	xx.xx (xx.xx - x.xx)		
	Day 6 (with in 6 hr)	n	xx	xx	x.xxxx#
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	
		Min, Max	xx, xx	xx, xx	
	CFB at Day 6 (with in 6hr)	n	xx	xx	x.xxxx*
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	
		Min, Max	xx, xx	xx, xx	

	Mean Diff (95% CI)*	xx.xx (xx.xx - x.xx)

Abbreviations: N = number of subjects in specified treatment group; n = number of subjects in specified category.
Note 1: #Mean difference, 95% CI and p value is calculated using ANOVA
Note 1: *Mean difference, 95% CI and p value is calculated using ANCOVA with baseline viral load as co-variate.
Reference listing XXXX

Programmer's Note 1: Similar table will be generated as follows:

Table X Change in Viral Load – PP Population

Table 9: Fold Change in RTPCR CT Value– Safety Population

	Visit	Statistics	Covixyl-V (N = xx)	Placebo (N = xx)	P -value*
CT Value	Day 1	n	xx	xx	x.xxxx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	
		Min, Max	xx, xx	xx, xx	
	Day 6 (with in 3 hr)	n	xx	xx	x.xxxx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	
		Min, Max	xx, xx	xx, xx	
	Fold Change at Day 6 (with in 3hr)	n	xx	xx	x.xxxx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	
		Min, Max	xx, xx	xx, xx	
		Mean Diff (95% CI)*	xx.xx (xx.xx - x.xx)		
	Day 6 (with in 6 hr)	n	xx	xx	x.xxxx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	
		Min, Max	xx, xx	xx, xx	
	Fold Change at Day 6 (with in 6hr)	n	xx	xx	x.xxxx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	

	Min, Max	xx, xx	xx, xx
	Mean Diff (95% CI)*	xx.xx (xx.xx - x.xx)	

Abbreviations: N = number of subjects in specified treatment group; n = number of subjects in specified category.
Note 1: Fold change in CT value will be estimated on the transformed data by calculating the ratio between Ct values at each time point 3hr and 6 hr versus the Ct value at baseline (at 0 min) for each patient i.e (Cttimepoint/Ctbaseline)
Note 2: *Mean difference, 95% CI and p value is calculated using Independent t-test or ANOVA
Reference listing XXXX

11.4.1.2 Secondary Efficacy Endpoints

11.4.1.2.1 Proportion of COVID-19 infection free subjects between the two treatment arms

Xxxxx

Table 10: Summary of infection free subjects – mITT Population

	Visit	Statistics	Covixyl-V (N = xx)	Placebo (N = xx)	P-value
COVID-19 infection free subjects	Day 1				x.xxxx*
	Negative	n(%)	xx(xx.x)	xx(xx.x)	
	Positive	n(%)	xx(xx.x)	xx(xx.x)	
		95% CI	xx.xx - xx.xx		
	Day 6 (within 3hrs)				x.xxxx*
	Negative	n(%)	xx(xx.x)	xx(xx.x)	
	Positive	n(%)	xx(xx.x)	xx(xx.x)	
		95% CI	xx.xx - xx.xx		
	Day 6 (within 6hrs)				x.xxxx*
	Negative	n(%)	xx(xx.x)	xx(xx.x)	
	Positive	n(%)	xx(xx.x)	xx(xx.x)	
		95% CI	xx.xx - xx.xx		

Abbreviations: N = number of subjects in specified treatment group; n = number of subjects in specified category.
Note 1: *p value for comparison between treatment group is calculated using Chi-square test.
Reference listing XXXX

Programmer's Note 1: Similar table will be generated as follows:

Table X Summary of infection free subjects – PP Population

11.3.1.2 Adjustments for Covariates

Xxxxx

11.3.1.3 Handling of Dropouts or Missing Data

xxxxx.

11.3.1.4 Interim Analysis and Data Monitoring

Not applicable

11.3.1.5 Multicenter Studies

Xxxxx

11.3.1.6 Multiple Comparison/Multiplicity

Not applicable

11.3.1.7 Use of an "Efficacy Subset" of Subject

Not applicable

11.3.1.8 Active-Control Studies Intended to Show Equivalence

Not applicable

11.3.1.9 Examination of Subgroups

Not applicable

11.3.2 Tabulation of Individual Response Data

Xxxxx

11.3.3 Drug Dose, Drug Concentration, and Relationships to Response

Not applicable

11.3.4 Drug-Drug and Drug-Disease Interactions

Not applicable

11.3.5 By-Subject Displays

Xxxxx

11.3.6 Efficacy Conclusions

Xxxxx

12. SAFETY EVALUATION

12.1 Extent of Exposure

Xxxxx

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events

Xxxxx

Table 11: Summary of Subjects with Overall Adverse Events – Safety Population

	Covixyl-V (N = xx) n(%)	**Placebo (N = xx) n(%)**	**Total (N = xx) n(%)**
Subjects with Adverse Events	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with Study Drug Related AEs	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with Serious AEs	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with Study Drug Related Serious AEs	xx (xx.x)	xx (xx.x)	xx (xx.x)
Seriousness Criteria			
Hospitalization	xx (xx.x)	xx (xx.x)	xx (xx.x)
Life-threatening	xx (xx.x)	xx (xx.x)	xx (xx.x)
Significant Disability	xx (xx.x)	xx (xx.x)	xx (xx.x)
Congenital Anomaly or Birth Defect	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other Medically Important Event	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with overall AEs by Severity			
Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)
Relationship to the Study Treatment			
Unrelated	xx (xx.x)	xx (xx.x)	xx (xx.x)
Possible related	xx (xx.x)	xx (xx.x)	xx (xx.x)
Definitely related	xx (xx.x)	xx (xx.x)	xx (xx.x)
Action taken with Study Treatment			
Dose Delayed	xx (xx.x)	xx (xx.x)	xx (xx.x)
Drug Withdrawn Temporarily	xx (xx.x)	xx (xx.x)	xx (xx.x)
Drug Withdrawn Permanently	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Applicable	xx (xx.x)	xx (xx.x)	xx (xx.x)
Outcome of the AEs			
Recovered/Resolved	xx (xx.x)	xx (xx.x)	xx (xx.x)

Recovered/Resolved with sequelae	xx (xx.x)	xx (xx.x)	xx (xx.x)
Recovering/Resolving	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Recovered/Not resolving	xx (xx.x)	xx (xx.x)	xx (xx.x)
Fatal	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown	xx (xx.x)	xx (xx.x)	xx (xx.x)
Action Taken for AE			
None	xx (xx.x)	xx (xx.x)	xx (xx.x)
Medication	xx (xx.x)	xx (xx.x)	xx (xx.x)
Non drug treatment	xx (xx.x)	xx (xx.x)	xx (xx.x)
Patient withdrawn	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other(Specify)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Surgery/Procedure	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N = number of subjects in specified treatment group; n = number of subjects in specified category
Note 1: Percentages are based on number of subjects in respective treatment groups in Safety population
Reference Listing xxxxxx

12.2.2 Display of Adverse Events

Xxxxx.

12.2.3 Analysis of Adverse Events

Xxxxx

12.2.4 Listing of Adverse Events by subjects

Xxxxx.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Xxxxx.

12.3.1 Deaths Listing of Deaths, Other Serious Adverse Events, and Other Significant

12.3.1.1 Death

Xxxxx

12.3.1.2 Other Serious Adverse Events

Xxxxx

12.3.1.3 Other Significant Adverse Events

Xxxxx

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other

Xxxxx

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Xxxxx.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject (Appendix 16.2.8) and Each Abnormal Laboratory Value

Xxxxx.

12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values Over Time

Xxxxx

12.4.2.2 Individual Subject Changes

Xxxxx

12.4.2.3 Individual Clinically Significant Abnormalities

Xxxxx

12.5 Vital signs, Physical findings, and other Observations related to Safety

12.5.1 Urine Pregnancy Test

Xxxxx

Table X: A Summary of Urine Pregnancy Test – Safety Population

Urine Pregnancy Test	Statistics	Covixyl-V (N = xx)	Placebo (N = xx)	Total (N = xx)
Positive	n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Negative	n(%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Abbreviations: N = number of female subjects with child bearing potential in specified treatment group; n = number of subjects in specified category
Note 1: Percentages are based on number of subjects in respective treatment groups in Safety population.
Reference listing xxxxxxx

12.5.2 Vital Signs

Xxxxx

Table X: A Summary of Results – Safety Population

Vital Signs Test Name (Unit)	Visit	Statistics	Covixyl-V (N = xx)	Placebo (N = xx)
Systolic Blood Pressure/(mmHg)	Day 1	n	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Min, Max	xx, xx	xx, xx
	Day 6	n	xx	xx
		Mean (SD)	xx.xx (xx.xx)	xx.x (xx.xx)
		Median	xx.xx	xx.x
		Min, Max	xx, xx	xx, xx
	CFB at Day 6	n	xx	xx
		Mean (SD)	xx.xx (xx.xx)	xx.x (xx.xx)
		Median	xx.xx	xx.x
		Min, Max	xx, xx	xx, xx
Systolic Blood Pressure/(mmHg)	Day 1	n	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Min, Max	xx, xx	xx, xx
	Day 6	n	xx	xx
		Mean (SD)	xx.xx (xx.xx)	xx.x (xx.xx)
		Median	xx.xx	xx.x
		Min, Max	xx, xx	xx, xx
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Abbreviations: N = number of subjects in specified treatment; n = number of subjects in specified category; CFB=Change from

baseline

Reference listing xxxxxx

Programmers Note 1: Continue the above table for all other vital signs for all the available visits for all subjects.

12.5.3 Physical Examination

XXXX

Table X: Physical Examination – Safety Population

Body System	Visit	Result	Statistics	Covixyl-V (N = xx)	Placebo (N = xx)
Skin	Day 1	Normal	n(%)	xx (xx.x)	xx (xx.x)
		Abnormal	n(%)	xx (xx.x)	xx (xx.x)
	Day 6	Normal	n(%)	xx (xx.x)	xx (xx.x)
		Abnormal	n(%)	xx (xx.x)	xx (xx.x)
ENT	Day 1	Normal	n(%)	xx (xx.x)	xx (xx.x)
		Abnormal	n(%)	xx (xx.x)	xx (xx.x)
	Day 6	Normal	n(%)	xx (xx.x)	xx (xx.x)
		Abnormal	n(%)	xx (xx.x)	xx (xx.x)
Head	Day 1	Normal	n(%)	xx (xx.x)	xx (xx.x)
		Abnormal	n(%)	xx (xx.x)	xx (xx.x)
	Day 6	Normal	n(%)	xx (xx.x)	xx (xx.x)
		Abnormal	n(%)	xx (xx.x)	xx (xx.x)

Abbreviations: N = number of subjects in specified treatment; n = number of subjects in specified category
Note 1: Percentages are based on number of subjects in respective group in Safety population.
Reference listing xxxxxxx

Programmer's Note 1: The table will continue for all other body systems.

12.5.4 Nasal Examination

XXXX

Table X: Nasal Examination for Signs and Symptoms – Safety Population

Signs and Symptoms	Visit	Statistics	Covixyl-V (N = xx)	Placebo (N = xx)
Inflammation-redness	Day 1			
	Present	n(%)	xx (xx.x)	xx (xx.x)
	Absent	n(%)	xx (xx.x)	xx (xx.x)
	Not Done	n(%)	xx (xx.x)	xx (xx.x)
	Day 6			
	Present	n(%)	xx (xx.x)	xx (xx.x)
	Absent	n(%)	xx (xx.x)	xx (xx.x)
	Not Done	n(%)	xx (xx.x)	xx (xx.x)
Swelling	Day 1			
	Present	n(%)	xx (xx.x)	xx (xx.x)
	Absent	n(%)	xx (xx.x)	xx (xx.x)
	Not Done	n(%)	xx (xx.x)	xx (xx.x)
	Day 6			
	Present	n(%)	xx (xx.x)	xx (xx.x)
	Absent	n(%)	xx (xx.x)	xx (xx.x)
	Not Done	n(%)	xx (xx.x)	xx (xx.x)

Note 1: Percentages are based on number of subjects in respective group in Safety population.
Reference listing xxxxxxx

Programmer's Note 1: The table will continue for all other signs and symptoms.

12.6 Safety Conclusion

Xxxxx

13. DISCUSSION AND OVERALL CONCLUSIONS

Xxxxx

CONCLUSION:

Xxxxx

14. LIST OF TABLES REFERED BUT NOT INCLUDED IN THE TEXT

xxxx

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