IRB Approved at the
Protocol Level
May 28, 2019

A Feasibility Study: A Safety Evaluation of the RheOx™ on Patients with Chronic Bronchitis in the United States

Study Number: CS003 **Version: 19APR2019**

Study Sponsor: Gala Therapeutics, Inc. (Corporate Headquarters)
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Study Device: RheOx™

PROTOCOL REVISION HISTORY	
Revision Date	**DESCRIPTION**
28MAY2018	Original Issue
25JUN2018	Updates made to address FDA questions as follows: • Section 3.2.1 added sustained (≥ 30 seconds) ventricular tachycardia • Section 7.1 added IVY heart rate alarm limits • Sections 7.2.2 and 7.2.4 added 6-section 3-lead EKG recording prior to initiation of energy delivery • Section 7.6.1 clarified arrhythmia stopping rule
27JUN2018	Updates made to address FDA questions as follows: • Section 3.2.1 added Respiratory Failure • Section 6.1 Inclusion Criteria added Subject has a SGRQ score of greater than or equal to 25 and CAT score of greater than or equal to 10. • Section 6.2 added exclusions for Asthma, Bronchiectasis, Uncontrolled GERD, severe Pulmonary Hypertension and infectious drug resistant infectious airway diseases • Section 7.2 Description of Visits including Figure 7.1 Study Procedures and Table 7.1 to include 1 week and 1-month post procedure follow-ups • Section 7.6.1 Study Stopping Rules added Pulmonary Hemorrhage and modified the pneumothorax criteria to require 3 or more subjects • Section 10.2 List of foreseeable adverse events added significant pulmonary bleeding and death as low occurrence
28JUN2018	Updates made to address FDA questions as follows: • Section 6.1 Inclusion Criteria added Subject has 1 or more COPD exacerbations, defined as an acute worsening in respiratory symptoms that requires additional treatment, in the 12-months prior to enrollment
12NOV2018	• Cover Page: Updated address for Gala Menlo Park Office • Synopsis: Revised number of clinical sites from 5 to 7 • Throughout Document: Replaced Gala Airway Treatment (GATS) with RheOx to reflect trademarked device name and minor punctuation/page formatting corrections • Schedule of Events Table 7.1: Changed Follow-up CT scan from 3 months to 6 months post-bronchoscopy #2; updated sections 7.2.7 and 7.2.8 accordingly. Removed 'phone call' from Visit #5 in table header to clarify the visit is in-office; this is consistent with section 7.2.5 and Figure 7.1. Changed the time period for the daily diary from entire study period (5 years) to only the first year.
31JAN2019	• Section 7.2.4 Visit 4/Bronchoscopy #2 added CT scan • Table 7.1 Schedule of Events: Added CT at Visit 4 prior to Bronchoscopy #2; removed Induced Sputum from Visit 2/Bronchoscopy #1 and Visit 4/Bronchoscopy #2 and moved superscripts to individual activities for additional clarity
19APR2019	• Synopsis: Revised number of clinical sites from 7 to 10

PROTOCOL REVISION HISTORY	
Revision Date	**DESCRIPTION**
	• Synopsis: Revised number of patients from 15 to 30 • Synopsis: Revised Other (tertiary) endpoints to include the Insomnia Sleep Index (ISI) and cough count • Section 3.2.3 was updated to include the Insomnia Sleep Index (ISI) and cough count • Section 7.2 clarified wording regarding rescheduling of follow-up visits due to COPD exacerbations • Section 7.4 schedule of events added visit windows, ISI and selected, optional polysomnography, cough counting monitor, and clarified wording regarding rescheduling of follow up visits due to COPD exacerbations • Section 10.2 added urinary retention to minor complications associated with anesthesia • References: added reference 21

STUDY ACKNOWLEDGMENT

Investigator's Statement:

I have read and understand Protocol No. CS003 and agree to conduct the study as outlined herein.

_____
Investigator's Name (please print)

_____
Investigator's Title

_____
Investigator's Signature

_____
Date

Sponsor Signature, Protocol Approval:

This study protocol, Protocol No. CS003, has been reviewed and approved by Gala Therapeutics, Inc., in accordance with Company policy and procedures and the US FDA, as warranted, under IDE requirements per 21 CFR part 812.

For: Gala Therapeutics, Inc.
230 Park Ave., Suite 2800
New York, NY 10169

_____
Name (please print)

_____
Signature

_____
Position/Title

_____
Date

STATEMENT OF COMPLIANCE

The clinical trial referenced herein will be conducted in compliance with this Protocol, and with local, State, and Federal requirements, including Good Clinical Practices, the overseeing IRB requirements, patient privacy requirements, and all applicable regulatory requirements.

Protocol Version: CS003

Revision Date: 19 April 2019

_____

Investigator's Name (please print)

_____

Investigator's Title

_____

Investigator's Signature

_____

Date

TABLE OF CONTENTS

1.0 INTRODUCTION 14
1.1 Background 14
1.2 Trial Justification 15
1.2.2 Opportunity for Intervention 15
1.3 Supporting Rationale – First-In-Human Trial (FIH) Overview 16
2.0 DEVICE DESCRIPTION 18
2.1 Device Identification 18
2.2 Device Manufacturer 18
2.3 Device Description 18
2.4 Intended Purpose and Study Population 21
2.5 Anticipated Changes During Investigation 21
3.0 STUDY OBJECTIVES 21
3.1 Study Objective 21
3.2 Outcome Measures 21
4.0 INVESTIGATIONAL SITES 22
5.0 STUDY DURATION 23
6.0 SUBJECT ELIGIBILITY 23
6.1 Inclusion Criteria 23
6.2 Exclusion Criteria 24
7.0 STUDY PROCEDURES 25
7.1 Treatment Plan 27
7.2 Description of Visits 27
7.3 Concomitant Medications / Treatments 30
7.4 Schedule of Events (Table 7.1) 32
7.5 Removal of Subjects 33
7.6 Early Termination or Suspension of Study 33
8.0 STATISTICAL CONSIDERATIONS 34
8.1 Study Design 34
8.2 Sample Size 34
8.3 Evaluable Cohort 34
8.4 Outcome Analysis 34
9.0 DATA MANAGEMENT 35

9.1 Data Entry 35
9.2 Subject Data Protection 35
9.3 Data Retention 35
9.4 Monitoring 35
10.0 ADVERSE EVENTS 36
10.1 Reporting Requirements 36
10.2 List of foreseeable adverse events related to investigational therapy and/or study procedure: 37
11.0 RISK-BENEFIT ASSESSMENT 38
11.1 Anticipated Risks 38
11.2 Anticipated Benefits 38
12.0 STUDY MANAGEMENT 38
12.1 Statement of Compliance 38
12.2 Institutional Review Board (IRB) 38
12.3 Investigator Responsibilities 39
12.4 Study Initiation 39
12.5 Amendments to the Clinical Investigational Plan (CIP) 40
12.6 Deviations from the Clinical Investigational Plan 40
12.7 Informed Consent Process 40
12.8 Device Accountability 40
12.9 Publication Policy 41
13.0 BIBLIOGRAPHY 42

PROTOCOL SYNOPSIS

Protocol Title	A Feasibility Study: A Safety Evaluation of the RheOx™ on Patients with Chronic Bronchitis in the United States
Study Number	CS003
Study Sponsor	Gala Therapeutics, Inc. Menlo Park, CA USA
Study Device	RheOx™
Design	Prospective, single-arm feasibility study
Objective	Primary: To assess the safety of the RheOx in patients with chronic bronchitis Secondary: To assess the clinical utility of the RheOx in patients with chronic bronchitis
Study Population	The study will treat up to 30 adult patients with chronic bronchitis at up to 10 clinical study sites in the United States Gala will conduct an interim safety analysis after 5 subjects complete the second RheOx procedure to assess the safety profile of the device and procedure and ensure it is safe to continue the study.
Study Period	Subjects receive treatment in the right lung first, followed by treatment of the left lung approximately 4-weeks later. The follow-up period will extend to 5 years following treatment of the second lung. Study follow-up visits will occur at 6-months, 12-months, 2, 3, 4 and 5 years after the second treatment.
Outcome Measures	The primary outcome of the study is safety. The primary safety analysis will be the incidence of serious adverse events of interest through 12 months defined as the following; • Death • COPD exacerbation, as defined as an acute worsening in respiratory symptoms requiring additional therapy, that requires a hospital stay of greater than 24 hours • Pneumothorax within 2 days of either Gala Treatment procedure • Pneumonia within 7 days of either Gala Treatment procedure, as defined as an increase in respiratory symptoms, fever, sputum production and or purulence with radiographic confirmation • Respiratory Failure as defined as a requirement for mechanical ventilatory support for > 24 hours • Arrhythmia requiring intervention or sustained ($\geq$ 30 seconds) ventricular tachycardia

The secondary outcome measures of clinical utility will be assessed by;

- The change from baseline at 6 and 12 months in St. George's Respiratory Questionnaire (SGRQ)
- The change from baseline at 6 and 12 months in COPD Assessment Test (CAT)

Hospitalization rates (not including the planned bronchoscopy procedures) from discharge from the initial RheOx Bronchial Rheoplasty procedure (Visit 2) through 12 months

Other (tertiary) endpoints

Other, tertiary and exploratory endpoints will also be assessed including changes from baseline to follow-up in:

- Responder rates utilizing established clinically meaningful thresholds for SGRQ (4 points)[17] and CAT (2 points)[16]
- Change in other QOL measures including CASA-Q and EXACT-PRO
- Change in lung function as measured by FEV_1 and FVC
- Change in sleep patterns as assessed by the Insomnia Sleep Index (ISI)
- Change in cough count as assessed by a cough counting monitor
- Mucin concentrations (MUC5AC, MUC5B) from induced sputum samples
- Quantitative High Resolution CT Scan (HRCT) metrics including airway volume, total airway count, and lobar volumes
- Device performance

In addition to the endpoints described above, additional safety analyses in support of the primary study outcome and to assess the totality of safety profile of RheOx, will be conducted.

Adverse events reported from the day of the index procedure through completion or termination of the study will be assessed. AEs and SAEs will be summarized using a standard medical coding dictionary (MedDRA). AEs and SAEs will be also analyzed by severity, relatedness to the device and/or procedure and within discrete time periods in relation to the index procedure.

COPD exacerbations will also be analyzed by severity (mild, moderate, and severe) based on commonly accepted clinical definitions as defined in GOLD 2018 Report[18].

Statistical Considerations

As this is a feasibility study, endpoints will not be powered for statistical significance. Descriptive statistics will be utilized to summarize and report on data for all subject and outcome variables.

Categorical data (e.g., age, gender) will be reported in frequency distributions. Certain dichotomous data (e.g., Adverse Events) will also be presented as rates. Continuous data (e.g., age, FEV_1) will be

summarized using mean, standard deviations, medians, minimums, maximums, and interquartile ranges.

All patients that enter the procedure room for the index RheOx Bronchial Rheoplasty procedure (Visit 2) will be included in the analysis.

Additional subgroup and other multivariable analyses may be performed including examination of the association between subject risk factors (e.g., age, gender) and trial outcomes, and the potential contributions of these factors.

LIST OF ABBREVIATIONS

6MWT	Six Minute Walk Test
AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
BAL	Bronchoalveolar lavage
CASA-Q	Cough and Sputum Assessment Questionnaire
CAT	COPD Assessment Test
CBC	Complete Blood Count
CIP	Clinical Investigational Plan
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT scan	Computed Tomography scan; also referred to as CAT scan
EC	Ethics Committee
EDC	Electronic Data Capture (electronic database)
EKG	Electrocardiogram; also referred to as ECG
EXACT-PRO	EXAcerbations of Chronic pulmonary disease Tool (EXACT) Patient Reported Outcomes
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
HHS	Depart of Health and Human Services
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IRE	Irreversible Electroporation
ISI	Insomnia Sleep Index
MCID	Meaningful Clinically Important Difference
mMRC	Modified Medical Research Council Dyspnea Scale
MRI	Magnetic Resonance Imaging

PFT	Pulmonary Function Test(s)
PI	Principal Investigator
RF	Radiofrequency
RFE	Radiofrequency Energy
SAE	Serious Adverse Event
SGRQ	St. George Respiratory Questionnaire
Tx	Gala Bronchoscopy Treatment
UADE	Unanticipated Adverse Device Effect

DEFINITIONS

Adverse Event (AE): any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, user or other persons, whether or not related to the investigational medical device [Reference ISO 14155:2011]

COPD Exacerbation: An acute worsening in respiratory symptoms that requires additional treatment

Mild: Treated with short acting bronchodilators only (SABDs)

Moderate: Treated with SABDs plus antibiotics and/or oral corticosteroids

Severe: Requires hospitalization and or visits to the emergency room. Severe exacerbations may also be associated with acute respiratory failure

Chronic Bronchitis: One form of COPD defined by GOLD guidelines and characterized by chronic productive cough for three months in each of two successive years in a patient in whom other causes of productive cough have been excluded

Serious Adverse Event (SAE): an adverse event that a) led to death, b) lead to serious deterioration in the health of the subject that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, or c) led to fetal distress, fetal death or a congenital abnormality or birth defect [Reference ISO 14155:2011]

Unanticipated Adverse Device Effect (UADE): any serious adverse effect on health or safety or any life-threatening problem or death cause by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan [Reference 21 CFR 812.3(s)]

1.0 INTRODUCTION

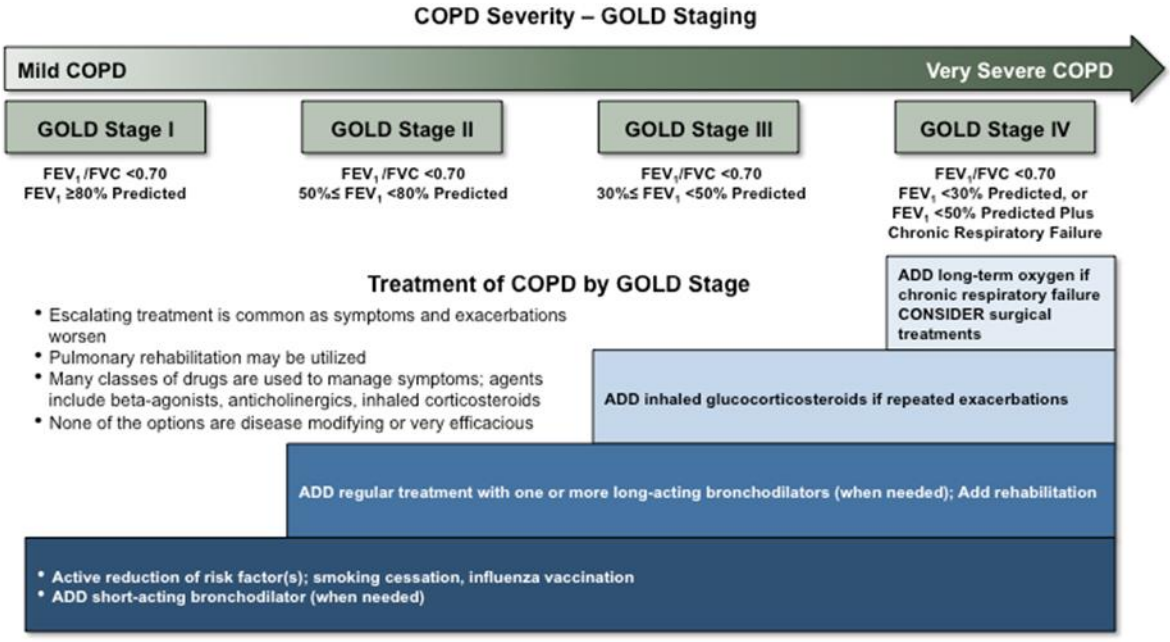
1.1 Background

Approximately 12 million patients in the United States, 13 million in the European Union and 4 million in Japan are diagnosed with Chronic Obstructive Pulmonary Disease (COPD) and millions more may have the disease without a diagnosis. COPD is the third leading cause of death in the United States. COPD causes serious long-term disability and early death. Currently, there is no cure for COPD and treatment aims simply to reduce exacerbations, reduce hospitalization and improve quality of life.

COPD severity is diagnosed by degree of FEV_1 reduction. FEV_1 is the volume of air exhaled by a patient in the first second when exhaling as hard as possible into a spirometer. Once diagnosed with COPD, drugs are prescribed based on standard guidelines (see Figure 1.1).

COPD is, however, most likely several different physiologic conditions that have been combined into one category. Most simply, emphysema and chronic bronchitis are two examples of subsets of COPD that vary physiologically.

Figure 1.1: COPD Severity and Interventions



Emphysema. Emphysema is a disease of the alveoli which are responsible for oxygen and carbon dioxide exchange. Inhaled toxins, from cigarette smoke in most cases, activate proteases leading to alveolar tissue destruction. As more alveoli are destroyed, patients cannot adequately oxygenate and carbon dioxide retention leads to chronic respiratory acidosis, which symptomatically manifests as shortness of breath.

Chronic Bronchitis. Chronic bronchitis is defined as the presence of cough with productive sputum for three months in duration for two consecutive years. It is a

disease of the airways, unlike emphysema which is a disease of the parenchyma (lung tissue) and alveoli. The pathophysiology of chronic bronchitis is not completely understood, but the leading theory extends from the British Hypothesis[1]. Noxious gases and particles are introduced into the respiratory tract by inhalation of cigarette smoke, leading to innate and adaptive inflammatory responses of the airway mucosa. Over time, the chronic inflammation leads to abnormal tissue repair and remodeling of the bronchial walls, most notably with an increase in the number and size of the bronchial mucus glands, defective cilia, and disruption of the epithelial barrier[2]. Abnormal, thick mucus is secreted into the airways that cannot easily be cleared and provides fertile ground for bacteria and other pathogens that would have otherwise been cleared. As more mucus accumulates in the airways, it obstructs air delivery to the alveoli resulting in decreased FEV_1[3].

1.2 Trial Justification

1.2.1 Chronic Bronchitis Is Associated with Worse Outcomes

Mucus hypersecretion is not only a histologic finding but also leads to worse clinical outcomes regardless of GOLD stage. In the Copenhagen City Heart Study, which followed 9,400 smokers, mucus hypersecretion was associated with FEV_1 decline[4]. Mortality was at least ten times greater for a patient with mucus hypersecretion for any given FEV_1 value as compared to a patient that did not have hypersecretion. Chronic bronchitis in GOLD 2 to 4 patients has also been associated with more frequent exacerbations, more severe exacerbations and poorer quality of life. This is consistent with literature showing, that while CB and airflow restriction (as measured by FEV_1) are both hallmarks of COPD[20], CB and airflow restriction are two distinct, albeit commonly associated disorders[18,19,20]. In fact, one study showed that airflow limitation was accompanied by chronic mucus hypersecretion in only 30% of airflow restricted patients aged 60 to 64 years[19]. Kim et. al. also showed that nearly 20% of GOLD 0 and GOLD 1 subjects and 30% of GOLD 2 subjects met the clinical criteria for chronic bronchitis.

In another study of patients who received lung volume reduction surgery for emphysema, the patients with the least mucus hypersecretion had the longest cumulative survival: 82% at 72 months as compared to 18% for the patients with the most severe mucus hypersecretion[5]. Therefore, a therapy to treat the mucus glands may lead to a relative reduction in the risk of death, improve quality of life, and ease the burden associated with frequent exacerbations in chronic bronchitis patients.

Several groups have proposed chronic antibiotics for patients with mucus hypersecretion to reduce the frequency of exacerbations due to bacterial infection. A study of azithromycin in COPD patients showed that use of this macrolide antibiotic as prophylaxis for one year increased the time to first exacerbation from 174 days to 266 days ($p<.001$) as compared to patients taking a placebo[6]. Besides the antibiotic's antimicrobial effect, other mechanisms of action of macrolides are well known including reduced mucus secretion, the inhibition of chloride secretion, and the direct inhibition of MUC5AC (the most common mucin in human airway mucus) production. The reduction in mucus secondary to azithromycin may have contributed to improvement in these outcomes.

1.2.2 Opportunity for Intervention

The standard guidelines, summarized in Figure 1.1, outline the recommended treatment algorithm for patients diagnosed with COPD. At all stages of disease,

reduction of risk factors including smoking and influenza vaccine are strongly recommended. Increasing pharmacological therapies are prescribed as the disease progresses. Despite the benefits of drug therapy, none are disease modifying even though healthcare systems spend over $25 billion per year on these therapies. While the drugs treat the symptoms of the disease, no therapy exists to reverse the pathophysiology of mucus hypersecretion.

Mucus hypersecretion is not only a prognosticator for worse morbidity and mortality, but also an opportunity for intervention. A device-based therapy to treat chronic bronchitis may reset chronic inflammation in the airways. Selective ablation of the mucus glands may improve daily cough, shortness of breath, frequency of exacerbations and overall morbidity and mortality[11]. The other cells and layers of the airway should be kept intact to maintain the barrier function, defend against pathogens, and expel mucus. The extracellular matrix should be left unchanged to allow for regeneration of all cell layers. Since these patients are frail, minimizing inflammation and acute exacerbations after the procedure are also priorities.

In a 21 patient trial, CryoSpray Ablation demonstrated sloughing of the epithelium and submucosal glands while some sections recovered after the initial treatment period showed regenerative changes[12]. This study establishes the proof of concept for ablating airway tissue for the treatment of chronic bronchitis.

To this end, Gala Therapeutics, Inc. (herein 'Gala') is developing RheOx using irreversible electroporation (IRE) to ablate the abnormal mucus glands of the epithelium and reduce the submucosal glands. Postoperatively, the therapy should allow for normal, healthy regeneration rather than a return to mucus hypersecretion and metaplasia.

1.3 Supporting Rationale – First-In-Human Trial (FIH) Overview

Gala initiated a FIH trial using the Gala System in March 2017. As of May 3, 2018, 25 patients were treated at 5 clinical sites in Australia, Chile and Austria (see Table 1.1 below).

Table 1.1: FIH Clinical Study Sites

Clinical Site	Location	Primary Investigators	# of Treated Patients
Otto Wagner Spital	Vienna, Austria	A. Valipour, MD	9
Clinica Alemana	Santiago, Chile	S. Fernandez-Bussy, MD	6
Macquarie University Hospital	Sydney, Australia	A. Ing, MD J. Williamson, MD	6
Royal Melbourne Hospital	Melbourne, Australia	D. Steinfort, MD L. Irving, MD	3
The Alfred Hospital	Melbourne, Australia	G. Snell, MD	1

Note: Data reported as of May 3, 2018

This study is currently under way and patients continue to be enrolled and treated.

Patients with a smoking history of at least 10 pack years and diagnosed with chronic bronchitis and moderate to severe chronic obstructive disease for a minimum of two years were considered for inclusion in the study. Consented patients were screened for eligibility and scheduled for bronchoscopy if eligible. Three bronchoscopies were performed per patient. Patients were treated in the right side airways using RheOx, previously referred to as the Gala Airway Treatment System (GATS), during the first bronchoscopy and then in the left side airways during the second bronchoscopy approximately one month later. The third bronchoscopy was for research purposes only and did not include RheOx Bronchial Rheoplasty. Brushings and BALs were collected prior to any treatments being delivered in all bronchoscopy procedures for assessment of changes from pre to post-treatment. A physical exam, pulmonary function tests, six-minute walk test, EKG and Quality of Life questionnaires (i.e., CAT and SGRQ) were completed at screening/baseline and all post-treatment follow-up assessments (i.e., bronchoscopy #2, bronchoscopy #3, 6-months and 12-months). Additionally, a CT scan is taken at screening/baseline and again at 3 months post-treatment Tx2.

Table 1.2: Bronchoscopy Schedule

Airway	Bronchoscopy #1 (Day 0)	Bronchoscopy #2 (Day 30)	Bronchoscopy #3 (Day 120)
Right	Treatment	No Treatment	Sample Collection Only
Left	No Treatment	Treatment	Sample Collection Only

A total of 47 bronchoscopies were completed where the Gala therapy was administered; 25 in the right side airways and 22 in the left side airways. The average age of the treatment patients was 66.3 years, ranging from 53 to 78, with a median 40 pack years smoking and FEV_1 % predicted of 59 with a range of 30 to over 90%. The patients averaged 428 meters on the six-minute walk test (6MWT) at screening. Despite the high 6MWT, the subjects still had severe symptoms of cough and mucus hypersecretion yet the impact on exercise performance was less pronounced, which may be indicative of this patient population.

Data reported as of May 3, 2018 supports a favorable safety profile with no device-related serious adverse events. There were no reported cases of sustained cardiac arrhythmias during or after the procedure. The data also supports favorable clinical utility with an average CAT score improvement of approximately 8 points at 3 and 6 months post-treatment. For reference, the Minimally Clinically Important Difference (MCID) is a reduction of 2 points. Similarly, the average SGRQ score improved by nearly 20 points at 3 and 6-months post-treatment. For reference, the MCID is a reduction of 4 points. Based on these results further clinical study is warranted.

2.0 DEVICE DESCRIPTION

2.1 Device Identification

RheOx™

Model: GTI-004-02

2.2 Device Manufacturer

Gala Therapeutics, Inc.

Menlo Park, California USA

2.3 Device Description

2.3.1 Principles of Operation

RheOx is designed to ablate abnormal mucus glands of the epithelium and reduce the mucus production of the submucosal glands. Postoperatively, the therapy should allow for normal, healthy regeneration of the epithelium rather than a return to mucus hypersecretion.

This device-based energy delivery system delivers high frequency short duration energy to the airway epithelium and submucosal tissue layers. By delivering energy to the mucus producing cells within these layers of the airway, mucus producing cell membranes become porous resulting in cell death. The death of these cells reduces mucus hypersecretion within the airways. This mechanism of inducing cell death is called Irreversible Electroporation (IRE). IRE is a well-characterized ablation technology that creates an electric field with ultra-short, high voltage current that non-thermally kills cells but maintains the extracellular matrix. IRE technology is commercially available and sold by Angiodynamics as the NanoKnife® Tissue Ablation System for the surgical ablation of soft tissue and is used for the treatment of various inoperable or difficult-to-reach tumors.

2.3.2 Description of Components

RheOx consists of two main components – a RheOx Generator (Figure 2.3.1) and a RheOx Catheter (Figure 2.3.2). Accessories include a cable to connect the catheter

to the generator, power supply cord, foot pedal, commercially available medical grade isolation transformer, and a data acquisition computer.

Figure 2.3.1: RheOx Generator (Front Panel)

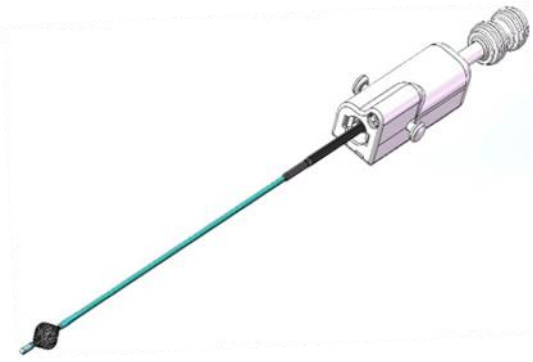


Figure 2.3.2 (A): RheOx Catheter

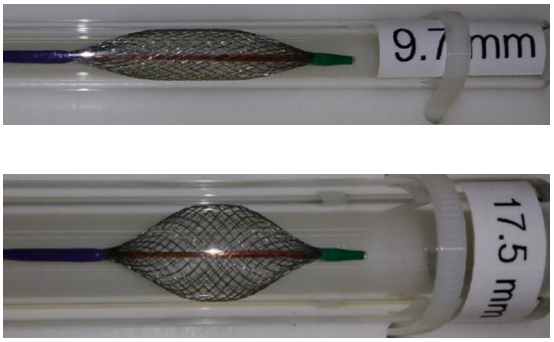


Figure 2.3.2 (B): Distal tip of RheOx Catheter. These images illustrate how the electrode contact area changes with airway diameter.

RheOx Generator. The RheOx Generator is a transportable non-sterile electrical device compatible for use in a bronchoscopy suite or operating room environments. It consists of hardware, software, a display touch screen user interface, a power supply cord and a foot switch. The RheOx Generator power supply may be detached and provides the means to safely and reliably connect to and disconnect from the hospital electrical system. It features controls to initiate and stop treatment as well as indicators to monitor the treatment and alert users.

The RheOx Generator interfaces with a commercially available cardiac monitoring device, such as the Ivy, to ensure reliable energy delivery synchronization with the patient's cardiac cycle thereby reducing risk of cardiac rhythm disturbances. The Generator's software algorithm tracks the cardiac cycle, only delivering energy during the S-T segment of a normal cardiac cycle. The Generator creates high

frequency short duration energy which is delivered to the airway cells via the RheOx Catheter.

RheOx Catheter. The RheOx Catheter is a sterile, single-use catheter designed for use by pulmonologists familiar with bronchoscopic techniques. The Catheter is designed with a single monopolar electrode at the distal tip which when expanded via the handle mechanism contacts the airway wall to deliver the energy to the targeted location. It is designed to treat airway diameters ranging from 5mm to 18mm.

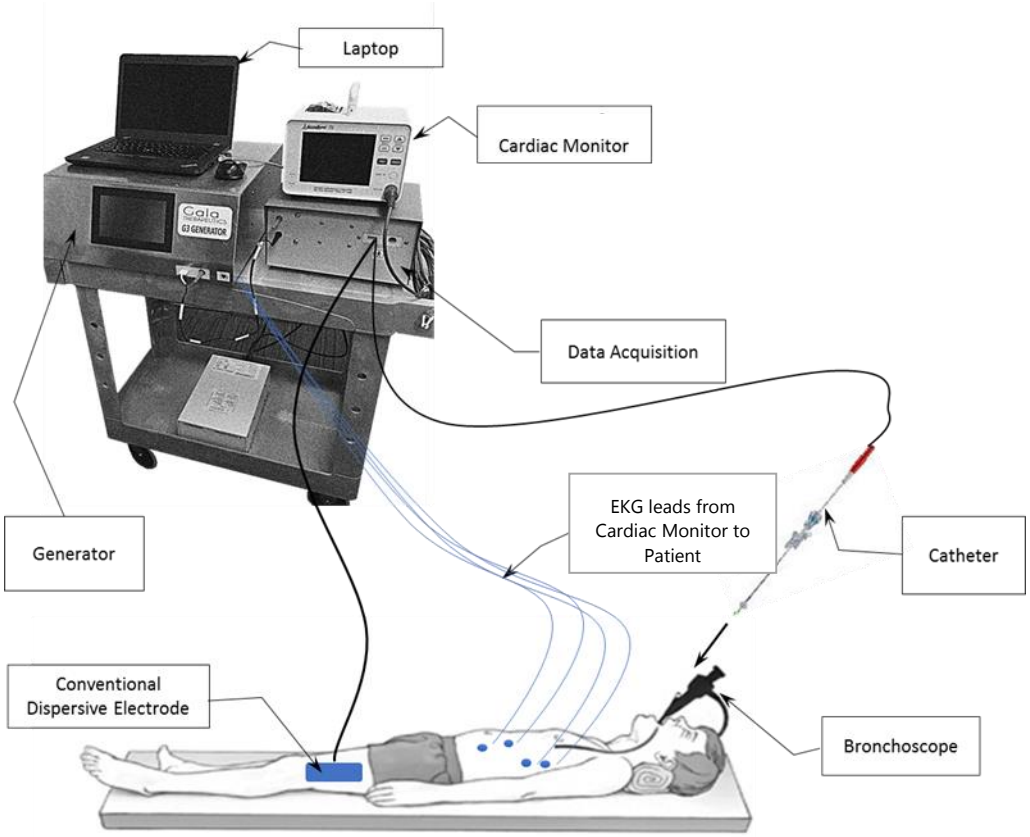


Figure 2.3.3: The RheOx system depicted in the clinical setting. The physician introduces the RheOx Catheter into the airway through a bronchoscope using standard bronchoscopic catheter techniques and then expands the electrode to contact the airway wall. Using the foot pedal, the RheOx Generator is activated, and monopolar energy is delivered in conjunction with a commercially available dispersive electrode applied to the patient's skin. The physician then moves the Catheter slightly up the airway to slightly overlap with the previous activation site and delivers the next energy pulse. The procedure is repeated until all target airway sites have been treated. Each activation lasts approximately 5 seconds.

The total number of activations is at the discretion of the treating physician in order to completely treat accessible airways in the designated treatment areas. The number of activations is dependent upon patient anatomy including airway diameter, airway length

and airway accessibility and typically range between 30 and 60 activations per lung. In some cases, bronchoscopists may be able to access more distal subsegmental airways, delivering additional activations occasionally totaling over 100 activations.

2.4 Intended Purpose and Study Population

RheOx is an investigational device intended to reduce mucus production and cough in patients with chronic bronchitis. Patients with a smoking history of at least 10 pack years who are diagnosed with chronic bronchitis for a minimum of two years will be considered for inclusion in the study.

The investigational device is to be used only in accordance with the approved Clinical Investigational Plan and IFU on subjects who have completed an informed consent form. Device use is limited to approved study investigators who have completed the requisite procedure and device training. Additional detail on the training program can be found in Section 4.2.

2.5 Anticipated Changes During Investigation

The feasibility of various components (e.g., ease of use) of the device system will be assessed during this clinical investigation. Modifications to device components may be made by the study sponsor to optimize device performance. Any changes that impact therapy delivery or instructions for use of the device system shall be communicated by the Sponsor to the clinical investigator(s) prior to implementation.

3.0 STUDY OBJECTIVES

3.1 Study Objective

Primary: To assess the safety of RheOx Bronchial Rheoplasty in patients with chronic bronchitis

Secondary: To assess the clinical utility of RheOx Bronchial Rheoplasty in patients with chronic bronchitis

3.2 Outcome Measures

3.2.1 Primary Outcome Measure: Safety

The primary outcome of the study is safety. The primary safety analysis will be the incidence of serious adverse events of interest through 12 months defined as the following;

- Death
- COPD exacerbation, as defined as an acute worsening in respiratory symptoms requiring additional therapy, that requires a hospital stay of greater than 24 hours
- Pneumothorax within 2 days of either Gala Treatment procedure
- Pneumonia within 7 days of either Gala Treatment procedure, as defined as an increase in respiratory symptoms, fever, sputum production and or purulence, with radiographic confirmation
- Respiratory Failure as defined as a requirement for mechanical ventilatory support for > 24 hours
- Arrhythmia requiring intervention or sustained ($\geq$ 30 seconds) ventricular tachycardia

3.2.2 Secondary Outcome Measure: Clinical Utility

The secondary outcome measures of clinical utility will be assessed by:

- The change from baseline at 6 and 12 months in St. George's Respiratory Questionnaire (SGRQ)
- The change from baseline at 6 and 12 months in COPD Assessment Test (CAT)
- Hospitalization rates (not including the planned bronchoscopy procedures) discharge from the initial RheOx Bronchial Rheoplasty procedure (Visit 2) through 12 months

3.2.3 Other Endpoints

Other, tertiary and exploratory endpoints will also be assessed including changes from baseline to follow-up in;

- Responder rates utilizing established clinically meaningful thresholds for SGRQ (4 points)[17] and CAT (2 points)[16]
- Change in other QOL measures including CASA-Q and EXACT-PRO
- Change in lung function as measured by FEV_1 and FVC
- Change in sleep patterns as assessed by the Insomnia Sleep Index (ISI)
- Change in cough count as assessed by a cough counting monitor
- Mucin concentrations (MUC5AC, MUC5B) from induced sputum samples
- Quantitative High Resolution CT Scan (HRCT) metrics including airway volume, total airway count, and lobar volumes
- Device performance

In addition to the endpoints described above, additional safety analyses in support of the primary study outcome and to assess the totality of safety profile of the RheOx Bronchial Rheoplasty, will be conducted.

Adverse events reported from the day of the index procedure through completion or termination of the study will be assessed. AEs and SAEs will be summarized using a standard medical coding dictionary (MedDRA). AEs and SAEs will be also analyzed by severity, relatedness to the device and/or procedure and within discrete time periods relative to the index procedure.

COPD exacerbations will also be analyzed by severity (mild, moderate, and severe) based on commonly accepted clinical definitions as defined in GOLD 2018 Report[18].

4.0 INVESTIGATIONAL SITES

4.1 Site Selection

Clinical sites and investigators will be chosen to participate in this study based on their qualifications and experience including;

- Expertise in the field of pulmonology and bronchoscopic techniques
- Study staff with appropriate credentials and or experience to accommodate the needs of the study

- Geographical location of site for representativeness
- Clinical experience with other studies or devices for bronchoscopic use

The site principal investigator is required to sign an Investigator's Agreement prior to initiating the study.

The study sponsor will maintain a listing of investigational sites and principal investigators, along with the names and addresses of all institutions where the investigation, or any part of the investigation, may be conducted. The current listing will be made available to the FDA at least annually or upon request. The study sponsor will also provide the FDA a with a list of all the IRB names and addresses and the associated IRB chairperson for each respective site.

4.2 Required Training

All sites and study personnel will be required to undergo protocol training prior to participation in the study. Completed training shall be documented in the study file.

Training will be conducted at the site initiation visit and as needed throughout the study to ensure proper execution of the protocol. It is the investigators responsibility to ensure proper training is administered and documented prior to delegation of any tasks to study staff.

Gala will also provide training to the designated research staff on the proper use of RheOx. Device training will be in accordance with the approved device IFU and study training plan and consist of both didactic and hands on training modules. Procedures for collection of biologic samples (i.e. induced sputum) will also be reviewed during the training. The training will supplement the information provided in the User's Manual. Training material will be provided to the site and stored for future reference in the study file or operational instructions binder.

Gala representatives will be available in clinic during all treatment procedures to answer any questions and to support the clinician and designated research staff upon request. Additional training will also be available upon request if there is a change in staff, or if procedural difficulties that require additional training are identified during the course of the study.

5.0 STUDY DURATION

This study is anticipated to be conducted over a six-year period encompassing site initiation and enrollment through completion of follow-up of the last enrolled patient.

6.0 SUBJECT ELIGIBILITY

6.1 Inclusion Criteria

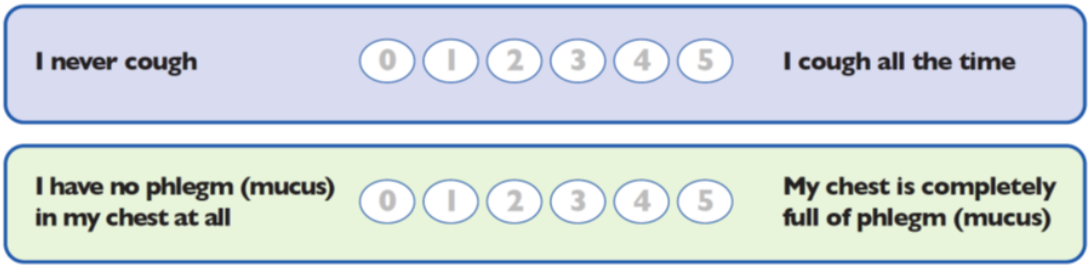
6.1.1 Subject is at least 40 years of age.

6.1.2 Subject has had chronic bronchitis for a minimum of two years, where chronic bronchitis is defined clinically as chronic productive cough for three months in each of two successive years in a patient in whom other causes of productive cough have been excluded.

6.1.3 Subject's responses to the first two questions of the COPD Assessment Test (CAT) must sum to at least 7 points. If the sum of the first two CAT questions is 6 points and the subject's total CAT score is greater than 20 points, the

subject may be enrolled. The first two questions of the CAT questionnaire are as follows:

“For each item below, place a mark (X) in the box that best describes you currently."



6.1.4 Subject has a pre-procedure post-bronchodilator FEV_1 percent predicted of greater than or equal to 30% and less than or equal to 80% within three months of enrollment.

6.1.5 Subject has had 1 or more COPD exacerbations, defined as an acute worsening in respiratory symptoms that requires additional treatment, in the 12-months prior to enrollment

6.1.6 Subject has a SGRQ score of greater than or equal to 25 and CAT score of greater than or equal to 10.

6.1.7 Subject has a cigarette smoking history of at least ten packs years.

6.1.8 Subject is, in the opinion of the principal investigator, able to adhere to and undergo two bronchoscopies.

6.1.9 Subject has provided signed informed consent.

6.2 Exclusion Criteria

6.2.1 Subject has lower respiratory tract infection (e.g., pneumonia, mycobacterium avium-intracellulare infection (MAI), tuberculosis, or severe COPD exacerbation (as defined per GOLD 2018 guidelines[18]) within the six weeks prior to the initial treatment bronchoscopy or mild or moderate COPD exacerbation (per GOLD guidelines) within 4 weeks of the procedure.

6.2.2 Subject is taking > 10 mg of prednisolone or prednisone per day.

6.2.3 Subject has an implantable cardioverter defibrillator or pacemaker.

6.2.4 Subject has a history of arrhythmia within past two years which include tachy-atrial arrhythmias, any sustained ventricular tachy-arrhythmias, or sinus bradycardia with heart rate less than 45 beats per minute.

6.2.5 Subject has history of unresolved lung cancer in last 5 years.

6.2.6 Subject has bullous disease as defined by bullae exceeding 3 cm in diameter on HRCT.

6.2.7 Subject has a pulmonary nodule or cavity that in the judgement of the investigator may require intervention during the course of the study.

6.2.8 Subject has prior lung surgery, such as lung transplant, LVRS, lung implant/prosthesis, metal stent, valves, coils or bullectomy. Prior

pneumothorax without lung resection is acceptable. Pleural procedures without surgery are acceptable.

6.2.9 Subject has emphysema of greater than or equal to 20% as quantified on baseline HRCT scan (low attenuation area less than -950HU).

6.2.10 Subject has clinically significant cardiomyopathy.

6.2.11 Subject has a change in FEV_1 >12% (or, for subjects with pre-bronchodilator FEV_1 below 1 L, a change of >200 mL) post-bronchodilator unless investigator can confirm by other means that subject does not have asthma.

6.2.12 Subject has severe bronchiectasis as outlined in the report of the CT scan of the chest by the interpreting radiologist or in the view of the PI, those findings bronchiectasis or any other significant second lung disease, are the main drivers of the patient's clinical symptoms.

6.2.13 Subject actively smoked (including tobacco, marijuana, e-cigarettes, vaping, etc.) within the last 6 months.

6.2.14 Subject has the inability to walk over 100 meters in 6 minutes.

6.2.15 Subject has clinically significant serious medical conditions, such as: congestive heart failure, angina or myocardial infarction in the past year, renal failure, liver disease cerebrovascular accident within the past 6 months, uncontrolled diabetes, uncontrolled hypertension or autoimmune disease.

6.2.16 Subject has uncontrolled GERD.

6.2.17 Subject has severe pulmonary hypertension.

6.2.18 Subject has a known sensitivity to medication required to perform bronchoscopy (such as lidocaine, atropine, and benzodiazepines).

6.2.19 Subject is pregnant, nursing, or planning to get pregnant during study duration.

6.2.20 Subject has received chemotherapy within the past 6 months or is expected to receive chemotherapy during participation in this study.

6.2.21 Subject receive treatment in another clinical study within 6 weeks of baseline.

6.2.22 Subject is on anticoagulation for cardiovascular indications and, at the discretion of the investigator, is unable to have anticoagulants (i.e., Aspirin, Plavix, Coumadin) withheld for the bronchoscopy procedure per institution's standard of care.

6.2.23 Subject has known airway colonization with resistant organisms, such as pseudomonas, methicillin-resistant Staphylococcus aureus (MRSA), Burkholderia cepacia complex, Mycobacterium Tuberculosis (MTB), Mycobacterium abscessus mucor or significant fungus.

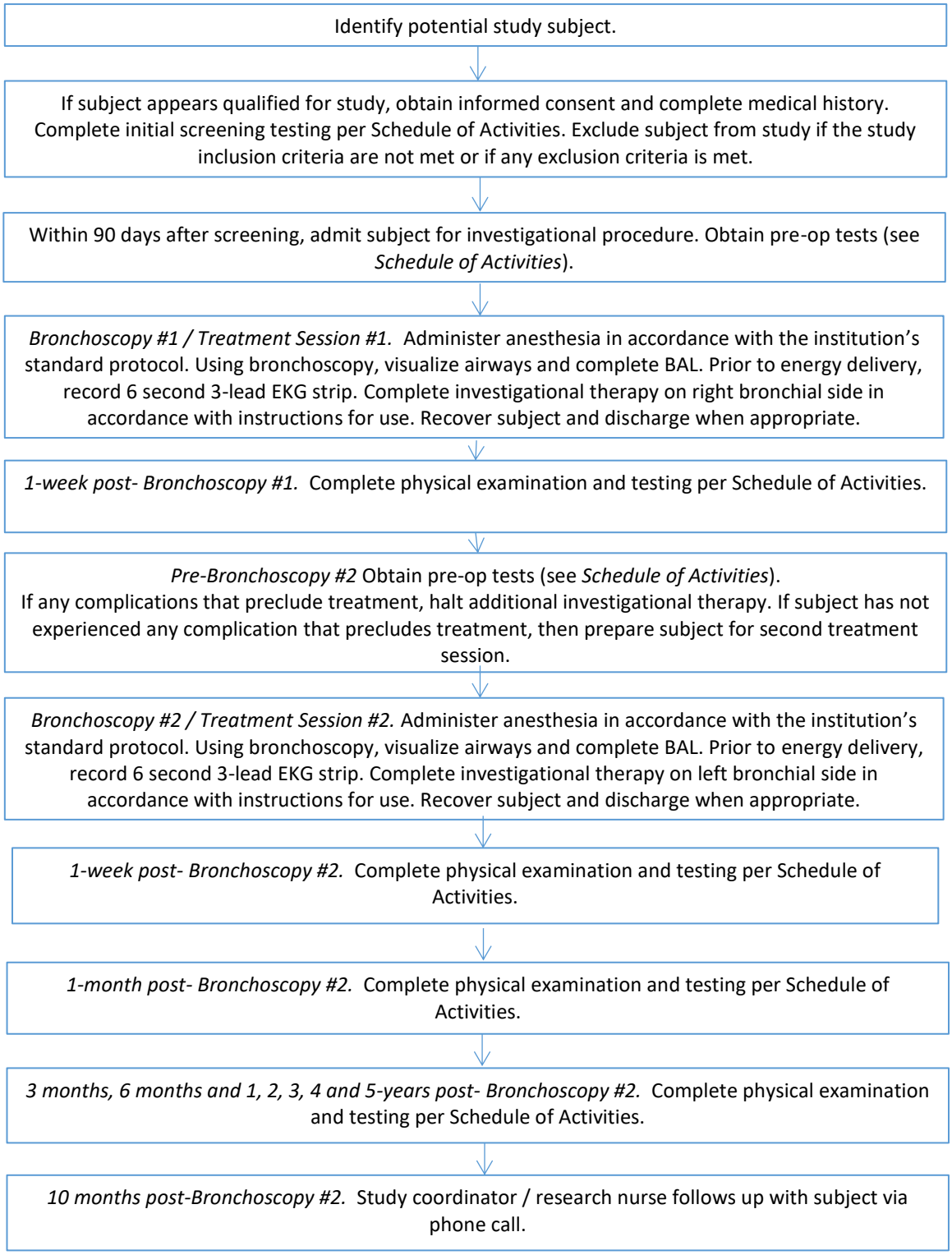
7.0 STUDY PROCEDURES

Figure 7.1 contains a flowchart of the study procedures. This research protocol does not require withholding or postponing any medically indicated customary health care. Subjects will be carefully monitored during the course of the trial. If complications occur, the investigator will use good clinical judgment and administer all necessary clinical care.

Note:

Patients are considered enrolled in the study when informed consent is signed, all screening criteria have been met, and the first RheOx treatment activation is administered.

Figure 7.1: Study Procedures



7.1 Treatment Plan

Following screening and enrollment, subjects will undergo two bronchoscopic procedures (Visit 2 and Visit 4) both of which include treatment with the investigational device. Bronchoalveolar Lavage (BAL) will also be completed during the bronchoscopy prior to the initiation of RheOx treatment.

Investigational treatment with RheOx will be administered to the right lung during bronchoscopy #1 (Visit 2) and to the left lung during bronchoscopy #2 (Visit 4). Each activation will deliver 5 packets of electrical pulses synchronized with the cardiac cycle such that 1 packet is delivered with each cardiac cycle.

The IVY cardiac monitor will be utilized to monitor cardiac activity during the RheOx Bronchial Rheoplasty in this study. The IVY will be set with heart rate alarm limits of less than 30 beats per minute (BPM) and greater than 130 BPM. Anesthesiologists assigned to the study will be trained on IVY alarm signal and its indication. Anesthesiologists will be instructed to use their best clinical judgement and follow standard of care procedure should the IVY monitor alarm during the bronchoscopy procedure.

The total number of activations is at the discretion of the treating physician in order to completely treat accessible airways in the designated treatment areas. The number of activations is dependent upon patient anatomy including airway diameter, airway length and airway accessibility and typically range between 30 and 60 activations per lung. In some cases, bronchoscopists may be able to access more distal subsegmental airways, delivering additional activations occasionally totaling over 100 activations.

Note:

A therapeutic bronchoscope having at least a 3.0 mm working channel, such as the Olympus model 1T180, is required for use with the RheOx Catheter.

Specimen/fluid from the BAL is used to assess pathogens and cell composition in the airways as well as markers for inflammation. Samples will be collected at each bronchoscopy and compared to determine whether any changes occur after the use of RheOx. BAL instructions are included in the study operational instruction manual.

7.2 Description of Visits

7.2.1 Visit #1. Screening and Enrollment

Subjects who meet the eligibility criteria and have signed an informed consent form may be enrolled in the study. Assessments performed exclusively to determine eligibility for this study will be done only after obtaining signed informed consent from the subject. Assessment performed for clinical indications (i.e., not exclusively to determine study eligibility) may be used for screening evaluation even if the studies were completed before informed consent was obtained.

All screening procedures must be completed within 90 days prior to start of study treatment.

Note: If the subject experiences a COPD exacerbation or other change in functional status between screening and the first bronchoscopy, screening procedures should be repeated as appropriate at the investigator's discretion. Refer to the Table 7.1 Schedule of Events for listing of required screening procedures.

General Screening Notes:

High Resolution CT Scan

High resolution computed tomography (HRCT) is incorporated as a tool to define subject inclusion criteria and to assess post treatment changes. CT acquisition will be per the CT Core Manual provided separately to each site upon completion of training by the designated CT core lab for this study.

7.2.2 Visit #2. Bronchoscopy #1 / Treatment Session #1

Eligible subjects are scheduled for the first bronchoscopy and treatment session within 90 days of completing screening procedures. Pre-operative procedures (e.g., physical exam, complete blood count) are completed in accordance with the Schedule of Events table prior to the bronchoscopy.

Note: Pre and post-bronchoscopy care (including medications) should be administered at the discretion of the treating physician per the institution's standard of care.

Upon successful completion of the preoperative procedures, the subject undergoes a bronchoscopy procedure in accordance with standard institutional protocol. Anesthesia is administered. The airways are visualized, and BAL completed. If any complications that preclude continued participation in the study are revealed, then the treatment is halted. If subject has not experienced any complications that precludes continued participation in the study, then RheOx therapy is administered to the target sites in the right lung in accordance with the instructions for use. The clinical investigator ensures FiO_2 does not exceed 40% during energy delivery. Prior to the initiation of energy delivery and during at least one energy delivery a 6 second 3 lead EKG strip is recorded. An EKG rhythm strip from anesthesia monitoring is adequate.

The subject is recovered in accordance with standard institutional procedures. The study investigator determines whether an overnight stay is clinically warranted, and the subject is discharged at the investigator's discretion. Any observed adverse events are reported accordingly.

Note: Subjects may be excluded or treatment delayed at the investigator's discretion if the patient has an active respiratory infection (e.g., common cold, pneumonia, MAI), COPD exacerbation or any other significant adverse event that may compromise the procedure.

Likewise, if at the time of the scheduled procedure the study physician determines the patient has clinical signs or findings (i.e., pulmonary nodule requiring follow-up, abnormal cardiac rhythm) that may adversely impact the

safety of the procedure, the procedure will be postponed pending treatment of the condition and reassessment of the patient.

7.2.3 Visit #3. 1-week Follow-up Visit

Subjects are scheduled for follow-up one week (7 days ± 3 days) following Bronchoscopy #1. The visit will include a physical exam and assessment of AEs and medications in accordance with the Schedule of Events table.

7.2.4 Visit #4. Bronchoscopy #2 / Treatment Session #2

Subjects are scheduled for follow-up 3-6 weeks following Bronchoscopy #1. Pre-operative procedures (e.g. CT Scan, physical exam, CBC) are completed in accordance with the Schedule of Events table prior to the bronchoscopy. Any observed adverse events are reported accordingly. If the subject has experienced any complications that preclude continued participation in the study, then additional treatment is halted.

Upon successful completion of the pre-operative procedures, the subject undergoes a bronchoscopy procedure in accordance with standard institutional protocol. Anesthesia is administered. The airways are visualized, and BAL completed. The RheOx Bronchial Rheoplasty is administered to the target sites in the left side lung in accordance with the instructions for use. The clinical investigator ensures FiO_2 does not exceed 40% during energy delivery. Prior to the initiation of energy delivery and during at least one energy delivery a 6 second 3 lead EKG strip is recorded. An EKG rhythm strip from anesthesia monitoring is adequate.

The subject is recovered in accordance with standard institutional procedures and observed overnight at the discretion of the study investigator. The subject is then discharged at the investigator's discretion. Any observed adverse events are reported accordingly.

Note: Bronchoscopy #2 may be delayed or halted at the investigator's discretion if the patient has an active respiratory infection (e.g., common cold, pneumonia, MAI), COPD exacerbation since treatment session #1 or any other significant clinical symptom that may compromise the procedure.

7.2.5 Visit #5. 1-week Follow-up

Subjects are scheduled for follow-up one week (7 days ± 3 days) following Bronchoscopy #2. The visit will include a physical exam and assessment of AEs and medications.

7.2.6 Visit #6. 1-month Follow-up

Subjects are scheduled for follow-up one month (1 month ± 7 days) following Bronchoscopy #2. The visit will include a physical exam and assessment of AEs and medications.

7.2.7 Visits #7 In-office Follow-up Visit (3 months post Bronchoscopy # 2)

Subjects will return for follow-up visits at 3 months ± 2 weeks after Bronchoscopy #2 (Visit 4). Refer to the Schedule of Events table for a complete listing of required tests.

7.2.8 Visits #8 In-office Follow-up Visit (6 months post Bronchoscopy # 2)

Subjects will return for follow-up visits at 6 months ± 4 weeks after Bronchoscopy #2 (Visit 4). A CT Scan will be performed as part of this visit. Refer to the Schedule of Events table for a complete listing of required tests.

7.2.9 Visit # 9 Phone Call Visit (10 months post Bronchoscopy # 2)

The study coordinator / research nurse calls the subject on the telephone 10 months ± 2 weeks. Any adverse events or changes in medication are reported accordingly. A study visit may be scheduled if clinically warranted.

7.2.10 Visits # 10, 11, 12, 13 and 14 In-office Follow-up Visits (Annual Follow-up post Bronchoscopy # 2)

Subjects will return for follow-up visits at 12 months ± 4 weeks after Bronchoscopy #2 (Visit 4) and annually thereafter for 5 years (± 4 weeks). Refer to the Schedule of Events table for a complete listing of required tests.

Note: If the subject experiences a COPD exacerbation or other change in functional status within 6 weeks of any scheduled follow-up visit, the investigator should consider rescheduling study follow-up visits based on his or her best medical judgement to allow for a true assessment of the patient's stable condition once the subjects symptoms have returned to normal. It is recommended that subjects return to clinical baseline for a minimum of two-weeks prior to undergoing study specific follow-up testing.

7.3 Concomitant Medications / Treatments

Subjects should be treated for COPD before enrollment according to the appropriate ATS guidelines at the discretion of the study investigator and will remain on current (pre-investigational treatment) bronchitis/COPD medications (e.g., long-acting bronchodilators (LABA), long-acting muscarinic antagonists (LAMA), inhaled corticosteroids (ICS)) through the 1-year evaluation unless adjustment is deemed appropriate or medically necessary by the study investigator. Effort should be made to hold dosing constant.

Subjects who are treated with more than 10 mg oral corticosteroids (prednisolone/ prednisone) daily are excluded. Patients treated with oral corticosteroids (prednisolone/ prednisone) ≤ 10mg per day may be enrolled in the study. Pre-procedural, peri-procedural or post-treatment corticosteroids (IV or oral) may be administered if medically necessary at the discretion of the study investigator.

If applicable, it is recommended subjects temporarily stop taking anticoagulants (e.g., warfarin, Xarelto) prior to each bronchoscopy, as directed by the study investigator. Aspirin may be taken at the discretion of the study investigator.

Perioperative antibiotics are not recommended unless deemed medically necessary by the study investigator. If necessary, a non-macrolide antibiotic (e.g., Cipro, Augmentin) is preferred.

7.4 Schedule of Events (Table 7.1)

Table 7.1: Schedule of Events

	Visit #1: Screening	Visit #2: Bronchoscopy #1	Visit #3: Follow-up 1 week Post-Bronchscopy #1	Visit #4: Bronchoscopy #2	Visit #5: Follow-up 1 week Post-Bronchoscopy #2	Visit #6: Follow-up 1 month Post-Bronchscopy #2	Visit #7: Follow-up 3 month Post-Bronchscopy #2	Visit #8: Follow-up 6 month Post-Bronchscopy #2	Visit #9: Follow-up Phone Call 10 month Post-Bronchscopy #2	Visit #10-14: Annual Follow-up 1 - 5 years Post-Bronchscopy #2
Window			± 3 days	-3 to +6 weeks	± 3 days	± 7 days	± 2 weeks	± 4 weeks	± 2 weeks	± 4 weeks
Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Medical History	X									
Exacerbations History	X	X	X	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Physical Exam	X	X[1]	X	X[1]	X	X	X	X		X
CBC & Blood Panel	X	X[1]		X[1]			X	X		X
Cotinine Test	X									
EKG	X	X[4]		X[4]			X	X		X
Spirometry	X			X[1]			X	X		X
DLCO/Body Pleth	X			X[1]			X	X		X
Six Minute Walk Test	X									
CT Scan	X			X[1]				X		
Bronchoscopy		X		X						
Bronchoalveolar lavage		X		X						
RheOx Bronchial Rheoplasty		X		X						
Induced Sputum Sample	X						X	X		X
SGRQ	X			X[1]			X	X		X
CAT Score	X			X[1]			X	X		X
CASA-Q	X			X[1]			X	X		X
ISI[5]	X			X[1]			X	X		X
Cough Counting Monitor[6]	X						X	X		X[7]
EXACT-PRO[8]	X	DAILY								

Note 1: Noted activities are completed prior to bronchoscopy.

Note 2: Adverse Events are noted before and after bronchscopy.

Note 3: Overnight Hospital Stay at discretion of PI

Note 4: An EKG is recorded prior to the initiation of RheOx procedure and during at least one energy delivery; anesthesia EKG may be used.

Note 5: Subjects with clinically significant insomnia at baseline as defined by a ISI score of $\geq$ 8 points[21,] may be asked to complete optional polysomnography testing at baseline and 3-months follow-up.

Note 6: In this study, VitaloJAK cough monitor is an exploratory outcome measure. Patients willing to participate are encouraged to wear the 24 hour cough monitor at the 4 visits specified, but it is not mandatory.

Note 7: 12-month visit only

Note 8: In this study, EXACT-PRO is an exploratory outcome measure to quantify and measure exacerbations of COPD. Patients are encouraged to complete the questionnaire daily during the first year (up to Visit #10), but it is not mandatory. Daily patient compliance will not be a reason for removal from the study.

Additional Notes on Schedule of Events:

Note: If Bronchoscopy #2 cannot be completed the subject should continue follow-up at 3 months, 6 months, 12 months and annually through 5 years following Bronchoscopy #1 (i.e., last treatment session).

Note: If the subject experiences a COPD exacerbation or other change in functional status within 6 weeks of any scheduled follow-up visit, the investigator should consider rescheduling study follow-up visits based on his or her best medical judgement to allow for an accurate assessment of the patient's stable condition once the subjects symptoms have returned to normal. It is recommended that subjects return to clinical baseline for a minimum of two-weeks prior to undergoing study specific follow-up testing.

7.5 Removal of Subjects

Subjects may be taken off the study treatment and/or removed from the study at any time at their own request. Subjects may also be withdrawn at the discretion of the investigator for safety, behavioral (e.g., subject not compliant with study treatment for more than two continuous weeks) or administrative reasons.

The reason(s) for discontinuation will be documented on the End of Study eCRF. Reasons for withdrawal may include:

- Patient voluntarily withdraws from treatment (follow-up permitted);
- Patient withdraws consent (termination of treatment and follow-up);
- Patient is unable to comply with protocol requirements;
- Patient experiences adverse reaction that makes continuation in the protocol unsafe;
- Investigator determines continuation on the study would not be in the patient's best interest;
- Patient becomes pregnant during treatment period;
- Patient is lost to follow-up.

7.6 Early Termination or Suspension of Study

7.6.1 Study Stopping Rules

Study enrollment and further treatment of any subject will be halted if any of the following serious adverse events are observed in a given subject;

- Death associated with the study investigational therapy or procedure
- Three or more subjects with a pneumothorax within 2 days of either Gala Treatment procedure
- Device related arrhythmias requiring cardioversion or sustained VT regardless of intervention
- Acute pulmonary hemorrhage requiring surgical intervention or embolization
- Unanticipated adverse device effect

The study may not resume enrollment until the study medical monitor, the sponsor and principal investigator have reviewed the observation and events

surrounding the observation to determine if the study should be halted or may continue.

7.6.2 Interim Safety Analysis

In addition to the study stopping rules, an interim safety analysis will be conducted after 5 subjects complete the second treatment (Visit 4) to ensure it is safe to continue study treatments. Enrollments and planned study visits/treatments should continue per the study protocol while the interim analysis is being conducted. The interim analysis will consist of a review of all AE and SAE data collected in the study at that point including an assessment of device and procedure relatedness. The data will be reviewed by the study medical monitor and a subcommittee of three Gala Therapeutics Scientific Advisory Board members, composed of experts in chronic bronchitis and interventional bronchoscopy procedures to ensure it is safe to continue the study. Patient demographics and procedural characteristics will also be included in the review. The review should confirm that the safety profile of the study is consistent with expectations set forth at the start of the study. Recommendations may include:

1. Continue the study without modification
2. Continue the study with modification or
3. Terminate the study

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design

This is a prospective, single arm feasibility study of RheOx in patients with chronic bronchitis. Neither subjects nor investigators will be blinded.

8.2 Sample Size

As this is an early feasibility study, up to 30 subjects will be enrolled and treated with the study device to assess the effect of the investigational device in the target population.

8.3 Evaluable Cohort

All subjects who have entered the treatment room for Visit #2 will be included in the safety endpoint analysis (Safety Population). Subjects who have received at least one treatment will be included in the evaluable cohort for clinical utility.

8.4 Outcome Analysis

Descriptive statistics will be utilized to summarize and report on data for all subject and outcome variables. Categorical data (e.g., age, gender) will be reported in frequency distributions. Certain dichotomous data (e.g., subjects with Serious Adverse Events) will also be presented as rates. Continuous data (e.g., age, FEV_1) will be summarized using mean, standard deviations, medians, minimums, maximums, and interquartile ranges. Additional subgroup and other multivariable analyses may be performed including examination of the association between subject risk factors (e.g., age, gender) and trial outcomes, and the potential contributions of these factors.

9.0 DATA MANAGEMENT

9.1 Data Entry

Source documents shall be maintained by the investigational sites throughout the course of the investigation. All findings in this investigation must be documented as source data, and therefore can be verified and audited. Source documentation may be paper or electronic and is defined as the first time the data appears and may include for example; all questionnaires, phone interview notes, clinical records, hospital records, surgery reports, death/autopsy reports, and any other material that contains original information used for clinical study data collection or adverse event reporting. It should be possible to verify the inclusion and exclusion criteria for the investigation from available source data. Source documents must include the subject identification number and a date.

Data obtained from each subject during the clinical trial will be entered in the electronic data capture (EDC) database within five working days of the report date. All applicable sections of the EDC case report forms (eCRFs) must be filled out completely. The EDC system and associated data collected over the course of the study will be managed per the approved study Data Management Plan.

9.2 Subject Data Protection

Upon enrollment in the study, each subject will be assigned a unique identifier in accordance with GCP. Subject data will be recorded using the unique identifier. The subject's name or any other identifying label will not be recorded on the CRFs.

In accordance with applicable regulations (e.g., HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study sponsor and/or their representatives and allow regulatory authorities such as FDA access to subject's medical information relevant to the study.

9.3 Data Retention

Study documentation includes all CRFs, data correction forms or queries, source documents, correspondence, monitoring logs and letters, and regulatory documents (e.g., CIP and amendments, IRB correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports necessary for the evaluation and reconstruction of the clinical research study.

The study sponsor or investigator(s) must retain all study documentation pertaining to the conduct of the study in accordance with applicable regulations. These documents shall be retained during this investigation and for a period of at least two years after the later of the following two dates: the date on which the investigation is terminated or completed, or the date of the last approval of marketing application in an ICH region.

9.4 Monitoring

The Sponsor, or designee, will monitor the clinical investigation in accordance with GCP and all applicable regulations. The Monitor must ensure that the investigation is conducted in accordance with the signed Investigator Agreement, the Clinical Investigational Plan, any conditions imposed by the IRB, and applicable regulations.

Monitoring intervals will occur as described in the clinical monitoring plan. The Monitor will notify the Sponsor within 24 hours upon becoming aware of any UADE not previously reported to the Sponsor. In the event the investigator is not complying with the study requirements, it is the Sponsor's responsibility to secure compliance.

10.0 ADVERSE EVENTS

10.1 Reporting Requirements

10.1.1 Adverse Events

Adverse events will be reported on the adverse event eCRF. All adverse events will be graded according to Medical Dictionary for Regulatory Activities (MedDRA).

Adequate information related to the adverse event must be supplied to the Sponsor to determine whether the adverse event is related to use of the investigational device. The study investigator should assess to the best of their ability relatedness of each AE to the study device and study procedure(s) according to the following categories; not related, possibly related, and probably related.

AE severity is assessed by the study investigator and recorded on the AE eCRF according to the following definitions;

- Mild (Grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (Grade 2): the event causes discomfort that affects normal daily activities.
- Severe (Grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (Grade 4): the patient was at risk of death at the time of the event.
- Fatal (Grade 5): the event caused death.

AEs collected over the course of the study will be regularly monitored by the study medical monitor and/or other company representatives or consultant advisors (if deemed necessary) to ensure the ongoing safety of the study.

10.1.2 Serious Adverse Events

All serious adverse events must be reported to the Sponsor within 24 hours after the investigator first learns of the event, regardless of presumed relationship to the device or trial. In addition, the investigator and the Sponsor will comply with IRB and FDA reporting requirements, inclusive of reporting requirements defined in 21 CFR 812.150.

10.1.3 Unanticipated Adverse Device Effect

An investigator shall submit to the sponsor a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

Reports relating to the patient's subsequent medical course must be submitted to the Sponsor via the study eCRFs until the event has subsided or, in case of permanent

impairment, until the event stabilizes, and the overall clinical outcome has been ascertained. For reported deaths, the investigator should supply the Sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).

The Sponsor is responsible for reporting all serious and unexpected adverse device effects to FDA in an expedited manner, and in accordance with all applicable federal regulations. The Sponsor will expedite the reporting in compliance with ICH GCP to all concerned investigators. The investigator will report to the IRB in accordance with institutional requirements, but no later than 7 calendar days of first knowledge.

10.2 List of foreseeable adverse events related to investigational therapy and/or study procedure:

- Sore throat (likely occurrence)
- Coughing (likely occurrence)
- Hemoptysis (likely occurrence)
- Minor complications associated with anesthesia (moderate likely occurrence) including nausea, vomiting, bruising at the site of injections, sore throat or hoarse voice, urinary retention
- Infection (moderately likely occurrence) including fever, pain or soreness
- Exacerbation (moderately likely occurrence) including shortness of breath, increased color and/or quantity of phlegm
- Bronchial perforation (low occurrence)
- Lung abscess (low occurrence)
- Gastroparesis (low occurrence)
- Pneumothorax (low occurrence) including severe chest pain, trouble breathing, death
- Airway stenosis (low occurrence) including wheezing, hoarseness, shortness of breath and/or respiratory distress
- Abnormal cardiac rhythm function (low occurrence) including arrhythmia, atrial fibrillation, ventricular fibrillation, death
- Allergic reaction (low occurrence) including abnormal breathing, difficulty swallowing, anxiety, chest pain, severe cough, lightheadedness or dizziness, sweating or fainting, swelling of the face, eyes or tongue
- Significant pulmonary bleeding (low occurrence)
- Significant complications associated with anesthesia (low occurrence) including damage to teeth, aspiration, respiratory failure, brain damage, and death
- Death (low occurrence)

Note: Likely occurrence is estimated to occur in more than 1 in 2 patients. Moderately likely occurrence is estimated to occur in 1 in 10 to 1 in 100 patients. Low occurrence is estimated to occur in less than 1 in 100 patients.

11.0 RISK-BENEFIT ASSESSMENT

11.1 Anticipated Risks

Refer to section 10.2 of this protocol for a detailed listing of potential risks (i.e., adverse events) of this clinical investigation. This protocol does not withhold or postpone any medically necessary treatment. If any complications are experienced, the study investigator will use good clinical judgment in the treatment of adverse events.

Based on prior literature, and preclinical and clinical studies completed, RheOx is expected to be safe for use in this clinical study.

As this is a feasibility study, unanticipated events may occur, however, every effort will be undertaken to ensure risks are minimized. The study is designed with a conservative, step-wise approach to treating each subject. Patients will be first treated in only the right airways and fully recovered for 30 days to allow for sufficient healing. The right airways will be visualized and assessed prior to further treatment on the left side. If the subject has experienced any complications that preclude continued participation in the study, then additional treatment is halted.

The study also has a planned interim analysis and stopping rules, discussed earlier, to ensure safety concerns are addressed throughout the study.

11.2 Anticipated Benefits

Gala's Chief Medical Officer, the Scientific Advisory Board (SAB) and the study Investigators have determined that this research study is justified because the overall potential benefit to the population outweighs its attendant risks. If the investigational treatment is successful, participating subjects may experience a reduction in symptoms, an improved quality of life and potentially reduced exacerbations associated with chronic bronchitis. All subjects will be symptomatic at baseline (per the study inclusion criteria), despite standard of care pharmacotherapy. Thus, additional benefit from the treatment may reduce the burden of disease on the healthcare system. Additionally, results of this study may lead to further development of a new, minimally invasive therapy, RheOx, which could lead to an alternative therapy to chronic bronchitis.

12.0 STUDY MANAGEMENT

12.1 Statement of Compliance

The study will be conducted in accordance with applicable regulations for clinical research, 21 CFR Part 812, ISO 14155, the ICH guidelines for good clinical practice and company standard operating procedures (SOPs). The study will be registered on www.clinicaltrials.gov.

12.2 Institutional Review Board (IRB)

The clinical investigational plan and site informed consent must be approved by the IRB for the given institution prior to any study-related activity. The investigator is responsible for complying with all applicable requirements established by the IRB.

The study sponsor will maintain a list of the names, addresses, and chairpersons of all IRBs that have or will be asked to review the investigation and a certification of IRB action concerning the investigation (when available).

12.3 Investigator Responsibilities

The Principal Investigator is responsible for ensuring that the clinical investigation is conducted according to the Investigator Agreement, this study protocol, the Clinical Trial Agreement, all applicable federal and local regulations, and any conditions of approval imposed by the reviewing IRB and/or FDA.

The Principal Investigator shall:

- Indicate acceptance of this study protocol in writing by signing the Investigator Signature page of this study protocol and any applicable amendments;
- Conduct this study in compliance with this study protocol and any applicable amendments;
- Create and maintain adequate source documentation throughout this study and make source documentation available as requested for monitoring visits or audits;
- Ensure the investigational device is used solely by authorized users at the site;
- Ensure the investigational device is used in accordance with this study protocol and product labeling;
- Refrain from implementing any modifications to this study protocol without agreement from Gala, the applicable IRB, and national regulatory authority as required;
- Promptly document and explain any deviation from the approved study protocol during the course of this study;
- Ensure the investigational site has an adequate staff, resources and training, and document delegations of duties throughout the study;
- Ensure study staff members have document study protocol training;
- Ensure adequate facilities exist and are maintained during this study;
- Ensure that maintenance and calibration of all equipment relevant to the clinical investigation is appropriately performed and documented as requested;
- Ensure the accuracy, completeness, legibility, and timeliness of all data reported to Gala (including source documentation as well as CRFs);
- Maintain accurate and complete device accountability records;
- Allow and participate monitoring and auditing activities as requested;
- Allow and participate in FDA inspection activities;
- Ensure all study-related records are retained as required; and
- Ensure accurate and timely preparation of reports required by applicable regulations.

Gala retains the right to terminate participating investigational sites for failure to comply with investigator responsibilities, or requirements imposed by applicable IRBs and the FDA.

12.4 Study Initiation

Prior to the initiation of the clinical investigation, the qualifications of the site Principal Investigator and staff, and adequacy of the clinical investigation sites shall be verified and documented. Prior to initiating patient enrollment at the investigational site, Gala

will conduct a Site Initiation Visit inclusive of training on the clinical investigation plan and operation of the device and procedure for the Principal Investigator and research staff. Study enrollment may not begin until the site receives notification that it has been activated by Gala and has received IRB approvals and completed SIV training.

12.5 Amendments to the Clinical Investigational Plan (CIP)

All amendments to the CIP will be agreed upon between the Sponsor and the clinical investigator(s) and will be recorded with a justification for the changes. The investigator is responsible for submitting all amendments of the CIP to their IRB in accordance with IRB procedures.

The study may be amended to expand the study to include additional subjects and/or longer therapy periods (i.e., > 6 months) if subjects are positively responding to the investigational therapy.

12.6 Deviations from the Clinical Investigational Plan

Protocol deviations should be avoided unless deemed necessary by the investigator to protect the life or physical well-being of a subject in an emergency. The site principal investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred.

All deviations from the approved CIP should be documented in the study file and reported to IRB as necessary per governing IRB policy and in accordance with §812.35(a). Except in an emergency, the sponsor should be made aware if any deviation from the CIP is anticipated that may affect the scientific soundness of the CIP or the rights, safety, or welfare of human subjects

All study variances will be reviewed by the Medical Monitor and study sponsor to determine the need to amend the CIP or to terminate the investigation.

12.7 Informed Consent Process

The investigator is responsible for obtaining and documenting informed consent from each participating subject in accordance with applicable regulatory requirements and the institution's procedures for clinical research. Informed consent should adhere to GCP and to ethical principles that have their origin in the Declaration of Helsinki. Only an IRB-approved ICF for this CIP may be used to document a subject's consent.

12.8 Device Accountability

Upon receipt of investigational products from the study sponsor, the Investigator is responsible for accountability of the investigational devices in accordance with applicable regulations. A device accountability log will be used to track device receipt, use, and return/disposal of the devices.

Study device should be stored in a secure environment with access provided only to key study personnel who have the appropriate authorization. It is investigator's responsibility to ensure that the study device is used only for study subjects under PI's personal supervision or under the supervision of a properly trained sub-Investigator. Study Device Accountability Log should be updated every time a device is received at the site, used in a subject, disposed of or returned to the

sponsor. During the study, devices that are intended to be disposable (e. g. catheter) may be disposed of at the site or returned to the study sponsor if requested.

Monitors will routinely verify that investigational product documentation is accurate and complete throughout the study including at the close-out visit.

The investigator must return unused devices to the sponsor at study completion, closing of the study site, or as requested by the sponsor.

12.9 Publication Policy

Any proposed publication or presentation (including a manuscript, abstract or poster) will be published, or submitted for publication, in accordance with the terms of the Clinical Trial Agreement.

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