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# Two Week Sub-Chronic Double-Blinded, Placebo Controlled Trial Designed to Determine if Sodium Pyruvate Nasal Spray Will Reduce the Symptoms, Duration and Replication of COVID-19 and Influenza Infections.

## Research Facility

Missouri State University
Trinity Healthcare
Dynamic DNA Labs
Springfield, MO

## Sponsor

## EmphyCorp/Cellular Sciences, Inc.

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Current Date: 2/21/2021
Current Version: CSI-COVID-19_007
**IND:50089**

**Signature Page**

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## 1.0 A Statement of the Objectives and Purpose of the Study.

### 1.1 Introduction

**Inhibition of Viral Replication and Reduction of the "Cytokine Storm" with EmphyCorp's Proprietary Compounds - Potential Treatment and Preventative for COVID-19 and Flu**

Flu and COVID-19 are known to cause mortality and morbidity in the elderly who are immunocompromised. However, it is often forgotten that both diseases afflict children, usually with mild symptoms. In rare cases, there is mortality caused by complications during Flu infection.

Since 2010, Flu has caused between 7,000-26,000 hospitalizations annually in children under five years old. Compared to that of COVID-19 which has accumulated a total of 3,240 hospitalizations in school-aged children. To date, 51 children, aged less than 18, have died in the United States from complications with COVID-19. Comparatively, the CDC has reported a range of 37-188 deaths annually in children under five years of age, from complications caused by the flu.

Potential proactive treatments, such as N115 (sodium pyruvate), would be of benefit to all populations, especially children that are afflicted by both viruses. In both animal and human trials, N115 reduced viral titers (number of viruses), and reduced the number, symptoms, and severity of seasonal flu respiratory tract infections in pregnant women, children, diabetic, and patients with COPD by over 52% annually.

In tissue culture studies, in human studies and in animal studies when inhaled or applied topically, sodium pyruvate inhibited the ability of many viral strains from replicating due to the ability of Sodium Pyruvate to increase the synthesis of Nitric Oxide that is needed to kill infections.

Mice studies conducted by Dr. Lupfer at Missouri State University substantiated our finding by testing nebulized N115 in flu (influenza A H1N1 virus) infected mice that decreased morbidity, weight loss, proinflammatory cytokines, and decreased viral titers (virus numbers) compared to the Placebo Control. Additionally, treated mice consumed more chow during infection indicating improved symptoms (same results reported in a pilot mice COVID-19 study). There were notable improvements in pro-inflammatory cytokine production (IL-1β) and lower virus titers (viral numbers) on days 7 post infection in mice treated with Sodium pyruvate compared to the Placebo Control animals. As pyruvate acts on the host immune response, metabolic pathways and not directly on the virus, our data demonstrate that sodium pyruvate is a promising treatment option that is safe, effective, and unlikely to elicit antiviral resistance.

Furthermore, they stated "we have preliminary data that suggest it may work similarly during other respiratory virus infections including COVID19/SARS-CoV-2. Proactive treatments with sodium pyruvate is not toxic and could be of benefit to children that are afflicted by many respiratory viruses".

**Sodium Pyruvate Ameliorates Influenza A Virus Infection In Vivo** - Online Research Posting on BioRxiv:
https://www.biorxiv.org/content/10.1101/2020.11.25.396978v1

A clinical survey of 367 patients over a two-year period demonstrated a statically significant decrease in the number, symptoms, and severity of seasonal Flu respiratory tract infections after using the 20mM sodium pyruvate nasal spray (EmphyCorp, N115). The number of flu or colds was reduced by 70% in Children and approximately 52% in Pregnant Women, Patients with Allergic Rhinitis, Diabetes, and Pulmonary Fibrosis.

In numerous human clinical trials (17, phase I, II, III clinical trials) submitted to the FDA, with Pulmonary Fibrosis, COPD and Cystic Fibrosis patients, N115 reduced nasal and lung inflammation and congestion by reducing inflammatory cytokines including the IL-6 cytokine that causes the so-called cytokine storm with no known adverse reactions.

In a Phase III Placebo Controlled Clinical Trial with Idiopathic Pulmonary Fibrosis Patients, N115 Non-Steroidal Nasal Spray demonstrated a statistically and clinically significant increase in Nasal Nitric Oxide, FEV-1, SaO2, FVC, FEV-1/FVC ratios (52% to 86%), and a significant reduction in coughing, nasal and lung inflammation. ***N115 alleviated the symptoms associated with the COVID-19 infections in Patients with COPD and Pulmonary Fibrosis.***

EmphyCorp has treated over 3 million Patients globally in 200 hospitals with no adverse events and has 17 human clinical trials that have been submitted to the FDA to support our NDA Phase III marketing application. Over a million patients in that group were patients with allergic rhinitis and as stated by the FDA 24% of their symptoms were caused by nasal infections predominantly colds and flu.

### 1.1.2 Background and Product Description

N115 is a sodium-pyruvate-based inhalation drug. It has been administered via several routes including intravenous, topical administration for hyperkeratotic disorders, and as an enteral supplementation since it is considered GRAS (Generally Regarded as Safe) by the FDA. Sodium pyruvate is used in many products including (Neosporin, Lubriderm, vaginal products, Viva Eye Drops, Ringers Solution, human IV solutions, and solutions to store red blood cells by the Red Cross, and to store human organs for transplant). Sodium pyruvate has been shown to protect neurons, lungs, hearts, muscles, cerebral metabolism, embryos, eyes, kidneys, cellular DNA and membranes from oxygen radical damage. Other approved uses in patients with a variety of medical disorders include Friedreich's disorder; and it is used as a therapeutic solution in open heart surgery, kidney surgery, and eye surgery.

Six different nasal spray formula combinations were tested for safety and efficacy in a series of studies with subjects who normally use nasal sprays. The sodium pyruvate concentrations were 5mM, 10mM, 20mM and 40mM. The sodium pyruvate was delivered in sterile sodium chloride solutions of either 0.45% or 0.90%. All formulas reduced inflammation in the nasal cavities and otherwise improved the nasal cellular morphology. There weren't any adverse events observed.

Additionally, safety and efficacy were tested for four weeks in patients with pulmonary fibrosis (PF), where it was determined that there was proven efficacy in reducing the conditions of PF, while no adverse events were reported. In a Phase III Placebo Controlled Clinical Trial with Idiopathic Pulmonary Fibrosis Patients, N115 demonstrated a statistically and clinically significant increase in FEV-1, SaO2, FVC, FEV-1/FVC ratios (52% to 86%), and a significant reduction in coughing, nasal inflammation, and congestion. Nasal inflammation and congestion block the release of nasal nitric oxide. Blockage of nitric oxide increases the rate and severity of infections. In our human Phase II/III Placebo Controlled Clinical Trials, N115 reduced nasal congestion and inflammation. In additional six human clinical trials with COPD patients submitted to the FDA, N115 demonstrated a significant decrease in nasal and lung inflammation, substantial increases in lung functions, and increased nitric oxide needed to kill invading bacteria and viruses. These are critical benefits for treating the symptoms of Covid-19, as lung inflammation leads to pneumonia and death. Improving lung function of Covid-19 patients can save lives. Increased nasal nitric oxide is a preventative to reduce the rate, duration and spread of the disease.

## 1.2 History of N115 Drug Use

N115 is all-natural, non-steroidal, and has no known side effects. It has been used successfully by over 2 million patients globally in over 200 hospitals during the past 5 years to treat nasal and lung inflammation, congestion in Patients with COPD, Allergic Rhinitis, Pulmonary Fibrosis, and Cystic Fibrosis. It has been used in Children, Diabetics, and Hypertensives, with efficacy and with no known side effects. It has even been shown to be safe

for use by Pregnant Women, for whom steroids are contraindicated as they increase the risk of low birth-weight babies.

### 1.3 Mechanism of Action

The upper and lower airways form one contiguous and functionally related organ that is critical to normal lung functions. The nasal cavity produces 900-1,100 parts per billion of nitric oxide, which is used to kill invading bacteria, fungi, and viruses, compared to the lungs which produce 4-48 parts per billion nitric oxide. Nasal nitric oxide is a natural defense against disease. In recent clinical studies, Nitric oxide is elicited and inhibits viral replication in pigs infected with porcine respiratory coronavirus. Nasal nitric oxide also produces clinically useful bronchodilation and has been shown to reduce pulmonary fibrosis. Blockage of nasal nitric oxide by inflammation or congestion, reduces the amount of nitric oxide reaching the lungs, which reduces critical lung functions, leading to increased lung and nasal infections, a reduced SaO2 level, reduced FEV-1 levels also leading to mouth breathing and coughing. Nasal nitric oxide is also essential because it 1) increases oxygenation in your blood by inhaling more nitric oxide, which is a vasodilator and bronchodilator that increases oxygen transport throughout the body. 2) Warms, moistens and filters the air. 3)Traps particles in nose hairs and mucous membranes. 4) Helps reduce the likelihood of developing colds, flu, allergies, and irritating cough. 5) Prevents nasal dryness. 6) Helps relieve stress and calm the body as it slows breathing. 7) Promotes healthy digestion. 8) reduces risks of developing snoring or sleep apnea. Nasal steroids and other OTC nasal treatments shut down the synthesis of nasal nitric oxide, which then leads to decreased lung functions and a 34% increase in infections.

As cited in hundreds of peer reviewed publications, naturally occurring nitric oxide in the nasal cavities is a primary defense in humans; it is needed to kill invading bacteria, fungi and viruses. **Nasal nitric oxide also prevents and reduces the rate and severity of viral infections, viral replication from Rhinoviruses, the Flu, and Coronavirus.**

Nitric oxide decreases significantly from the normal levels found in young healthy adults when compared to patients with Asthma, COPD, Diabetes, Cystic Fibrosis, and Primary Ciliary Dyskinesia. The rate of infection increases with decreasing levels of nasal nitric oxide.

### 1.4 Nasal nitric oxide and COVID-19 infections.

Nasal Nitric Oxide reduces the rate, duration and severity of viral infections in healthy young children and in healthy adults from the Flu, Rhinovirus and Coronavirus. It's been demonstrated that Nitric oxide is elicited and inhibits viral replication in pigs infected with porcine respiratory coronavirus. Nasal Nitric Oxide levels decreases from normal levels found in healthy adults, in patients with asthma (87%), COPD (73%) CF (44%) and Primary Ciliary Dyskinesia (7%). The rate of infections increases with decreasing levels of nasal nitric oxide. Young children, 6-17 years of age, produce (142%) more nitric oxide than healthy adults, which may explain their resistance to COVID-19. Recently, researchers announced that a high percentage of COVID-19 infected patients that were hospitalized were Diabetics or were Pre-Diabetic. The literature has reported that elevated levels of glucose in patients with diabetes mellitus cause a deficiency in the production of nitric oxide by blunting nitric oxide synthesis,

which may explain their susceptibility to COVID-19. N115 increases nitric oxide and is safe for use by Patients with Diabetes.

As cited in hundreds of peer reviewed publications, naturally occurring nitric oxide in the nasal cavities is a primary defense in humans. Nitric Oxide is needed to kill invading bacteria, fungi and viruses, and prevents/reduces the rate, duration and severity of viral infections, viral replication from the Common Cold, Rhinoviruses, the Flu, and Coronavirus. N115 Increases Nasal Nitric Oxide thus is a preventative to reduce the rate and spread of the disease.

Most Diabetic, Hypertensives, Pulmonary Fibrosis and Cystic Fibrosis Patients have very low nasal nitric oxide which makes them more susceptible to viruses and lung infections. The rate of infection increases with decreasing levels of Nasal Nitric Oxide making them more susceptible to all infections including COVID-19. Elevated levels of glucose in patients with diabetes mellitus cause a deficiency in the production of nitric oxide by blunting nitric oxide synthesis, which may explain why diabetics have a high susceptibility to COVID-19.

**2.0 COVID-19 and flu Infection.**

COVID-19 and flu can be understood by the region of the lung that is infected. Mild disease will be confined to the conducting airways and severe disease will involve the gas exchange portion of the lung. Both flu and COVID-19 are a major health concern and can be devastating, especially for the elderly. COVID-19 is the disease caused by SARS-CoV2 the virus. Although much is known about the mortality of the clinical disease, much less is known about its pathobiology. Although details of the cellular responses to this virus are just emerging, a probable course of events can be postulated based on past studies with SARS-CoV. Based on the cells that are infected, COVID-19 can be divided into three phases that correspond to different clinical stages of the disease**.** Stage #1: Asymptomatic state (Initial 1–2 days of infection); Stage #2: Upper airway and conducting airway response (Next few days), and, Stage #3 Hypoxia, ground glass infiltrates, and progression to ARDS. Flu can also result in a descending, progressive disease resulting in pneumonia and ARDS in severe cases.

**Purpose and Objectives of the Studies.**

A COVID-19 Non-Steroidal Nasal Spray Treatment and Preventative that can get athletes, students and the general population, that test positive for Covid-19, back playing and back to work much faster than a 14-day quarantine and as a Preventative to help reduce the rate, duration and spread of the virus, is critical to the world. In testing patients with the saliva/sputum test developed by Yale University, it was discovered that some actively infected patients may be asymptomatic, but remain infected, in some cases for three weeks or longer. Thousands of data points have been collected with the saliva/sputum tests on the duration of the infection in COVID-19 patients. This data will be used as a historical baseline to demonstrate a reduction and duration of the infection in patients that use the N115 nasal spray.

This will be an on-going trial that will study the effects of a 20mM sodium pyruvate in 0.9% sodium chloride nasal spray solution on COVID-19 viral infections of patients with proven COVID-19 infections.

1. Nasal-pharyngeal swabs that are currently FDA approved for testing COVID-19 patients, will be used to determine if an individual is actively infected.

2. Covid-19 positive individuals will receive the nasal spray that will be used three times per day. This spray will be placebo control (15 patients, 0.9% sodium chloride with 0.02% benzalkonium chloride) or N115 treatment (15 patients, 20mM sodium pyruvate in 0.9% sodium chloride with 0.02% benzalkonium chloride). Study staff and subjects will be blinded.
3. Patients will return for testing again every other day to determine how fast the nasal spray reduces the viral load and infection, compared to the viral loads and infection on Day Zero, historical baselines, and placebo.

EmphyCorp Rx N115 Non-Steroidal Nasal Spray increases nasal nitric oxide and has the potential of reducing the rate and spread of COVID-19 among healthy individuals, diabetics, and others. Nasal steroids and other OTC nasal treatments shut down the synthesis of nasal nitric oxide which increases the rate of infections. This would indicate that the use of EmphyCorp's Rx N115 Nasal Spray by healthy individuals including Adults, Children, Pregnant Women, and Diabetics that are currently infected with COVID-19 without other underlying health conditions, could reduce the rate, duration and spread of infection.

## 3.0 Mechanism of Action of N115

Sodium pyruvate is a natural antioxidant, and as an antioxidant has been shown to significantly reduce inflammatory agents throughout the human body including the lungs and nasal passages. The reduction of inflammatory agents including IL-6 the cause of the cytokine storm in COVID-19 patients. Nasal congestion does not allow nitric oxide to be produced by nasal cells and released into the nasal cavities. A previous study with Pulmonary Fibrosis patients clearly demonstrated a significant increase in exhaled nitric oxide, and since nitric oxide has been shown to kill virus, including COVID-19, this trial is being designed to determine if the N115 Sodium pyruvate-based nasal spray will i increase in nasal nitric oxide to the extent that COVID-19 viral loads are reduced or eliminated.

In over six human clinical trials submitted to the FDA, with pulmonary fibrosis, COPD and Cystic fibrosis patients, N115 reduced lung inflammation by reducing inflammatory cytokines including the IL-6 cytokine that causes the so-called cytokine storm in COVID-19 patients and did this with no known adverse reactions.

In a Phase III Placebo Controlled Clinical Trial with Idiopathic Pulmonary Fibrosis Patients, N115 Non-Steroidal Nasal Spray demonstrated a statistically and clinically significant increase in Nasal Nitric Oxide, FEV-1, SaO2, FVC, FEV-1/FVC ratios (52% to 86%), and a significant reduction in coughing, nasal and lung inflammation. N115 increases Oxygen by reducing hypoxemia, and it also reduces lung inflammation, inflammatory cytokines, and coughing. These are critical benefits for treating the symptoms of Covid-19, as lung inflammation leads to pneumonia and death.

## 4.0 Pre-Clinical and Clinical History and Studies

### 4.1 Pre-Clinical Experience and Studies

As part of Cellular Science's IND submissions, five animal studies were conducted with solutions of differing concentrations of sodium pyruvate. These included a "Maximum Tolerated Nose Dose" study in rabbits (2000X the therapeutic human dose) and a 180-day nose only

inhalation study in which rats were exposed to 100 times the sodium pyruvate level expected to be administered to humans. No product related adverse reactions were observed or reported in any animal study, and the drug regimens were judged to be safe as determined by the FDA.

Rat studies in which the effect of multiple intratracheal administrations of sodium pyruvate on lung injury caused by bleomycin were conducted. Two weeks after the bleomycin insult, there was a significant ($p<0.01$) reduction in total cells found in the bronchoalveolar lavage containing sodium pyruvate, compared to the sodium chloride control, indicating a reduction in airway inflammation. It was concluded that sodium pyruvate was effective in reducing inflammation and lung damage in this chronic fibrotic stage of lung injury. (It should be noted that this type of injury with subsequent fibrotic infiltration is typical of the fibrosing group of interstitial diseases in humans including COVID-19.)

## 5.0. Qualifications of the Principal Investigator.

Dr. Lupfer has 15 years experience studying respiratory pathogens, developing antiviral drugs and vaccines, and studying the immune response to respiratory pathogens. Dr. Lupfer has designed the trial and will analyze final clinical data. Dr. Abraham is a clinician and will head the clinical research and data collection.

## Identification of the Research Facility

### 5.1. Research Facilities

Missouri State University in collaboration with Trinity Healthcare and Dynamic DNA labs in Springfield Missouri.

### 5.2. Institutional Review Board

### 5.3 Study Objectives

Primary Objective

a. The primary objective is to evaluate the effects of inhaled nasal sodium pyruvate (N115) in patients with confirmed COVID-19 or flu infections by determining changes in the duration of an active infection by PCR from nasal.

Secondary Objective

**a.** The second objective is to evaluate the ability of the inhaled nasal sodium pyruvate therapy in subjects with COVID-19 or flu infections to improve symptoms by the use of a patient diary and by collecting periodic vital signs, especially body temperature, blood pressure and pulse/Ox.

### 5.4. Study Design Overview

Individuals that are symptomatic for COVID19/influenza will initially be tested by Dynamic DNA Labs or Trinity Healthcare (Screening Visit). If positive for COVID19/influenza, patient will then be solicited for participation in the trial within 24 hours. After signing Informed Consent, women of child-bearing age will provide a urine sample to test for pregnancy. They will be randomly assigned to either the placebo or drug groups in a double blinded fashion and be given a data logbook, or clinical app for their phone, in which they will record the number of coughs and other flu-like symptoms they experience each day. Patients will be contacted by phone and/or sent reminders through a clinical phone app every two days to review symptoms and protocol compliance and patients will be tested via nasal swab every other day. This will continue every other day until the subject tests negative for COVID-19/ influenza (which is

defined as a 2-Log reduction in virus titer or less than 1000 copies of viral RNA) or 14 days, whichever comes first. Personnel collecting swabs will wear N95 mask and face shield, disposable examination gloves and disposable gown while collecting nasal swabs from patients. Samples will be collected outdoors, weather permitting, or in a well ventilated room in inclement weather.

## 6.0. The criteria for patient selection and for exclusion of patients, and an estimate of the number of patients to be studied.

### 6.1. Subject Selection

6.1.1 Number of Patients to be Studied

Fifteen patients with confirmed COVID-19 infection will be enrolled in the trial in the drug group and fifteen with confirmed COVID-19 infection will be enrolled in the trial in the placebo group. An additional fifteen patients with confirmed influenza infection will be enrolled in the trial in the drug group and fifteen with confirmed influenza infection will be enrolled in the trial in the placebo group. Efforts will be made to include women and minorities. The study will be double blinded to subjects and study investigators.

### 6.2. Inclusion Criteria

**6.2.1.** Individuals with a confirmed COVID-19/influenza viral infection, as determined by a qualified laboratory test. A nasal swab or saliva test analyzed by qPCR for COVID19 or rapid flu test from nasal swab for influenza.

**6.2.2.** Individuals who agree to abstain from sexual intercourse, or agree to use condoms or vaginal diaphragms or other devices designed to prevent contraception, during the entire course of the study

### 6.3. Exclusion Criteria

**6.3.1.** Viral infections other than COVID-19 or influenza.

**6.3.2.** Clinically significant cardiac disease including uncontrolled congestive heart failure and unstable angina

**6.3.3.** Pregnancy

**6.3.4.** Females of child bearing potential age not on adequate contraception or lactating

**6.3.5.** Subjects receiving systemic corticosteroid treatment within one month of Screening Visit

**6.3.6.** Subjects Less than 18 years of age

**6.3.7.** Hospitalization within last 6 months due to acute exacerbation of airway disease

**6.3.8.** Subjects with a clinically significant abnormal chest x-ray within past 12 months

**6.3.9.** Medication changes within one month of study entry

**6.3.10.** Subjects who have participated in another investigation drug treatment study within the previous month.

**6.3.11.** Subjects with a current history of alcohol or recreational drug abuse.

**6.3.12.** Subjects who have taken dietary supplements containing pyruvate within 24 hours prior to the screening visit.

### 6.4 Inclusion of Women and Minorities

Every attempt will be made to include all genders, and minorities that present with an active COVID-19 or flu infection that are not exempted due to exclusion criteria.

## 7.0. A Description Of The Design Of The Study, Including The Kind Of Control Group To Be Used, If Any, And A Description Of Methods To Be Used To Minimize Bias On The Part Of Subjects, Investigators, And Analysts.

### 7.1. Assignment Of Subject Number And Randomization

This is a placebo controlled double blinded trial. Upon enrollment, each subject will be sequentially issued a unique subject number starting at 100. Once a number has been assigned to a subject, it cannot be re-assigned to another subject. Subjects will be encouraged to complete the study, although they may withdraw at any time without prejudice. Termination will be reported to the sponsor in a timely manner. Details of the reason(s) why a subject is dropped from the study will be documented. Enrollment will continue until the number of subjects specified in the protocol has been attained. The data from all subjects that have been given a study compound will be retained for analysis.

### 7.2. Randomization

The subjects will be randomized to the placebo control or N115 drug study groups.

### 7.3. Study Design

#### 7.3.1. Pre-study Visit

A pre-study visit will occur and the eligibility of the subject for inclusion determined. COVID19 or influenza positive patients will sign an Informed Consent (paper or eConsent), and a list of current medications will be taken. Urine samples from child-bearing aged women will be collected and analyzed for pregnancy (or last menstrual cycle recorded). During this visit, any flu-like symptoms will be noted, temperature, Pulse/Ox and blood pressure will also be measured. During this pre-study visit, the patients are to continue with their normal therapy, if any.

#### 7.3.2. Study Visit 1

Only COVID19 or influenza single positive subjects meeting enrollment criteria will be enrolled after review of health information collected in the pre-study visit. The correct use of the N115 sodium pyruvate nasal spray will be demonstrated to COVID-19 or influenza infected subjects, and the subjects that have been confirmed to have an infection will administer their first dose while monitored in the clinic or via telehealth. (Nasal spray can be delivered to patient at time of telehealth visit by currier). The patients will be told to spray each nostril three times, three times per day: morning, mid-day, and evening. Patients will also be instructed on filling out the Daily Data Log form or in the use of the clinical symptoms app, which will be used to record administration of the drug doses, any flu-like symptoms, and any perceived adverse events.

#### 7.3.3 Study Visit 2 etc.

At home or on-site follow-up visits will occur every two days after Study Visit 1. During this visit, a nasal swab will be taken to determine if the patient still has an active infection. Temperature, Pulse/Ox and blood pressure will also be examined during these visits. Study monitors will review the Daily Data Log form/ Clinical app and compliance with study protocol of N115 administration will be reviewed. If needed, additional bottles of N115 nasal spray will

be delivered to the patient in the clinic or via currier.

This process of testing every two days will continue until the particular subject proves to be virus free (2 Log or greater decrease in viral RNA or less than 1000 viral RNA copies) or 14 days, whichever is first. When the patient is virus free, he/she will be excused from the study. If the subject is virus free, they will be asked to provide a second nasal swab within 24 hours to verify the negative result.

**7.3.4 Telephone Communication**

Subjects will be instructed to call the clinic should they be experiencing any self-perceived adverse events, or if they have any study-related questions. All telephone information will be documented.

**7.3.5. Products Description (How Administered)**

The product is an all-natural patented 20 mM sodium pyruvate in 0.9% sodium chloride nasal spray solution with 0.02% benzalkonium chloride as a preservative. The plastic bottle contains 30 mL. It is non-steroidal. Patients will forcibly expel air from their lungs and then will administer three sprays per nostril while inhaling strongly so that the drug is transported through the nose and into the lungs. The drug is to be administered three times per day (morning, mid-day, and evening). The product comes with instructions for administration (three sprays per nostril).

**7.4 Concomitant Therapy**

No concomitant therapy is prescribed for this study, but the subjects may continue to use their normal therapy as long as they list it as a current medication. The Principal Investigator may prescribe "rescue medication" should it be required by any of the patients. Patients may continue taking nutritional supplements. safety. Subjects may not use any of the following during the trial or for one week before enrollment in the trial: all intranasal medications or lavages, antihistamines, steroids or anti-inflammatory medications of any kind. Subjects also may not currently be taking any antiviral or antibiotic medications.

## 8.0. The Method For Determining The Dose(S) To Be Administered, The Planned Maximum Dosage, And The Duration Of Individual Patient Exposure To The Drug.

This is a constant dose study. The amount of delivered sodium pyruvate was determined in clinical trials to be three sprays of 20 mM sodium pyruvate in 0.9% sodium chloride solution per nostril, and this is repeated 3x per day (morning, midday, and evening). The dose was determined by evaluating the data from both animal and human studies (cited above).

## 9.0. A Description Of The Observations And Measurements To Be Made To Fulfill The Objectives Of The Study.

Observations for safety will include a pregnancy test for women of child-bearing age, blood oximetry, and vital signs.

Observations for efficacy will include evaluation of sore throat, congestion, erythema, the number of daily coughs, and flu-like symptoms. Perceived adverse events will be monitored.

Premature Withdrawal

The patients can withdraw from the study at any time, and for any reason. All data collected from these patients will be analyzed. Reasons for withdrawal will be recorded to ensure that it was not due to an adverse event.

**8.2 Testing Schedule-Sub-Chronic Phase of COVID-19 or flu positive patients**

| Test | Pre-study visit | Day 0 Visit 1 | Day 2 | Day 4 | Day 6 | Day 8, etc. |
|---|---|---|---|---|---|---|
| **Clinic Visit or telehealth check** | | + | + | + | + | + |
| **Informed Consent** | + | | | | | |
| **Medical History** | + | + | | | | |
| **Physical Exam/** | + | | | | | |
| **Observe Administer Drug** | | + | + | | | |
| **Pregnancy Test for Females** | + | | | | | |
| **Concurrent Medications Reviewed** | + | + | + | + | + | + |
| **Symptom Data Logbook (Clin. App.)** | | + | + | + | + | + |
| **Adverse Events Reviewed** | | + | + | + | + | + |
| **Nasal Swab for virus titer** | | + | + | + | + | + |

**12.0 Safety Testing**

**12.1 Physical Exam**

**12.2 Efficacy Tests**

12.2.1 Nasal swab test for COVID-19 or influenza virus analyzed by qPCR.

**13.0 <u>A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk</u>**

Tests and analyses will be conducted every other day during the study. If any aberrant values occur, the Clinical Coordinator will determine if that patient should continue the study or be removed. All aberrant values that occur during the study will be considered adverse events.

**14.0. <u>Safety Precautions Included in this Study</u>:**

The 20 mM nasal sodium pyruvate inhalation has been administered to both healthy humans and humans with lung diseases, without the occurrence of any SAE.

- First administration of nasal spray monitored via telehealth on in clinic.
- The initial nasal spray will be administered under the supervision of medical staff.

- If a subject develops any adverse event during the follow-up period after study drug administration, the subject will be treated to a satisfactory resolution before being discharged from the clinic.

• Subjects will remain in contact via telehealth or in the clinic for 30 minutes after the initial inhalation of the nasal spray.

• Follow up telephone communications, as needed.

• If at any time the patient shows severe signs of disease or complications, they shall be removed from the study by the physician (Dr. Abraham) and treated using proven methods for COVID19 or flu. These include, but are not limited to, antiviral drugs (Tamiflu, remdesivir, etc.), convalescent serum, oxygen and critical care. Treatment decisions will be made by Dr. Abraham, the patient's physician or an emergency care physician as needed. The patient may also withdraw from the study at any time, and for any reason, and seek traditional standard of care for COVID19 or flu.

• Severe signs of disease or complications include abnormal blood pressure (low or high), resting blood $O_2$ below 90%, apnea, fever over 103° F, altered mental state, impaired renal function, hemorrhaging or other severe symptoms.

**15.0 Product Evaluation Questionnaire**. This information will not be collected in the current study as it has been collected in numerous prior studies.

**16.0 Daily Data Logbook:**

Subjects will use this diary card or a clinical phone app to record the number of their coughs per day and flu-like symptoms, any self-perceived adverse events, and any medication changes during the study.

**17.0 Urinalysis**: Samples may be taken and analyzed to determine if any females of child bearing age are pregnant

**18.0 Study Management**

**18.1 Case Report Forms**

Case Report Forms (CRF) will be supplied by Cellular Sciences and the testing facility. Data will be recorded in the CRFs according to the following:

Instructions to data entry personnel and Monitor:

(a)Explain all missing data and include reference to any original data that is not contained in the study file. If a space is blank because the item was not done, mark the item "N/A". If the item is not applicable to the individual case, mark the item "N/A". If an item is unknown, mark the space "UNK". Legibly write or print all entries in black ink. If an entry error has been made, draw a single straight line through the wrong entry and enter the correct data above it. Please initial and date all such changes. DO NOT ERASE OR OPAQUE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date the clarification.

**18.2. Data Collection, Management, and Statistical Analysis**

The data management staff at the research clinic and lab (Trinity Healthcare and Dynamic DNA Labs) will collect and manage the data. Monitoring and auditing of the data will be

conducted by a staff member of Cellular Sciences remotely.

The basic statistical analysis will be repeated measurements of Analysis of Variance using baseline measurements as a covariant per subject. Group comparisons of N115 to placebo will be analyzed by ANOVA followed by Chi Square, Fisher Exact, and other appropriate significance tests. Data will be compared to placebo controls and current publicly available matched data and observed values compared. Time dependence in viral titer reduction will also be compared. Dr. Lupfer will be responsible for the statistical analysis. Analysis will be performed blinded.

**18.3. Study Monitoring**

A Study Monitor who will be responsible for auditing data will be appointed by Cellular Sciences. The Monitor will visit the clinical site two or three times during the trial to assure that all data are being collected and that the Case Report Forms are completed and correctly filled out. Alternatively, virtual visits may be conducted due to COVID19 exposure concerns.

**18.4. Data from Patients Who Withdraw from the Study**

If a subject withdraws from a study, the data collected on the subject to the point of withdrawal will remain part of the study database and will not be removed.

The investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review and address the maintenance of privacy and confidentiality of the subject's information.

If a subject withdraws from the interventional portion of the study but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). In accordance with FDA regulations, IRB approval of informed consent documents would be required (21 CFR 50.25, 56.109(b), 312.60, 312.66, 812.100).

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

**18.5. Product Packaging**

The product packaging has complied with FDA regulations. The nasal spray will be contained in a sterile plastic vial that can be squeezed to administer the correct dosage. The packaging meets 21CFR312.6 including the statement "New Drug - investigational use only." The vials necessary for each study period (i.e. ~14 days) will be placed in a plastic bag with the patient's number.

**18.6. Product Storage Requirements**

18.6.1 At Research Center

The products are to be stored at room temperature, but not above 85$^{o}$F

18.6.2 In Home

The products are to be stored at room temperature, but not above 85°F

### 18.7. Record Retention

All records will be kept by the clinic for a period of three years. After that, they will be sent to Cellular Sciences.

### 18.8. Additional Studies

No additional studies are planned at this time.

## 19.0 Reports on Adverse Events

### 19.1 Definition of an Adverse Event

CTCAE term (Adverse event description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 3.0. A copy of the CTCAE version 3.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/ctc.html).

"Expectedness": Adverse events can be "Expected" or unexpected.

Attribution of the adverse event (Section 4.8.5):

Definite – The adverse event *is clearly related* to the study treatment.
Probable – The adverse event *is likely related* to the study treatment.
Possible – The adverse event *may be related* to the study treatment.
Unlikely – The adverse event *is doubtfully related* to the study treatment.
Unrelated – The adverse event *is clearly NOT related* to the study treatment.

A serious adverse event (SAE) is defined as *any expected or unexpected adverse event* (AE, generally equivalent to CTCAE ver 3.0 grades 3, 4 or 5) that is *related or unrelated* to the intervention that results in any of the following outcomes:

- Death
- A life-threatening event
- In-patient hospitalization (not required as part of the treatment) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Causes cancer
- Is an overdose

Certain medical events that may not result in death, be life-threatening, or require hospitalization, may also be considered a serious adverse event when appropriate medical or surgical intervention is necessary to prevent one of the outcomes listed above.

Unexpected Adverse Event - Any event in which the severity or specificity is not consistent with the risk information described in the protocol, and the event is not anticipated from the subject's disease history or status.

Expected Adverse Event - Any event in which the severity or specificity is consistent with

the risk information described in the protocol or is anticipated based on the subject's medical history.

Important medical events that may not be immediately life-threatening or that do not result in death or hospitalization may be considered SAEs when, on the basis of appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

All deaths, regardless of cause, must be reported for patients on study and for deaths occurring within 30 days of last study drug dose.

### 19.2. Examples of Adverse Events

- Inter-current illnesses
- Injuries
- New symptomatology (this does not include symptoms expected as a result of the subject's condition unless it is beyond what is normally expected)
- Significant laboratory abnormalities
- New abnormal physical exam findings
- Significant exacerbation of pre-existing conditions

### 19.3. Recording and Documentation of Adverse Events

Any adverse event (i.e., a new adverse event or an exacerbation of a pre-existing condition) with an onset date after study drug administration should be recorded as an adverse event on the Case Report Form (CRF). All adverse events must be recorded on the appropriate CRF regardless of the severity or relationship to study medication.

An adverse event or laboratory abnormality with an onset date before study drug administration is considered to be pre-existing in nature. These pre-existing events, will be noted in the CRFs.

All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be recorded on the Florida Advanced Medical Research Adverse Events form

### 19.4 Investigator Report of a "Serious Adverse Event" to Cellular Sciences

Cellular Sciences (Sponsor) must be notified immediately regarding the occurrence of any SAE that occurs after the first dose of study drug has been administered. The procedures for reporting SAEs are as follows:

- Complete the "Serious Adverse Event Report."
- Email the SAE Report to Cellular Sciences (see below) within 24 hours of the investigator's knowledge of the event.
- These preliminary reports must be followed by detailed descriptions that include copies of hospital case reports, autopsy reports, and other documents when requested and applicable.
- The contact information for reporting SAEs is as follows:

Following the first dose of the drug product, the Investigator or designee must report the occurrence of any serious adverse event to Cellular Sciences within one (1) business day, regardless of the causal assessment to study medication. A photocopy or facsimile of the Serious Adverse Event page of the CRF must be provided to:

Ronald J. Amen, Ph.D. Alain Martin, Ph.D.

Director
Cellular Sciences
18101 Catherine Circle
Villa Park, CA 92861
ronald.amen@techenterprises.org

Director
Cellular Sciences
84 Park Ave
Flemington, NJ 08822
dr.martin@erols.com

### 19.5 IRB Notification

The Investigator is responsible for promptly notifying the Institutional Review Board of all serious adverse events and providing appropriate documentation. The Investigator should notify the IRB as soon as is practical. Notification should be in writing where this is required by local regulatory authorities and in accordance with the local institutional policy.

Adverse events must be reported to the Investigator and IRB according to definitions and guidelines at http://www.infosci.coh.org/ocrqa/forms/guidance.doc and which are defined herein. AEs will be monitored by the PMT. Less than serious adverse events will be reported only at the time of protocol continuation reports.

Cellular Sciences may request additional information from the Investigator to ensure the timely completion of accurate safety reports.

### 19.6 Attribution

For reporting purposes, attribution is the assessment of the likelihood that an AE is caused by the research agent or protocol intervention. The attribution is assigned by the treating physician/Principal Investigator after considering the clinical information, the medical history of the subject, and past experience with the research agent/intervention. This is recorded using the Adverse Event Report (COH AER) form (http://resadmin.coh.org/doc /irb3820.doc) in one of five categories scored as the following: 5=related, 4=probably related, 3=possibly related, 2=unlikely related, and 1=unrelated.

### 19.7. Post-study Adverse Events

The Investigator will notify Cellular Sciences of any serious adverse event he/she becomes aware of that occurs at any time after a subject has completed study participation, if in the Investigator's judgment the event may be reasonably related to the medication used in the study. The Investigator will follow the subject until the adverse event resolves or becomes stable.

## 20.0 References


1. Hardman, J. Et al. The pharmacological basis of therapeutics. Ninth edition 1996 pages 137 and 356
2. Moncada, S. et al Nitric Oxide: physiology, pathophysiology, and pharmacology. 1991 Pharmacological Reviews Vol. 43 no2 pp109-141
3. Nathan, C. Nitric oxide as a secretory product of mammalian cells. FASEB journal vol. 6 Sept. 1992 pp3051-3064
4. Mukala, K. et al. Personally measured weekly exposure to NO2 and respiratory health among preschool children. Euro. Respir. J. Vol. 13 pp1411-1417. (8)
5. Stanko R.The power of Pyruvate 1999 (9)
6. Kelly, F. et al. Antioxidant kinetics in lung lavage fluid following exposure of humans to nitrogen dioxide. Am. J. Respir. Crit Med. Vol. 154 1991 pp1700-1705(10)
7. Lehninger 1981 Biochemistry (12)
8. Comhair, S. et al. Rapid loss of superoxide dismutase activity during antigen-induced asthmatic response. Lancet vol. 355 Feb. 19 2000. (13).
9. Nicola J Roberts, Simon J Lloyd-Owen, Fernando Rapado, Irem S Patel, Tom MA Wilkinson, Gavin C Donaldson, Jadwiga A Wedzicha. Relationship between chronic nasal and respiratory symptoms in patients with COPD Respiratory Medicine Volume 97, Issue 8, August 2003, Pages 909–914.
10. Lamas DJ, Kawut SM, Bagiella E, et al. Delayed access and survival in idiopathic pulmonary fibrosis: a cohort study. Am J Respir Crit Care Med 2011; 184: 842–847.
11. Mermigkis C, Stagaki E, Tryfon S, et al. How common is sleep-disordered breathing in patients with idiopathic pulmonary fibrosis? Sleep Breath 2010; 14: 387–390.
12. Kreuter M, Ehlers-Tenenbaum S, Schaaf M, et al. Treatment and outcome of lung cancer in idiopathic interstitial pneumonias. Sarcoidosis Vasc Diffuse Lung Dis 2015; 31: 266–274.
13. Ilng AJ, Ngu MC, Breslin AB. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. Am J Respir Crit Care Med 1994; 149: 160–167.
14. Kilduff CE, Counter MJ, Mermigkis C, Bouloukaki I, Antoniou K, et al. Obstructive sleep apnea should be treated
15. in patients with idiopathic pulmonary fibrosis. Sleep Breath 2015; 19: 385–391.
16. Birring SS, Ing AJ, Chan K, et al. Obstructive sleep apnoea: a cause of chronic cough. Cough 2007; 3: 7.
17. Jung HK, Choung RS, Talley NJ. Gastroesophageal reflux disease and sleep disorders: evidence for a causal link and therapeutic implications. J Neurogastroenterol Motil 2010; 16: 22–29.
18. Chan KK, Ing AJ, Laks L, et al. Chronic cough in patients with sleep-disordered breathing. Eur Respir J 2010; 35: 368–372.
19. Eskiizmir G, Kezirian E. Is there a vicious cycle between obstructive sleep apnea and laryngopharyngeal reflux disease? Med Hypotheses 2009; 73: 706–708.
20. Chan K, Ing A, Birring SS. Cough in obstructive sleep apnoea. Pulm Pharmacol Ther 2015; 35: 129–131.
21. Boulet LP, Coeytaux RR, McCrory DC, et al. Tools for assessing outcomes in studies of chronic cough: CHEST guideline and expert panel report. Chest 2015; 147: 804–814.
22. Lee KK, Matos S, Evans DH, et al. A longitudinal assessment of acute cough. Am J Respir Crit Care Med 2013; 187: 991–997.
23. Lechtzin N, Hilliard ME, Horton MR. Validation of the cough quality-of-life questionnaire in patients with idiopathic pulmonary fibrosis. Chest 2013; 143: 1745–1749.
24. Morice AH, Kastelik JA, Thompson R. Cough challenge in the assessment of cough reflex. Br J Clin Pharmacol 2001; 52: 365–375.
25. Spinou A, Birring SS. An update on measurement and monitoring of cough: what are the important study endpoints? J Thorac Dis 2014; 6: Suppl. 7, S728–S734.
26. Birring SS, Spinou A. How best to measure cough clinically. Curr Opin Pharmacol 2015; 22: 37–40.
27. Lee JS, Collard HR, Anstrom KJ, et al.Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials. Lancet Respir Med 2013; 1: 369–376.
28. Raghu G, Rochwerg B, Zhang Y, et al.An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. Am J Respir Crit Care Med 2015; 192: e3–e19.
29. Vertigan AE, Kapela SL, Ryan NM, et al. Pregabalin and speech pathology combination therapy for refractory chronic cough: a randomised controlled trial. Chest 2016; 149: 639–648.
30. Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. Lancet 2012; 380: 1583–1589.
31. Patel AS, Watkin G, Willig B, et al. Improvement in health status following cough-suppression physiotherapy for patients with chronic cough. Chron Respir Dis 2011; 8: 253–258.
32. Kreuter M. et al., European Respiratory Journal, 2016 International consensus statement on idiopathic pulmonary fibrosis. U Costabel et al., European Respiratory Journal, 2001

33. Van MJ. Manen, Surinder S. Birring, Carlo Vancheri, Vincent Cottin, Elisabetta A. Renzoni, Anne-Marie Russell, Marlies S. Wijsenbeek Cough in idiopathic pulmonary fibrosis European Respiratory Review Sep 2016, 25 (141) 278-286; DOI: 10.1183/16000617.0090-2015
34. Rossaint, R. et al Inhaled nitric oxide: its effect on pulmonary circulation and airway smooth muscle cells. Euro Heart Jour. 1993 vol. 14 Supp. Pp133-140
35. Mattes, K. et al. NO in exhaled air is correlated with markers of eosinophilic airway inflammation in corticosteroid-dependent childhood asthma. Euro Respir J. 1999 vol. 13 pp1391-1395
36. Artlich, A. et al. Childhood asthma: exhaled nitric oxide in relation to clinical symptoms. Euro Respir. J. Vol. 13 pp1395-1401.
37. Jobsis, Q. et al. Sampling of exhaled nitric oxide in children: end expiratory plateau, balloon and tidal breathing methods compared. Euro Respir. J. Vol. 13 pp1406-1410.
38. Mukala, K. et al. Personally measured weekly exposure to NO2 and respiratory health among preschool children. Euro. Respir. J. Vol. 13 pp1411-1417.
39. Stanko R.The power of Pyruvate 1999
40. Kelly, F. et al. Antioxidant kinetics in lung lavage fluid following exposure of humans to nitrogen dioxide. Am. J. Respir. Crit Med. Vol. 154 1991 pp1700-1705
41. Roberts, J. et al. Inhaled nitric oxide and persistent pulmonary hypertension of the new borns. The new England journal of Medicine Feb 27, 1997 pp 605-610
42. Comhair, S. et al. Rapid loss of superoxide dismutase activity during antigen-induced asthmatic response. Lancet vol. 355 Feb. 19 2000.
43. Stewart RM, et al. Hydrogen peroxide contracts airway smooth muscle: a possible endogenous mechanism. Respir. Physiol 1981 45: 333-342.
44. Rhoden KJ, Barnes PJ: Effect of hydrogen peroxide on guinea pig tracheal smooth muscle in vitro: role of cyclo-oxygenase and airway epithelium. Br. J Pharmacol 1989 98: 325-330
45. Motojima S, et al. Toxicity of eosinophil cationic proteins for guinea pig tracheal epithelium in vitro. Am Rev Respir Dis 1989 139: 801-805
46. Sporn PH, et al. Hydrogen peroxide induced arachidonic acid metabolism in rat alveolar macrophage. Am Rev Respir Dis 1988 137: 49-56
47. Postma, D.S. et al Association between nonspecific bronchial hyperreactivity and superoxide anion production by polymorphonuclear leukocytes in chronic air flow obstruction. Am. Rev Respir Dis. (1988) 137: 57-61
48. Alving, K. Methodological aspects of exhaled nitric oxide measurements Euro Respir Rev 1999: 9: 68, 208-211
49. Kharitonov, S. Exhaled nitric oxide and carbon monoxide in asthma. Euro Respir. Rev. 1999, 9: 68, 212-216
50. Gouw, P. et al. Stimuli affecting exhaled nitric oxide in asthma. Euro Respir. Rev. 1999; 9: 68, 219-222
51. Kharitonov, S. Exhaled nitric oxide and carbon monoxide in respiratory diseases. Euro Respir. Rev. 1999; 9: 68, 223-226
52. Barnes, P. The effect of drugs on exhaled nitric oxide. Euro Respir. Rev. 1999; 9: 68, 231-233.
53. Baraldi, E. et al. Application of exhaled nitric oxide measurement in pediatrics. Euro Respir. Rev. 1999; 9: 68, 234-240.
54. Lundberg, J. Nitric oxide in the nasal airways. Euro Respir. Rev. 1999; 9: 68, 241-245.
55. Culpitt, S. The measurement of hydrogen peroxide in airways disease. Euro Respir. Rev. 1999; 9: 68, 246-248.
56. Montuschi, P. Isoprostanes and other exhaled markers in respiratory diseases. Euro Respir. Rev. 1999; 9: 68, 249-253.
57. Robertson, FM, Gene expression and cellular sources of inducible nitric oxide synthase during tumor promotion. Carcinogenesis 1996 Sept;17(9): 2053-9
58. Soler MN, et al, Gene therapy of rat medullary thyroid cancer by naked nitric oxide synthase II DNA injection. J Gene Med 2000 Sept-Oct;2(5):433-52
59. Wang HH, B 16 melanoma cell arrests in mouse liver induces nitric oxide release and sinusoidal cytotoxicity a natural hepatic defense against metastasis. Cancer Res 2000 Oct 15;60(20): 5862-9
60. Brennan PA. The action and interactions of nitric oxide in solid tumors. Eur J Surg Oncol 2000 Aug, 26(5): 434-7
61. Rieder J, et al. Different patterns of inducible nitric oxide synthase gene expression in ovarian carcinoma cell lines. Anticancer Res 2000 sept-Oct;20(5A):3251-8
62. Hurst JR Upperairway.3:Sinonasalinvolvementinchronic obstructive pulmonary disease. *Thorax* 2010; 65:85–90.
63. Shingo Noguchi et al. Nitric oxide exerts protective effects against bleomycin-induced pulmonary Fibrosis in mice. Respiratory research 2014 15:92

64. M. Yoshida et al. The effect of low dose inhalation of nitric oxide in patients with pulmonary Fibrosis, Eur Respir. J 1997; 10: 2051-2054
65. Yong GL et al. Outpatient inhaled nitric oxide in a patient with idiopathic pulmonary fibrosis: a bridge to lung transplant. J Heart lung transplant 2001 Nov; 20(11): 1224 7
66. Ian M Balfour-Lynn et al Reduced upper airway nitric oxide in cystic fibrosis Archives of diseases in childhood 1996; 75: 319-322
67. Ferguson E et al. Changes in nasal nitric oxide concentrations associated with symptoms of common cold and treatment with topical decongestants. Acta Otolaryngology 1997 Jul; 117(4); 614-7
68. Westerveld et al. Inhibition of nitric oxide synthase by nasal decongestants. Eur Respir J 2000 sept 16(3): 437-44
69. Li Lisha, wang Ruiqi, Guan kai. Treatment effect of sodium pyruvate nasal spray on allergic Rhinitis. J clin Otorhinolaryngol head neck surg (chian) vol 31 iss 2 p102-109
70. Baraldi E. et al. Effect of topical steroids on nasal nitric oxide production in children with perennial allergic.