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Clinical Study Protocol

A Comparison of Technegas® and Xenon 133 Planar Lung Imaging in Subjects Referred for Ventilation Scintigraphy

Protocol Number: CYC-009

Phase 3 Study

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Sponsor Approval

Name and Title *(Signature and title of Sponsor's Responsible Party)*	Date

Sponsor Approval (continued)

Name and Title *(Signature and title of Sponsor's Study Statistician or other responsible party)*	Date

Investigator's Signature

Investigator's Printed Name

Investigator's Signature Date

1 Study Synopsis

Name of Sponsor: Cyclomedica Australia Pty Ltd Unit 4 1 The Crescent Kingsgrove, NSW 2208 Australia		*(For National Authority Use Only)*
Name of Finished Product: Technegas		
Name of Active Ingredient: Tc-99m labeled carbon		

Title of Study:

A Comparison of Technegas® and Xenon 133 Planar Lung Imaging in Subjects Referred for Ventilation Scintigraphy

Protocol Number:

CYC-009

Investigators and Study Center(s):

To be determined

Phase of Development:

Phase 3

Primary Objectives:

1. To demonstrate the non-inferiority of Technegas compared to Xenon 133 (Xe-133) ventilation studies, using planar scintigraphic imaging, with respect to their pulmonary ventilatory distribution in subjects that are candidates for ventilation imaging.
2. To assess the safety profile of Technegas by monitoring adverse events (AEs), pulse oximetry, and vital signs pre- and post-Technegas administration.

Methodology:

The design of this study is a Phase 3 within-subject non-inferiority trial of Technegas ventilation imaging compared to Xe-133 ventilation imaging. Subjects referred for ventilation scintigraphy will have undergone a chest X-ray, and will undergo planar Xe-133 imaging followed by planar Technegas imaging. Xe-133 images will include site-specific standard of care wash-in and wash-out views. Site-specific standard of care Xe-133 images are most commonly either posterior and posterior oblique image views or alternatively posterior and anterior image views. Technegas images will include a six view image set: anterior, posterior, left posterior oblique, right posterior oblique, left anterior oblique, and right anterior oblique views.

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The **non-inferiority margin** to be used in this study was principally determined from a study conducted under Protocol CYC-010. Using the same efficacy assessments as planned for this study; the CYC-010 study compared a first read and second re-read of 75 Xe-133 lung images, spaced at least 4 weeks apart, to establish a non-inferiority margin for two successive reads of Xe-133 images. Since Xe-133 is an approved agent for ventilation imaging, it by default is considered non-inferior to itself, and hence provides a suitable limit for establishing the non-inferiority of Technegas compared to Xe-133.

Primary assessments of efficacy will be based on three blinded readers' assessments of the Technegas and Xe-133 ventilation images in independent reading sessions. In each reading session, readers will visually divide each lung into three regions of approximately equal size arranged craniocaudally and designated as the right and left apical, mid and basal regions. Based on the image set presented, readers will provide a ventilation score for each lung region: 0 = absent ventilation, 1 = decreased ventilation, or 2 = normal ventilation. For the blinded reads of the Xe-133 images, readers will be presented with all acquired ventilation image views for a subject and will assign a single ventilation score to each region. For the reads of the Technegas images, readers will first be presented with the subset of ventilation image views that match the views acquired with Xe-133 and will assign ventilation scores to each lung region based on those views. They will then be presented with the additional Technegas image views and will assign a second score based on the complete set of Technegas images. The ventilation scores will be used to derive a binary agreement score for the paired Technegas and Xe-133 images by subject and lung region. For the primary endpoint analysis, agreement scores will be determined from matching Technegas and
Xe-133 image views only. Agreement scores based on all Technegas image views compared to the Xe-133 images will provide a secondary efficacy endpoint.

After approximately 40 subjects have completed the study, an interim pilot blind read of the Xe-133 and Technegas ventilation images will be conducted to assess the viability of the planned efficacy measurements for comparing the Technegas and Xe-133 image sets for demonstrating non-inferiority. If it is determined that the initial study design and efficacy parameters are not viable due to the differences in the image sets being acquired,

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the protocol will either be amended in accordance with Agency input, or the study may be terminated. The readers performing the interim blind read will not be used for the final blind read of images, and unless imaging parameters change, the images from these first 40 subjects will be included in the final read of images.

Number of Subjects Planned:

Two hundred and forty (240) subjects who complete the study are planned. The subject must have completed all Xe-133 and Technegas planar ventilation imaging as required by the protocol, and the images must be of interpretable image quality according to site investigators' assessments.

Diagnosis and Main Criteria for Inclusion:

- Male or female subject at least 18 years of age.
- Subject is a candidate for ventilation imaging.
- Subject must be willing and able to provide informed consent.
- Subject must be stable and able to undergo Xe-133 planar imaging and Technegas planar imaging.
- Subject must be willing and agree to complete study procedures.
- Subject is using adequate birth control, if female and fertile. Adequate birth control is defined as surgical sterilization, hormone contraceptive use or intrauterine device (IUD).
- Female subject has a negative urine or serum pregnancy test.
- Subject has had or is scheduled to have a chest X-ray within 24 hours prior to the investigational imaging study.

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Investigational Drug, Dose and Mode of Administration:

The investigational drug is Technegas. Technegas consists of aerosolized particles of carbon labeled with Tc-99m that are dispersed in high purity argon gas. It is manufactured at point of use before administration using a computer controlled and operated automated synthesis module (TechnegasPlus Generator System).

Subjects will inhale Technegas aerosol until an adequate amount of radioactivity has localized in the lungs. The amount required for imaging should produce 1.5-2.5 kilo-counts per second (kcps) in the posterior projection as measured on a gamma camera. This equates to approximately 1.1 millicurie (mCi) (40 Megabecquerel [MBq]).

Reference Therapy, Dose and Mode of Administration:

Xenon 133 (Xe-133) gas, an approved imaging agent for assessment of pulmonary function and for imaging of the lungs, will be used as the comparator.

Subjects will be administered between 10-30 mCi (370-1110 MBq) of Xe-133 for planar ventilation imaging.

Study Duration:

Study duration is approximately one to two days. Subjects will undergo screening procedures. Immediately thereafter, qualified subjects will be enrolled in the study. The subject will first undergo a Xe-133 planar imaging study. As soon as practical, but no longer than 24 hours after completing the Xe-133 imaging study, subjects will undergo a Technegas planar imaging study.

Criteria for Evaluation:

Efficacy:

The **primary endpoint** is the percent agreement between Technegas and Xe-133 obtained from the blinded readers' ventilation assessments of matching image views. It will be derived as follows. Comparing a reader's Technegas and Xe-133 ventilation scores for each subject, a binary agreement score will be obtained for each lung region: if the Technegas and Xe-133 ventilation scores are the same for the region, it is assigned an agreement score of 1, otherwise it is assigned a score of 0 for no agreement. Each blinded

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reader's agreement scores for the subjects' lung regions will be analyzed to determine an overall estimate of percent agreement and its confidence interval.

Secondary endpoints are: percent agreement between Technegas and Xe-133 based upon blinded readers' ventilation assessments of all image views (not just matched image views); percent agreement between Technegas and Xe-133 for the subgroups of subjects with and without pleural effusion (as observed in subjects' chest X-rays); percent agreement measuring inter-observer agreement between pairs of blinded readers for their Technegas ventilation scores, and for their Xe-133 ventilation scores; and by lung-region kappa statistics measuring inter-observer agreement between pairs of blinded readers for their Technegas ventilation scores and for their Xe-133 ventilation scores.

Safety:

All subjects will be evaluated for safety throughout the study. Vital signs (systolic blood pressure, diastolic blood pressure, pulse, and respiratory rate) and pulse oximetry will be collected prior to Xe-133 administration (baseline safety) and at various times during the study up to 15 minutes post-Technegas administration. AEs will be monitored throughout the study until subject discharge.

Statistical Methods:

Tabulation of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software. All testing and confidence intervals will use a two-sided significance level of 5%, unless otherwise stated.

Efficacy:

Each blinded readers' binary agreement scores will be analyzed using a generalized linear model with SAS® PROC GENMOD. The logit function (log odds ratio) will be specified as the link function, and subject will be specified as a repeated measure to allow for correlations between lung regions within a subject. The estimate of the intercept of the model using generalized estimating equation (GEE) methodology will provide an overall estimate of the agreement and its 95% confidence interval in terms of the log odds ratio; simple algebra will be used to obtain the corresponding estimates and confidence intervals

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in terms of percent agreement (PA).

The non-inferiority hypothesis to be tested is:

H_0: PA ≤ 60% versus H_A: PA > 60%

If the lower boundary from the 95% confidence interval for the PA difference is greater than 60%, Technegas will be considered non-inferior to Xe-133 with respect to the measurement of pulmonary ventilatory distribution.

Study Success Criteria: For the study to be deemed a success, the null hypothesis must be rejected for PA for at least two of the blinded readers for the primary efficacy endpoint.

Inter-observer agreement between pairs of readers of Technegas images, and between pairs of readers of Xe-133 images will be evaluated using the GEE methodology that takes into account correlations between lung regions within a subject. Ninety-five percent (95%) confidence intervals will be obtained for the agreement. In addition, by lung-region kappas will be obtained for pairs of readers of Technegas images and pairs of readers of Xe-133 images.

Safety:

Frequency distributions will be used to summarize the qualitative safety data, including adverse events, clinically significant changes in vital signs, and clinically significant oxygen saturation measurements that fall below 90%.

Summary statistics will be provided for all continuous safety data including change in vital signs and oxygen saturations. Paired t-tests or the signed rank test will be used to test for statistically significant changes over time.

2 Table of Contents

3 Abbreviations

Abbreviation	Definition
AE(s)	Adverse Event(s)
AP	Anteroposterior
CFR	Code of Federal Regulations
CRA(s)	Clinical Research Associate(s)
CRF(s)	Case Report Form(s)
CV	Curriculum Vitae
DTPA	Diethylenetriamine Pentaacetic Acid
DVT	Deep Vein Thrombosis
ECRF(s)	Electronic Case Report Form(s)
EDC	Electronic Data Capture
EPA	Environmental Protection Agency
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GEE	Generalized Estimating Equation
GCP(s)	Good Clinical Practice(s)
I-131	Iodine-131
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC(s)	Independent Ethics Committee(s)
In-111	Indium-111
IND	Investigational New Drug
IRB(s)	Institutional Review Board(s)
IUD	Intrauterine Device
kcps	Kilo-counts per Second
LAO	Left Anterior Oblique
LPO	Left Posterior Oblique
MBq	Megabecquerel
mCi	Millicurie
µg	Microgram
mm Hg	Millimeters of Mercury
MITT	Modified Intent-to-Treat
Mo-99	Molybdenum-99
$Na^{99m}TcO_4$	Sodium Pertechnetate
ng/L	Nanograms per Liter
nm	Nanometer

Abbreviation	Definition
PA	Percent agreement
PAS	Patient Administration Set
PE	Pulmonary Embolism
PPS	Per Protocol Set
RAO	Right Anterior Oblique
RPO	Right posterior Oblique
SAE(s)	Serious Adverse Event(s)
SUSAR	Serious and Unexpected Suspected Adverse Reaction
SOP(s)	Standard Operating Procedure(s)
Tc-99m	Technetium-99m
WHO	World Health Organization
Xe-133	Xenon-133

4 Background Information

Xenon 133 (Xe-133) remains the only approved pulmonary ventilation imaging agent commercially available in the United States. Xenon-133 gas has been shown to be valuable for diagnostic inhalation studies for the evaluation of pulmonary function and for imaging the lungs.[1]

Technegas has been in clinical use for lung scintigraphy since its original approval in Australia in 1987. Technegas and/or the TechnegasPlus Generator and Technegas carbon crucibles (also known as "Pulmotec" in the European Union [EU]) are now marketed in 51 countries world-wide. In some countries, the Technegas system is approved as a device. In the EU, the TechnegasPlus Generator is approved as a device while the crucible is controlled as a drug.

According to the EANM Guidelines for Ventilation/Perfusion Scintigraphy (2009), "Technegas has minimized the problem of hotspots in patients with obstructive lung disease and is according to clinical experience better than the best liquid aerosols" (p. 92) for ventilation imaging and "is preferred over DTPA in patients with COPD" (p. 97).[2]

The development of Technegas as a ventilation imaging agent for approval in the United States has been ongoing for the past 15 years. Current Technegas clinical development focuses on a structure delineation type of indication (ventilatory imaging) for use in general ventilatory scintigraphy. The proposed indication is: Technegas is indicated for ventilatory scintigraphy in adult patients. This indication is similar to the approved indication for Xe-133 inhalation imaging and will be supported by this structural imaging non-inferiority study.

This Phase 3 study directly compares planar ventilation image views obtained using Technegas with those obtained using Xe-133, with a goal to establish the equivalence (acceptable agreement) of the two sets of images for assessing pulmonary ventilatory distribution.

4.1 Description of Investigational Product

Technegas is a structured ultra-fine dispersion of Technetium-99m (Tc-99m) labeled carbon particles produced by a TechnegasPlus Generator. Technetium-99m labeled carbon aerosol, delivered from the TechnegasPlus Generator system, distributes to normally ventilated regions of the lungs. This distribution occurs as a result of its small and uniform particle size. Initial deposition into the lungs is monitored by placing a gamma camera over the lungs and having the subject inspire Technegas until a desired count rate for pulmonary imaging is achieved. Typically a subject may need to inhale Technegas for only a few breaths. If needed, the subject can take a rest breath (breathe normal air or oxygen) between Technegas inhalations.

The size distribution of Technegas delivered from the TechnegasPlus® Generator is well controlled such that the median particle diameter size is 177 nm and ranges from 159-206 nm, and the ratio of the particle thickness to diameter is usually about 1:10.[3]

It is well established that particles smaller than 500 nm behave like true gases, distributing to the most peripheral regions of the lungs.[4] Following distribution, Technegas particles do not pass through the alveolar membrane to enter the systemic circulation.[5,6] Once deposited in the periphery of the lungs (below the level of the bronchociliary elevator), Technegas particles do not undergo diffusion, or exhibit other means of re-distribution, but are gradually cleared by lung macrophages.

Technegas particles initially deposited in the upper regions of the lung are removed by bronchociliary clearance and gastrointestinal elimination without absorption.[3] Time-lapsed cinegraphic images of the chest region have documented that Technegas particles, initially deposited in the upper regions of the lung, are cleared by the bronchociliary elevator. The web site of The John Curtain School of Medical Research, Australian National University, includes a cinegraphic illustration of this clearance mechanism.[7] The cine image illustrates the upward movement of the radioactive particles followed by swallowing, transit through the esophagus and delivery into the stomach.

Because Technegas does not undergo redistribution, it is possible to obtain as many different image projections as desired. The ability to obtain multiple images is considered to be a definite advantage for assessing regional ventilation which displays focally decreased activity ("cold" regions) images. In this study, Technegas planar image views will include a six view image set: anterior, posterior, left posterior oblique (LPO), right posterior oblique (RPO), left anterior oblique (LAO), and right anterior oblique (RAO) views. Xenon 133 planar image views will be determined based on the site-specific standard of care which most commonly is posterior/posterior oblique or anterior/posterior image views collected during wash-in and wash-out.

Technegas formation is achieved by using a high-purity carbon crucible loaded with sodium pertechnetate ($Na^{99m}TcO_4$). The Tc-99m sodium pertechnetate is first evaporated to dryness using gentle heating in the presence of argon. Technegas particles are formed by rapidly heating the crucible to approximately 2750°C ± 50ºC in an atmosphere of high-purity argon (99.99%). Individual particles appear as hexagonal shaped single, flat technetium metal crystals encapsulated within a carbon sheath. Data from an unpublished report (R. Browitt, R. Stephens, June 2005) showed the total particle output of one Technegas dose is in the range of 1.35×10^6 particles per cm^3.[8]

These small, discrete individual particles begin agglomerating inside the chamber within minutes of formation, reaching an equilibrium particle size distribution with a median size of 177 nm.[2] Equilibrium is established as a net result of continuous agglomerate formation with

larger agglomerates depositing on the internal surface of the chamber. While the agglomeration and deposition equilibrium results in a reproducible particle size distribution, the concentration of particles per unit volume decreases with time. Inhalation of Technegas must occur within 10 minutes of manufacture.[3]

The average concentration of carbon particles produced during a Technegas generation is approximately 370 nanograms per liter (ng/L). Given no losses during the administration to the patient, the total extractable output would thus contain on average 2.2 microgram (µg) of carbon. Because losses are expected, and patients do not inhale the complete contents of each Technegas generation, the actual carbon inhaled by the patient will be less than 2.2 µg of carbon.[3] Inhalation of the amount of radioactivity recommended for multiple view imaging corresponds to about 1 µg of carbon inhaled per Technegas administration (Internal Report).

4.2 Summary of Nonclinical Studies

The nonclinical testing strategy for Technegas was guided by the nature of the drug product's ingredients, and considerations for a radiopharmaceutical administered by inhalation to assess pulmonary structures.

The biodistribution of radioactivity from Tc-99m after administration of Technegas was examined in nonclinical studies sponsored or conducted by Tetley Manufacturing, Ltd. (Sydney, New South Wales, Australia) during the mid-1990s, with supplementation by the European licensee, Medgenix Diagnostics, a division of MDS Nordion S.A. (Fleurus, Belgium).[3] No additional pharmacokinetics studies of Technegas were undertaken by Cyclomedica. The distribution of Technegas particles following intravenous administration is much the same as analogous medical tracers, such as Tc-99m sulfur colloid injection and Tc-99m albumin colloid injection with the exception that the radioactive tagging for Technegas is particularly stable (i.e., there is little leaching of pertechnetate) in keeping with its physical makeup.

Coghe, Votion and Lekeux compared the biodistribution of radioactivity after inhalation of Technegas, krypton-Kr 81m gas or Tc-99m diethylenetriamine pentaacetic acid (DTPA) aerosol by healthy (free from respiratory disorder) calves. Using external gamma-ray scintigraphy and region of interest analysis of scintigrams, these authors concluded that the Tc-99m DTPA liquid in air aerosol more poorly escaped impaction in the large conducting airways. Technetium-99m radioactivity appeared in the forestomachs (the first three compartments of the ruminant stomach) after inhalation of either Tc-99m labeled DTPA aerosol or Technegas, which was attributed to swallowed saliva and respiratory secretions. The appearance was more frequent and intense with Tc-99m DTPA aerosol.[9]

The nonclinical testing strategy regarding chemical toxicity of the drug was based upon the

nature of the carrier (elemental carbon) and route of administration. There are two ingredients to the drug product, an elemental technetium core surrounded by a synthetic graphite shell. Thus, exposure of the patient to Technegas is limited to pharmacologically inert, elemental carbon. In consideration of this, no safety pharmacology studies were conducted of Technegas.

No nonclinical laboratory studies of Technegas were undertaken to evaluate its chemical toxicity profile. The literature establishes safe exposure limits to inhaled particulate graphite in the context of other sources of human exposure. The level of exposure to inhaled particulate graphite from the anticipated clinical dose of Technegas is well within the limits for the material established in that body of regulatory literature. The patient's particulate exposure during a medical imaging session is approximately equivalent to one or two days' exposure to particulates in ambient air that meets Environmental Protection Agency standards.

4.3 Radiation Dosimetry

In data from an unpublished report (M. Stabin, May 2, 2008), serial whole body images were obtained following the inhalation administration of Technegas to human subjects in a completed phase 1 investigational trial. The image data were processed by region of interest analysis to determine tissue residence time. Radiation dosimetry estimates were calculated and shown to compare favorably to those from Tc-99m imaging procedures.[10]

4.4 Summary of Risks and Benefits

4.4.1 Warnings, Precautions, and Contraindications

For specific information concerning warnings, precautions and contraindications for the investigational drug, the investigator is asked to refer to the appropriate section of the Investigator's Brochure. Because of the possibility of AEs from both the procedure and the investigational drug, a fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should be immediately available.

4.5 Route of Administration, Dosage, Dosage Regimen and Treatment Period

The recommended activity of Tc-99m sodium pertechnetate to be added to the crucible ranges between 6.8 and 19 mCi (250-700 MBq). For adults, adequate images are obtained after approximately 1.1 mCi (40 MBq) of Technegas deposits in the lungs.[9] The radioactive dose allows for sufficient count rates to obtain high quality images across a range of body habitus in a reasonable imaging time.

Technegas consists of aerosolized particles of carbon labeled with Tc-99m that is dispersed in high-purity argon gas. It is manufactured at the point of use minutes before administration using a computer-controlled and operated automated synthesis module (TechnegasPlus Generator). It may only be necessary for a subject to inhale Technegas over a few breaths. If needed, the subject can take a rest breath (breathe normal air or oxygen) between Technegas inhalations.[3]

4.6 Treatment Compliance

Trained clinical staff will be responsible for initiating and completing Technegas administration and ventilation imaging. The trial will be conducted in compliance with this protocol, Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

5 Study Objectives and Purpose

The primary objectives and purpose of this study are:

1. To demonstrate the non-inferiority of Technegas compared to Xenon 133 (Xe-133) ventilation studies, using planar scintigraphic imaging, with respect to their pulmonary ventilatory distribution in subjects that are candidates for ventilation imaging.
2. To assess the safety profile of Technegas by monitoring AEs, pulse oximetry, and vital signs pre- and post-Technegas administration.

6 Trial Design

This is a Phase 3 within-subject non-inferiority trial of Technegas ventilation planar imaging compared to Xe-133 ventilation planar imaging. Subjects will be males and females at least 18 years of age who have been referred for ventilation scintigraphy for any medical reason. Subjects will have undergone a chest X-ray, and during the study will undergo planar Xe-133 imaging followed by planar Technegas imaging.

Xe-133 images will be obtained per site-specific standard of care at each investigational site, which most commonly is posterior/posterior oblique image views or anterior/posterior image views collected during wash-in and wash-out. Technegas images will include a six view image set: anterior, posterior, LPO, RPO, LAO, and RAO views.

Enrollment will continue until 240 subjects have completed the study. This number of subjects is expected to provide 90% power for demonstrating the non-inferiority of Technegas compared to Xe-133 in the assessment of ventilation imaging. The non-inferiority margin to be used in this study was primarily determined from a separate study conducted under Protocol CYC-010.

Primary assessments of efficacy will be based on three blinded readers' assessments of the Technegas and Xe-133 ventilation images in independent reading sessions. The primary efficacy endpoint will use only the subset of Technegas image views that match the site specific-standard views obtained for Xe-133. Specifically, if only anterior/posterior images are collected with the Xe-133 ventilation study for a subject, then initially anterior/posterior image sets will be assessed for the subject's Technegas ventilation study. Likewise, if posterior/posterior oblique images are collected with the Xe-133 ventilation study, the posterior/posterior oblique images from the Technegas study will be assessed. Following the initial primary assessment of the subset of matched Technegas image views, readers will assess the complete set of Technegas images for a secondary efficacy endpoint. Ventilation will be scored in each of three regions of approximately equal size for each lung arranged craniocaudally and designated as the right and left apical, mid and basal regions, respectively. Ventilation in each region will be assigned a ventilation score: 0 = absent ventilation, 1 = decreased ventilation, 2 = normal ventilation. These scores will be used to derive a binary agreement score for the paired Technegas and Xe-133 images. The agreement scores will be analyzed to provide an estimate of overall percent agreement between the Technegas and Xe-133 images.

After approximately 40 subjects have completed the Xe-133 and Technegas image sessions, an interim blinded read of the images will be conducted. Agreement between Xe-133 and Technegas will then be analyzed to assess the viability of the planned efficacy measurements. If it is determined that changes need to be made, either the CYC-009 clinical protocol will be amended with the Agency's input and agreement or the study will be terminated. The

readers performing the pilot blind read will not be used for the final blind read of images. However, the images from these first 40 subjects will be included in the final read of images unless the imaging parameters change.

6.1 Primary and Secondary Efficacy Endpoints

6.1.1 Primary Efficacy Endpoint

The primary endpoint is the percent agreement between the Technegas and Xe-133 obtained from blinded readers' ventilation assessments of matching image views. It will be derived as follows. Binary agreement scores for each subject's six lung regions will be obtained: if the Technegas and Xe-133 ventilation scores are the same for a lung region, the region is assigned an agreement score of 1, otherwise it is assigned a score of 0 for no agreement. Each blinded reader's agreement scores for the subjects' lung regions will be analyzed to determine an overall estimate of percent agreement and its confidence interval.

6.1.2 Secondary Efficacy Endpoints

The secondary endpoints include:

1. Percent agreement between Technegas and Xe-133 obtained from blinded readers' ventilation assessments of all image views acquired with Technegas (i.e. not limited to the matched image views).
2. Percent agreement between Technegas and Xe-133 for the subgroups of subjects with and without pleural effusion as noted in subjects' chest X-rays, from blinded readers ventilation assessments.
3. Percent agreement measuring inter-observer agreement between pairs of blinded readers for their Technegas ventilation scores, and for their Xe-133 ventilation scores.
4. By lung-region kappa statistics measuring inter-observer agreement between pairs of blinded readers for their Technegas ventilation scores and for their Xe-133 ventilation scores.

6.1.3 Safety Endpoints

All subjects will be evaluated for safety throughout the study. Vital signs (systolic blood pressure, diastolic blood pressure, pulse, and respiratory rate) and pulse oximetry will be collected prior to Xe-133 administration (baseline safety) and at various times during the study up to 15 minutes post-Technegas administration. Adverse events will be monitored throughout the imaging study until subject is discharged.

6.2 Randomization and Blinding

This is an open-label, non-randomized clinical trial. All subjects will undergo Xe-133 planar imaging and Technegas planar imaging. Subjects will undergo Xe-133 inhalation and imaging first, followed by Technegas inhalation and imaging as soon as practical and no longer than 24 hours after completing the Xe-133 imaging. Because of the rapid clearance of Xe-133 from the lungs and the low, non-interfering energy of Xe-133 photons, a wash-out period is not required.

While the Xe-133 will not interfere with the Technegas images, it is recognized that there will be potentially confounding effects of Xe-133 and Technegas on safety parameters.

The primary efficacy data will be from a blinded read managed by Certus International, a contract research company and imaging core lab located in Bedford, NH and St. Louis, Missouri. Three experienced nuclear medicine physicians will be selected to perform independent blinded reads. The readers will have experience reading Xe-133 ventilation images, as well as experience reading DTPA ventilation scans. Like Technegas, DTPA is a particulate based ventilation imaging agent. Training in reading Technegas scans will also be provided. Each reader will independently assess both the Xe-133 images and the Technegas images in separate sessions. Each image set will be assigned a unique random code number, which will govern the order in which the subjects' images are read. The readers will be shown a recent anteroposterior or posteroanterior chest X-ray of the lungs but will be blinded to subject identity, reason for the ventilation scan, results of procedures and to any other subject information.

Additional details on the blinded read are provided in the Imaging Charter.

6.3 Treatment, Dosage, and Dosage Regimen

6.3.1 Investigational Drug Dose and Mode of Administration:

The investigational drug is Technegas. Technegas consists of aerosolized particles of carbon labeled with Tc-99m that are dispersed in high purity argon gas. It is manufactured at point of use before administration using a computer controlled and operated automated synthesis module (TechnegasPlus Generator System).

The recommended activity of Tc-99m sodium pertechnetate to be added to the Technegas crucible ranges between 6.8 and 19 mCi (250-700 MBq). For adults, adequate images are obtained after approximately 1.1 mCi (40 MBq) of Technegas deposits in the lungs.[9]

Subjects will inhale Technegas aerosol until radiation monitors positioned over the lungs indicate that an adequate amount of radioactivity has localized in the lungs. The amount required for imaging is 1.5-2.5 kcps in the posterior projection as measured on a gamma

camera. This equates to approximately 1.1 mCi (40 MBq).

6.3.2 Reference Therapy, Dose and Mode of Administration:

Xenon 133 gas, an approved imaging agent for assessment of pulmonary function and for imaging of the lungs, will be used as the comparator. Subjects will be administered between 10-30 mCi (370-1110 MBq) of Xe-133 for planar ventilation imaging.

6.4 Study Period

The period from enrollment to pre-Xe-133 inhalation will serve as the baseline period for safety assessments. The treatment period begins at the time of Technegas inhalation and extends through the post-Technegas imaging safety assessment.

During Visit 1, screening procedures and enrollment occur. The subject will then undergo Xe-133 inhalation and planar imaging. Subjects will then undergo Technegas inhalation and planar imaging as soon as practical and no longer than 24 hours after completing the Xe-133 imaging.

6.5 Discontinuation Criteria

6.5.1 Subject Discontinuation or Termination

Every subject has the right to terminate his or her participation in the study at any time without providing reasons. A subject's participation will terminate immediately upon his/her request. However, every attempt should be made by the investigator to complete the safety assessments to ensure the subject experiences no AEs.

If a subject chooses to withdraw from the study, the investigator should attempt to obtain the reason for withdrawal and document this on the case report form (CRF).

The termination of a subject's participation in the study should be considered by the investigator or sponsor and/or designee in the case of a serious adverse event (SAE).

The subject may be withdrawn from the study at any time at the discretion of the investigator or sponsor. The reason for such withdrawal should be fully documented on the CRF. Potential reasons for withdrawal of the subject include, but are not limited to, withdrawal of informed consent, death, subject lost to follow-up, enrollment of a subject subsequently found to have not met inclusion and/or exclusion criteria or study or site termination by the sponsor.

6.5.2 Study or Site Termination

The sponsor retains the right to terminate or suspend an investigator or site from participation in the study and/or to terminate or suspend the entire study at its sole discretion. Potential reasons for site or study termination include, but are not limited to, serious safety concerns, the inability of a site or sites to carry out the study as agreed to in the protocol, repeated enrollment of subjects that do not meet inclusion or exclusion criteria or repeated protocol deviations.

In the event of premature investigator, site or study termination, investigators will be promptly informed of the termination or suspension, as will the institutions, regulatory authorities, and Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs).

6.6 Accountability of Investigational Drug

6.6.1 Receipt of Investigational Drug

Shipment of investigational TechnegasPlus generator and Technegas crucibles and the Patient Administration Set (PAS) from the sponsor to the investigator or other designated persons cooperating with the investigator will be accompanied by a receipt form, which will describe the batch and/or lot number(s) and the amount of investigational drug or supplies provided for the study. The form(s) will be signed, dated, returned to the sponsor and a copy will be maintained in the site file.

6.6.1.1 TechnegasPlus Generator

All sites will have the use of a dedicated TechnegasPlus Generator for study purposes.

6.6.1.2 Technegas Crucibles

Crucibles will be supplied to the sites with documentation regarding lot/batch number and shipment amounts. The groups of 10 crucibles are packaged in a molded polyvinyl chloride pack with a printed cardboard sliding cover and labeled “for Investigational Use only”. Crucibles must be stored at a controlled room temperature of 8° to 30°C (46° to 86°F) in a secure area. Accountability will be performed on those crucibles used for the trial. The crucible is broken automatically following Technegas generation to prevent accidental re-use which would result in erratic yields. The debris is collected in a tray beneath the contacts, and will contain a residue of radioactivity. It should be treated as low level radioactive waste. Residual radioactivity in used crucibles will be allowed to decay and they will be disposed of according to the study site’s standard operating procedures (SOPs).

6.6.1.3 Technegas Patient Administration Set (PAS)

A single-use-only Technegas PAS will be supplied for each subject. Batch and/or lot numbers will be tracked and accountability will be performed for all PAS used for the trial. Unused PAS will be stored in a secure location. Residual radioactivity in used PAS will be allowed to decay and they will be disposed of according to the study site's SOPs.

6.6.1.4 Argon Gas Source

Investigational sites will obtain their own high-purity (≥ 99.99%) medical-grade argon gas supplied by a qualified vendor in stand-alone cylinders. It will be handled according to the investigational site's SOPs and the instructions provided in the TechnegasPlus Technegas Generator User Manual (TechnegasPlus Generator User Manual)[11]. Documentation of the Argon supplier's name, the batch number if applicable and cylinder tracking information will be maintained at the investigational site.

6.6.1.5 Source of Tc-99m Sodium Pertechnetate Injection

All Tc-99m will be obtained from the investigational site's molybdenum-99 (Mo-99)/Tc-99m generator or a local radiopharmacy, which must be approved by the state or national regulatory authority in its respective location. Documentation of the generator manufacturer name, lot number and date of manufacture must be maintained at the investigational site in their study records.

The Tc-99m will be in the form of sodium pertechnetate ($Na^{99m}TcO_4$), which must meet USP requirements for Tc-99m sodium pertechnetate injection. The amount of radioactivity dispensed, date and time dispensed, time injected and amount of radioactivity injected must be tracked and recorded on the CRFs.

6.6.2 Disposition of Unused Investigational Drug

Upon completion of the study, the investigator will return all unused investigational drug to the sponsor or will dispose of it according to pre-arranged methods and procedures agreed upon by the sponsor.

7 Selection and Withdrawal of Subjects

A minimum of 240 subjects are required to complete this study. The study is open to all subjects satisfying inclusion and exclusion criteria.

All subjects enrolled into the study will receive a subject number that will consist of a two-digit site number, followed by a three-digit consecutive number of enrollment. An example of a subject number would be 02001, representing the first subject enrolled from Site 2.

7.1 Inclusion Criteria

Subjects may be enrolled if they meet the following requirements:

1. Male or female subject at least 18 years of age.
2. Subject is a candidate for ventilation imaging.
3. Subject must be willing and able to provide informed consent.
4. Subject must be stable and able to undergo Xe-133 planar imaging and Technegas planar imaging.
5. Subject must be willing and agree to complete study procedures.
6. Subject is using adequate birth control, if female and fertile. Adequate birth control is defined as surgical sterilization, hormone contraceptive use or intrauterine device (IUD).
7. Female subject of child-bearing potential has a negative urine or serum pregnancy test.
8. Subject has had or is scheduled to have a chest X-ray within 24 hours prior to the investigational imaging study.

7.2 Exclusion Criteria

1. Subject has been administered any other radiopharmaceutical within a timeframe that might cause interference with study imaging.
2. Subject is a pregnant or lactating female.
3. Subject has received Technegas in the past.
4. Subject has received an investigational drug within 30 days prior to dosing.
5. Subject is hemodynamically unstable.

7.3 Withdrawal or Termination of Participation

Every subject has the right to terminate his or her participation in the study at any time

without providing reasons. A subject's participation will terminate immediately upon his/her request.

A subject who signs the informed consent form, but discontinues study participation *without inhaling Technegas* is termed a withdrawn subject. Subjects may withdraw themselves or may be withdrawn by the investigator. Data collection for withdrawn subjects will cease at the time of their withdrawal.

Subjects may withdraw or be withdrawn for any of the reasons listed below:

- Did not meet inclusion/exclusion criteria
- Withdrew consent
- Lack of compliance with study procedures
- Investigator decided it is in the subject's best interest to be withdrawn

A subject who signs the informed consent form and then undergoes Technegas inhalation, but does not complete all of the imaging procedures and/or all of the safety assessments is termed an **incomplete subject**.

Whatever the reason for lack of study completion, the investigator should attempt to collect and report the required Technegas safety data.

A subject who meets all inclusion criteria and no exclusion criteria, undergoes Technegas inhalation and completes all study procedures is termed a **complete subject.**

8 Treatment of Subjects

Subjects will undergo Xe-133 and Technegas inhalation and imaging. Safety will be monitored pre- and post-inhalation of Technegas by assessing changes in vital signs and, blood oxygen saturation by pulse oximetry, and physical examination.

8.1 Treatment Administered

8.1.1 Technegas

Technegas will be manufactured at point of use immediately before administration using the TechnegasPlus Generator.

Subjects will inhale approximately 1.1 mCi (40 MBq) of Technegas for image acquisition.

8.1.1.1 TechnegasPlus Generator

The TechnegasPlus Generator is a microprocessor-controlled device consisting of a 6-liter shielded, sealed generation chamber. The chamber is housed above two (2) electrodes between which a carbon crucible is inserted. A drawer in the front of the generator provides access to the electrodes.

Technegas is produced by vaporization in the generation chamber. The TechnegasPlus Generator includes several automatic security features that allow safe and efficient generation and delivery of the Technegas.

The 6-minute purge phase with argon gas before each generation assures the elimination of air from the sealed chamber. In addition, for each Technegas generation, an automatic leak test is performed during this purge stage.

To assure an accurately reproducible yield and quality of Technegas, a phototransistor is used to monitor and maintain crucible burn temperature of around 2750ºC ± 50ºC over a 15-second interval. If the acceptable temperature cannot be maintained over a prescribed period, then the TechnegasPlus Generator prohibits the delivery of Technegas to the subject. If the acceptable temperature is maintained over a shorter defined burn period, then the user is notified that the yield could be low. The user then has the option to administer the product to the subject. For the purposes of this protocol, burns that produce a low yield will not be given to study subjects.

Technegas is intended to be administered to the subject within 10 minutes after its generation. After this time, the generator stops delivery to the subject in order to prevent accidental use of expired Technegas.

See the TechnegasPlus Generator User Manual (supplied separately) for complete details and instructions.[10]

8.1.1.2 Investigational Agent Preparation

A carbon crucible, pre-moistened with ethanol to assist in the complete loading of the crucible's reservoir, is fitted between electrodes and loaded with the required activity of Tc-99m sodium pertechnetate in approximately 0.14 mL saline (standard Mo-99/Tc-99m generator eluate). The volume and loading time should be recorded on the CRF. Any additional Tc-99m sodium pertechnetate added to the crucible should be recorded as well. The chamber is closed for the evaporation cycle during which a small electric current is used to heat the crucible to approximately 70ºC. High-purity argon gas is also passed over the crucible and purges the generation chamber of air and moisture.

The eluate must evaporate to dryness and leave a white crust of salt (sodium chloride and Tc-99m sodium pertechnetate) on the carbon crucible. Technegas is then generated in a short heating cycle where a large electric current is used to rapidly heat the carbon crucible to a temperature of 2750ºC ± 50ºC for 15 seconds, in an atmosphere of high-purity argon.

The resulting vapor and argon mixture is inhaled by the subject through a disposable PAS, which is a mouthpiece valve-filter transfer tubing assembly. Residual, unused Technegas is purged from the generation chamber with high-purity argon into an exhaust-trapping filter before the chamber can be opened and reloaded for the next cycle.

As the carbon crucibles are intended for single-use, the machine automatically breaks the crucible to prevent accidental re-use. The debris is collected in a tray beneath the electrodes.

8.1.1.3 Argon Gas Source

Argon gas will be supplied by a qualified vendor in stand-alone cylinders and will be medical-grade high-purity 99.99% argon. Documentation of the batch and cylinder tracking information will be maintained at all sites.

8.1.1.4 Source of Tc-99m Sodium Pertechnetate

All Tc-99m sodium pertechnetate will be obtained from Mo-99/Tc-99m generators approved by state or national regulatory authorities in their respective regions or from local radiopharmacies. Documentation for Technetium received from a local radiopharmacy, such as prescription, radiopharmacy log, delivery receipt, etc, as applicable for a site, will be kept at the site.

8.1.2 Xe-133 Preparation

Xenon Xe-133 gas will be prepared and administered according to the investigational site's standard practice for subjects presenting for ventilation imaging. The radioactivity at time of loading and the start and stop times of inhalation will be captured in the CRF.

8.2 Concomitant Medication

Concomitant medications are any medications, including over-the-counter preparations, which the subject receives within 24 hours prior to signing informed consent through completion of the study. If a Tc-99m MAA perfusion study occurs following Technegas imaging but within this time period, the MAA and radioactive dose associated with the study should be considered a concomitant medication.

All medications given prior to and during the study will be recorded on the CRF. Documentation will include information concerning generic or trade names, indication, total daily dose (including units), route of administration, date of administration, and date of termination. All medications and therapies will be coded using WHODRUG®.

8.3 Subject Compliance

Subjects will be monitored by clinical personnel during each visit of this study. Subjects who are not compliant with the procedures outlined in this protocol should be withdrawn from the study at the discretion of the investigator or the Sponsor.

8.4 Protocol Deviations

An investigator may not deviate from the protocol, except when necessary to eliminate an immediate hazard (risk) to the rights, safety or welfare of a subject. The investigator must notify the sponsor immediately and not enroll any additional subjects or administer the investigational drug to any subsequent subjects until the immediate hazard is eliminated from the study protocol or otherwise resolved. The investigator must notify the sponsor of all protocol deviations and must notify the IRB/IEC of any protocol deviations following the IRB/IEC standard procedures.

9 Imaging

The same camera should be used to obtain planar Xe-133 and planar Technegas images. Planar scintigraphy with a nuclear medicine gamma camera will be used to image the distribution of both Xe-133 and Technegas. Imaging will first be performed with Xe-133 followed by Technegas. Because of the rapid clearance of Xe-133 from the lungs and the low, non-interfering energy of Xe-133 photons, a washout period is not required.

9.1 Xe-133 Ventilation and Imaging

Xe-133 ventilation and imaging should be performed in accordance with the standard of care for Xe-133 administration and imaging at the investigational site, which will be documented at the Site Qualification visit. Images should be labeled to indicate when each phase of the study begins (first breath, wash-in, wash-out). The wash-in/wash-out protocol for Xe-133 ventilation imaging used at each investigational site will be documented in the study files.

9.2 Technegas Ventilation and Imaging

Technegas inhalation will be performed after the Xe-133 portion of this study. Because of the rapid clearance of Xe-133 from the lungs and the low, non-interfering energy of Xe-133 photons, a washout period is not required. Technegas is administered by inhalation through the PAS within 10 minutes after preparation. This consists of a plastic tube connected to the TechnegasPlus Generator, fitted with a mouthpiece, one-way flow values and expiration filter.

The subject will be instructed to breathe through the mouthpiece in one of the methods described below:

- Slow, deep breathing from the residual functional capacity (end of calm expiration) followed by a 5-second breath-hold (recommended method)
- Normal breathing with deep inhalations without breath-holding
- Rapid and deep inspirations from the residual functional capacity followed by a breath-hold of about 5 seconds at the end of the inspiration

The count rate should be monitored until a rate of 1.5-2.5 kcps is achieved. This typically requires 1 to 5 breaths, but additional breaths may be necessary to achieve this target. The number of inhalations required to achieve the target counting rate should be recorded on the CRF, along with the time of the first inhalation and time of the final inhalation. To yield uniform apex-to-base deposition, it is recommended that the subject is ventilated in the supine position on the scanning bed with a detector positioned under the bed to monitor the lung count rate.

The same dual-headed camera used for Xe-133 imaging will be used to collect Technegas images in multiple projections.

Technegas images will include a six view image set:

- anterior view
- posterior view
- left posterior oblique view
- right posterior oblique view
- left anterior oblique view
- right anterior oblique view

Additional details and specifications related to the Technegas ventilation and imaging are provided in the Imaging Manual.

10 Assessment of Efficacy

Primary assessments of efficacy will be based on three blinded readers' independent assessments of the Technegas and Xe-133 ventilation images in independent, randomized reading sessions. Readers will be selected as having experience reading both Xe-133 and DTPA ventilation scans. Readers will also receive training on reading Technegas ventilation images.

In each reading session readers will be blinded to all clinical information except the chest X-rays required for this study. At the start of each case read, with the aid of the subject's chest X-ray, a reader will visually divide each lung into three regions of approximately equal size arranged craniocaudally and designated as the right apical, left apical, right mid, left mid, right basal and left basal regions. The readers will then assess each lung region for ventilation, assigning the region a ventilation score on a three-point scale:

0 = absent ventilation

1 = decreased ventilation

2 = normal ventilation.

If a lung region is completely obscured (as a result of pleural effusion for example), or if a lung region is completely absent as a result of lung resection, the region will be designated a score of 99 to indicate that ventilation cannot be assessed.

10.1 Blinded Read of Xe-133 Images

The Xe-133 planar ventilation images will be read by three (3) expert readers, blinded to all clinical information except the chest X-rays required for this study. Each reader will independently assess the images identified only by a random code number, which will dictate the order of presentation of images to the readers. Together with a subject's chest X-ray, a reader will be presented with all acquired ventilation image views for a subject. The reader will visually divide each lung into three regions of approximately equal size as described above and will assign a single ventilation score to each lung region.

Additional details on the blinded read are provided in the CYC-009 Imaging Charter.

10.2 Blinded Read of Technegas Images

In separate reading sessions, the same three readers who assessed the Xe-133 ventilation images will also assess the Technegas planar ventilation images. Again, the readers will be blinded to all clinical information except chest X-rays and the Technegas images will be identified by a random code number, distinct from the Xe-133 assigned code number. Each reader will independently assess the images presented in the order of their assigned code

numbers.

Two sequential reads will be conducted of Technegas ventilation images. In the first read of a case, a reader will be presented with the subject's chest X-ray and the subset of ventilation image views that match the views acquired with Xe-133 for that subject. The reader will visually divide each lung into three regions of approximately equal size as described above and then will assign ventilation scores to each lung region based on those views. He/she will then be presented with the additional Technegas image views and will assign a second score based on the complete set of Technegas images for the subject. If the second ventilation score for a region differs from the first, the reader will be asked to document the basis for the changed score.

The ventilation scores obtained from the first Technegas read of the subset of image views that match the Xe-133 image views will be used to determine agreement with Xe-133 for the primary efficacy endpoint. The ventilation scores obtained from the read of all Technegas image views will provide a secondary efficacy endpoint of agreement with Xe-133.

Additional details on the blinded read are provided in the Imaging Charter.

11 Assessment of Safety

Subjects will be screened prior to enrollment in the clinical trial to ensure that they meet all eligibility criteria, which are designed to exclude subjects for whom participation may not be safe. Women who are of childbearing potential must have a negative pregnancy test as part of the eligibility assessments.

11.1 Screening/Baseline Assessments

1. Subject is evaluated against the inclusion/exclusion criteria.
2. If subject meets inclusion/exclusion criteria informed consent will be obtained and a subject number will be assigned.
3. Demographic data is obtained (date of birth, gender, and ethnicity).
4. Allergies (including known food, environmental, and drug allergies) are documented.
5. Medical and surgical history is obtained including concomitant medications, smoking history and reason for Xe-133 ventilation imaging.

The following clinical and laboratory studies will be obtained at screening and must be performed within 24 hours prior to the first imaging study:

1. Physical examination including auscultation of the lungs and heart, and height and weight
2. Chest X-ray in either anteroposterior view or posteroanterior view. A chest X-ray obtained within 24 hours of signing the Informed Consent may be used in subjects with no significant clinical change.
3. Clinical chemistry and hematology
4. Serum or urine pregnancy test (for females of childbearing potential)

11.2 Safety Indicators

Safety will be monitored by the following parameters: vital signs (systolic and diastolic blood pressure, respiratory rate and pulse rate), oxygen saturation of the blood using pulse oximetry, and adverse event assessments during and post-administration of Xe-133 and Technegas inhalation.

If a clinically significant change from baseline is observed, and it represents a worsening of a clinical condition for any safety parameter, the change will be considered an AE, it will be documented on the AE page of the CRF, and the investigator will continue to monitor the subject until the parameter returns to baseline levels or until the investigator judges that

follow-up is no longer necessary.

11.2.1 Clinical Laboratory Measurements

Subjects will have blood drawn during screening to obtain clinical laboratory measurements. Blood samples will be sent for analysis by a central laboratory.

The following clinical chemistry measurements will be obtained: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, chloride, carbon dioxide (CO_2), serum creatinine, direct bilirubin, gamma-glutamyl transpeptidase (GGT), glucose, lactate dehydrogenase (LDH), serum phosphorus, potassium (K^+), sodium (Na^+), total bilirubin, total cholesterol, total protein, uric acid.

The following hematology measurements will be obtained: hemoglobin (Hgb), hematocrit (Hct), red blood cell count (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), mean platelet volume (MPV), white blood cell count (WBC), white blood cell differential, including lymphocytes, neutrophils, monocytes, eosinophils, and basophils.

11.2.2 Physical Examinations

A physical examination will be performed by a physician during screening and the findings recorded on the CRF.

11.2.3 Vital Signs

Vital signs must be obtained and recorded, including:

- Systolic and diastolic blood pressure millimeters of mercury (mm Hg)
- Pulse rate (beats/minute)
- Respiratory rate (breaths/minute)

The same position and arm should be used each time vital signs are measured for a given subject.

Vital signs will be collected within 30 minutes prior to the Xe-133 imaging study. These will be considered baseline measurements. Additional vital signs will also be taken following completion of the Xe-133 imaging, but prior to Technegas imaging.

Vital signs will be taken at approximately 10 minutes (± 5 minutes) prior to Technegas

inhalation and within 15 minutes following completion of the Technegas imaging.

The following changes (increases or decreases) in vital signs from pre-study baseline values are considered to be clinically significant and require commentary:

- systolic blood pressure > 45 mm Hg
- diastolic blood pressure > 30 mm Hg

Any clinically significant worsening changes will be documented on the AE page of the CRF.

11.2.4 Oxygen Saturation of the Blood using Pulse Oximetry

Oxygen saturation of the blood using pulse oximetry will be collected within 30 minutes prior to the Xe-133 study. This will be considered the baseline measurement. Oxygen saturation will also be taken following completion of the Xe-133 imaging, but prior to Technegas imaging.

Oxygen saturation will be taken at approximately 10 minutes (± 5 minutes) prior to Technegas inhalation and within 15 minutes following completion of the Technegas imaging.

The investigator will assess and comment if oxygen saturation falls below 90%. Attributability of any changes below 90% will be assessed as follows:

1 = Attributable to disease; no follow-up required

2 = Attributable to Xe-133 procedure; no follow-up required

3 = Possibly attributable to Technegas, FOLLOW-UP REQUIRED

Any oxygen saturation measurements with clinically significant changes below 90% and possibly attributable to Technegas will be repeated at appropriate intervals following the procedure until the values return to baseline or until the investigator and the Medical Monitor agree that further follow-up is no longer clinically relevant.

Any changes considered clinically significant and assessed as "3 = Possibly attributable to Technegas, FOLLOW-UP REQUIRED" will be documented on the AE page of the CRF.

11.3 Adverse Events

An AE is any untoward medical occurrence in a subject administered an investigational drug, which does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable or unintended sign (e.g., an abnormal laboratory finding), symptom, or disease

temporally associated with the use of the study drug, whether or not it is considered to be study drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of the drug.

All AEs, ascertained through subject interview, physical examination or other means will be recorded on the AE page of the CRF. Adverse events will be recorded beginning at the time the subject signs the informed consent. Any AEs recorded before Technegas inhalation will be considered a pre-treatment AE.

Any AE that is on-going at the completion of the imaging study will be followed by the investigator until resolution or until the principal investigator and the Medical Monitor agree that further follow-up is no longer clinically relevant.

11.3.1 Suspected Adverse Reaction

Suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reactions are the subset of all adverse events for which there is reasonable possibility that the drug caused the event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event.

11.3.2 Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

11.3.3 Unexpected Adverse Events

An unexpected AE is any AE for which the specificity or severity is not consistent with the current Investigator's Brochure, the general investigational plan, or other product labeling.

11.3.4 Serious Adverse Events

A SAE is any AE, regardless of causality that:

- Results in death.
- Is life-threatening. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- Requires subject hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or

disease existed before the subject was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).

- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject, or may require medical or surgical intervention to prevent one of the outcomes listed in the definition for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

In this subject population, hospitalization for lung disease, lung surgery, to treat pulmonary embolism (PE) or an underlying deep vein thrombosis (DVT) that may have caused PE is an expected event and actual admission may occur before or after a subject is enrolled in the study; therefore, hospitalization for lung disease, lung surgery or to treat DVT and/or PE which was the triggering factor for study enrollment will not be considered an SAE.

Planned hospital admissions or surgical procedures for an illness or disease which existed before the subject was enrolled in the trial or before study drug was given, are not to be considered AEs unless they occur at a time other than the planned date.

11.3.5 Severity of Adverse Events

Severity is defined according to the following criteria:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with normal daily activities
Severe	Inability to perform normal daily activities

The terms "serious" and "severe" ARE NOT synonymous. The term "severe" is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious," which is based on subject/event outcome or action criteria described above and are usually associated with events that pose a threat to a subject's life or functioning.

A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

11.3.6 Relationship to Study Drug

Relationship to study drug administration will be determined as follows:

None	No relationship between the experience and the drug; related to other etiologies such as concomitant medications or subject's clinical state.
Unlikely	The current state of knowledge indicates that a relationship is unlikely.
Possible	A reaction that follows a plausible temporal sequence from use of the drug and follows a known response pattern to the suspected drug. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Probable	A reaction that follows a plausible temporal sequence from the use of the drug and follows a known response pattern to the suspected drug. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
Definite	A reaction that follows a plausible temporal sequence from use of a drug and follows a known response pattern to the suspected drug.

11.4 Procedures for Reporting AEs, SAEs and Suspected Unexpected Serious Adverse Reactions (SUSARs)

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the AE section of the CRF. Any clinically relevant deterioration in any safety assessment is considered an AE and must be recorded on the AE section of the CRF.

All AEs will be noted and evaluated on the CRF with a full description of the nature, onset,

duration, severity, attribution, and outcome of the event. All AEs will be coded using MedDRA. Any treatment used to alleviate the AE(s) will also be recorded.

Adverse event recording and reporting will conform to International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines for Clinical Safety Data Management.

When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. All AEs should be recorded using standard medical terminology.

All SAEs that occur during the course of the study, as defined by the protocol, must be reported immediately by the investigator to the Medical Monitor by telephone or fax within 24 hours of the time the investigator first becomes aware of the SAE. Such preliminary reports should be followed with a detailed written description (within 5 days) which will include copies of hospital records and other documents when applicable.

All SAEs must be reported whether or not considered causally related to the study product. An SAE form will be provided to each clinical study site.

The investigator is required to document in full the course of the SAE, including any therapy given to the subject. The information collected will include, at a minimum, the following: subject number, description of the event and an assessment by the investigator as to the severity of the event and relatedness to study product. Follow-up information on the SAE may be requested by Cyclomedica. The SAE must also be recorded on the AE section of the CRF.

The investigator will also inform the sponsor of any relevant follow up information and the outcome of the SAE as soon as possible in a follow-up report.

Medical Monitor Contact Information:

11.4.1 Suspected Unexpected Serious Adverse Reaction (SUSAR)

The Sponsor must submit an Investigational New Drug (IND) Safety Report to the United States Food and Drug Administration (FDA) for any suspected adverse reaction that is both serious and unexpected. Before submitting the report, the sponsor will need to ensure that the event meets the following criteria:

- Suspected adverse reaction
- Serious
- Unexpected

If the AE does not meet all three of the definitions, it should not be submitted to the FDA in an IND Safety Report. The Sponsor, with input from the Medical Monitor, will evaluate the information and decide if there is a reasonable possibility that the drug caused the AE and therefore meets the definition of suspected adverse reaction. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

A written IND Safety Report must be submitted to FDA within 15 calendar days since the determination that the suspected adverse reaction or any other information qualifies for reporting.

Unexpected fatal or life-threatening suspected adverse reactions must be reported to FDA in an expedited report no later than 7 calendar days after the Sponsor's initial receipt of information.

12 Schedule of Efficacy and Safety Assessments

12.1 Visit 1

During Visit 1, screening procedures are performed, informed consent is obtained and documented with signature and date, and eligible subjects are enrolled. The investigators will be asked to record the purpose for a subject's Xe-133 ventilation imaging, and based on their recent chest X-ray indicate whether pleural effusion is present for the subject.

Subjects will undergo Xe-133 ventilation imaging. This will be followed as soon as practical by the Technegas imaging procedure. Because of the rapid clearance of Xe-133 from the lungs and the low, non-interfering energy of Xe-133 photons, a washout period is not required.

The Sponsor must be notified if Xe-133 and Technegas imaging sessions are to be performed in separate visits. The Sponsor will grant approvals only on a case-by-case basis. If the second imaging procedure must be done during a separate visit occurring within 24 hours of the first visit, this will result in an additional visit for the subject.

If a Tc-99m MAA perfusion study is planned for the subject as part of their standard of care at this visit, it must occur after Technegas imaging is complete, and after the post-Technegas imaging safety assessments, within 15 minutes post-imaging, have been captured.

12.2 Schedule of Efficacy and Safety Assessments

	Visit 1						
		Xe-133			Technegas		
		Prior to Inhalation (≤ 30 min.)	Ventilation and Imaging	Post-Imaging	Prior to Inhalation (10 ± 5 min.)	Ventilation and Imaging	Post- Imaging (≤ 15 min.)
	Screening	Baseline					
Inclusion/Exclusion	x						
Informed Consent	x						
Demographics	x						
Pregnancy Test	x						
Medical History	x						
Physical Exam	x						
Chest X-ray	x						
Clinical Labs	x						
Vital Signs		x		x	x		x
Oxygen Saturation		x		x	x		x
Ventilation Imaging			x			x	
Adverse Events	x	Monitored throughout the study					
Concomitant Medication	x	Monitored throughout the study					

13 Statistical Analysis

13.1 General Considerations

The primary presentations and analyses will be based on data pooled across study centers. Relevant summaries for individual centers, or combinations of centers, also may be presented for primary data. Standard descriptive statistics will be used to summarize data, including one- and multi-way frequency tables for discrete or categorical variables, and mean, median, standard deviation, minimum, maximum for continuous variables.

All data collected and entered into the study database will be provided in data listings by variable type presenting individual subject values. All testing and confidence intervals will use a two-sided significance level of 5%, unless otherwise specified.

Additional details concerning the planned statistical methodologies are provided in the Statistical Analysis Plan.

13.2 Analysis Populations

Three analysis data sets will be defined for the study:

- Modified Intent-to-Treat (MITT) Set will consist of all subjects who are enrolled in this study and receive any dose of Technegas treatment; it will be the analysis set for the safety analyses.
- Full Analysis Set (FAS) will consist of subjects who completed all of the ventilation imaging on the study, and both sets of Xe-133 planar scans and the Technegas planar scans are of interpretable image quality according to site investigators' assessment.
- Per Protocol Set (PPS) will consist of those subjects in the FAS who are compliant with regard to the Technegas and Xe-133 procedures (dosing and imaging), and have no other major protocol violations.

13.2.1 Disposition

Subject disposition will be summarized and will include:

- Number of subjects screened
- Number of subjects enrolled in the study
- Number of subjects included in the MITT set
- Number of subjects withdrawn from the study and the reason for withdrawal
- Number of subjects in the FAS

- Number of subjects in the PPS

The screening data for all subjects who were screened but not enrolled into the study will be provided in a separate data listing. These subjects will not be included in any other listings, tabulations, or analyses.

13.2.2 Baseline Characteristics

Demographic data, including age, gender, race, ethnic group, and reason for ventilation imaging will be summarized using descriptive statistics.

Abnormal medical histories and prior/concurrent medications will be summarized using counts and percents. Prior/concurrent medications will be coded using the World Health Organization (WHO) classification system. Prior and concurrent medication use overall and by WHO medication classification will be summarized using counts and percentages.

13.3 Efficacy Evaluations

13.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is percent agreement between Technegas and Xe-133 obtained from each blinded reader's ventilation scores of matching image views.

The agreement statistic will be derived from the ventilation scores as follows. Binary agreement scores will be obtained for each subject's six lung regions: if the Technegas and Xe-133 ventilation scores are the same for a lung region, the region is assigned an agreement score of 1, otherwise the region is assigned a score of 0 for no agreement. The subjects' binary agreement scores will provide the basis for an overall estimate of percent agreement and confidence interval for each of the three readers.

In the case of a missing ventilation score (score = 99) as a result of a reader assessing a region as obscured or absent, the binary agreement score will be determined as follows. If both Technegas and Xe-133 scores are missing for the region, the binary agreement score will be missing for the region. If the score is missing for one of the imaging modalities and not the other, then the region will be assigned a score of 0 for no agreement.

13.3.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

1. Percent agreement between Technegas and Xe-133 obtained from blinded readers' ventilation scores based on all image views collected for Technegas and Xe-133.
2. Percent agreement between Technegas and Xe-133 for the subgroups of subjects with

and without pleural effusion as noted in subjects' chest X-rays, from blinded readers ventilation scores.

3. Percent agreement measuring inter-observer agreement between pairs of blinded readers for their Technegas ventilation scores, and for their Xe-133 ventilation scores.
4. By lung-region kappa statistics measuring inter-observer agreement between pairs of blinded readers for their Technegas ventilation scores, and for their Xe-133 ventilation scores.

13.4 Efficacy Analyses

13.4.1 Primary Efficacy Analyses

The primary analysis will be conducted on the FAS for Technegas and Xe-133 matched image views. Each blinded readers' binary agreement scores will be analyzed using a generalized linear model with SAS® PROC GENMOD. The logit function (log odds ratio) will be specified as the link function, and subject will be specified as a repeated measure to allow for correlations between lung regions within a subject. The estimate of the intercept of the model using generalized estimating equation (GEE) methodology will provide an overall estimate of the agreement and its 95% confidence interval in terms of the log odds ratio; simple algebra will be used to obtain the corresponding estimates and confidence intervals in terms of percent agreement (PA).

The non-inferiority hypothesis to be tested is:

$$H_0: PA \leq 60\% \text{ versus } H_A: PA > 60\%$$

If the lower boundary from the 95% confidence interval for PA is greater than 60%, Technegas will be considered non-inferior to Xe-133 with respect to the measurement of pulmonary ventilatory distribution.

Study Success Criteria

For the study to be deemed a success, the null hypothesis must be rejected for at least two of the blinded readers.

13.4.2 Secondary Efficacy Analyses

The same methodology as described for primary efficacy analyses in the previous section will be applied to the binary agreement scores between Technegas and Xe-133 obtained from blinded readers' ventilation scores based on all image views, both for the FAS and PPS analysis datasets. The methodology will also be applied to the agreement scores between Technegas and Xe-133 for the subgroups of subjects with and without pleural effusion.

Inter-reader percent agreement between pairs of blinded readers Technegas ventilation

scores and their 95% confidence intervals will be obtained using the same methodology described for the primary efficacy endpoint. Analyses will be performed for both FAS and PPS. For comparison, the inter-reader percent agreement will be obtained in the same manner for Xe-133 ventilation scores.

By lung region, inter-reader kappa statistics and their 95% confidence intervals will be calculated for pairs of blinded readers using the three by three tables of the frequencies of ventilation scores for Technegas as displayed:

Ventilation Score Reader I	Ventilation Score Reader J		
	0	1	2
0	N_{00}	N_{01}	N_{02}
1	N_{10}	N_{11}	N_{12}
2	N_{20}	N_{21}	N_{22}

where N_{ij} represents the agreement frequency for a cell. For comparison, the by-region inter-reader kappas based on the blinded readers' ventilation scores for Xe-133 scans will also be obtained.

13.5 Non-Inferiority Margin

The non-inferiority margin used in the analysis of the primary endpoint of this study was principally determined from a separate study conducted under Protocol CYC-010. In Study CYC-010, six blinded readers read 75 Xe-133 planar ventilation imaging studies in two read sessions separated by a minimum of 4 weeks. The readers scored the six regions of the lung using the same ventilation scoring metric to be used in this protocol. The two sets of assessments from the read and re-read of the Xe-133 images were used to determine a measure of agreement between successive reads of Xe-133 lungs scans for each of the readers, and the compilation of the six readers' estimates were then used to establish a 95% tolerance interval for the population of readers. The lower bound of the tolerance interval was 62%. Since Xe-133 is an approved agent for ventilation imaging, it by default is considered non-inferior to itself, and hence the read/re-read results provide a suitable limit for establishing the non-inferiority of Technegas compared to Xe-133.

When comparing Xe-133 and Technegas imaging, it is recognized that there are inherent differences between the imaging performed with Xe-133 and Technegas: Xe-133 imaging includes both wash-in and wash-out views, while Technegas imaging has no equivalent to the wash-in/wash-out views but collects additional views. This has the potential to result in differences in ventilation scoring which are not clinically relevant. For example, in subjects that have regions of pleural effusion, on Xe-133 the region would likely be scored as

1=decreased ventilation based on retention visible in wash-out views, whereas on Technegas it would be scored as 0=absent ventilation. Only a small percentage of subjects are expected to exhibit such discrepancies and to account for this, a small adjustment was made to the non-inferiority margin obtained from the CYC-010 study from 62% to 60%. The anticipated agreement between Technegas and Xe-133 imaging is 70%. The standard error of the agreement for the Xe-133 to Xe-133 image comparison among the six readers from study CYC-010 was 4.6% and thus a lower confidence interval bound of 2 standard errors also supports a non-inferiority margin of about 60%. Thus the non-inferiority margin planned for this study is 60%.

13.6 Rationale for Sample Size

Using the normal approximation to the binomial distribution for calculation of the sample size, and the proportion associated with the non-inferiority margin (P0) to estimate the standard deviation, the following table provides sample size requirements for testing the hypotheses:

$$H_0: PA \leq P0 \text{ versus } H_A: PA > P0$$

where PA (percent agreement) has expected true values of 70% to 75%, and the non-inferiority margin (P0) is 60%.

Table Sample Size for 90% Power and 0.025 One-sided Type 1 Error

Non-inferiority Margin P0 (%)	Expected True Value PA (%)	Required Sample Size (N)
60	70	240
	71	197
	72	164
	73	139
	74	119
	75	103
Calculations performed with PASS 14[12]		

The planned sample size for the study is 240 subjects who have completed Xe-133 and Technegas ventilation imaging, and the images are of interpretable quality (FAS). This sample size will provide 90% power to establish that agreement between the blinded read assessments of Xe-133 and Technegas is better than 60%, assuming an expected true level of agreement between Xe-133 and Technegas of 70%.

13.7 Interim Analysis

After approximately 40 subjects have completed the study, an interim pilot blind read of the Xe-133 and Technegas ventilation images will be conducted to assess the viability of the planned efficacy measurements for comparing the two sets of images. If it is determined that the initial study design and efficacy parameters are not viable due to the differences in the image sets being acquired, the protocol will either be amended in accordance with Agency input, or the study may be terminated. The readers performing the pilot blind read will not be used for the final blind read of images, and unless imaging parameters change, the images from these first 40 subjects will be included in the final read of images.

13.8 Safety Endpoints

Safety endpoints include:

1. Incidence of treatment emergent AEs.
2. Change (post minus baseline) in vital signs at each time-point post Xe-133 and Technegas administration. The measurements within 30 minutes prior to Xe-133 inhalation will serve as the baseline.
3. Incidence of clinically significant changes in blood pressure (defined Section 11.2.3).
4. Change (post minus baseline) in oxygen saturation at each time-point post Xe-133 and Technegas administration. The measurements within 30 minutes prior to Xe-133 inhalation will serve as the baseline.

13.9 Safety Analyses

The summary and analysis of safety data will be conducted on the modified ITT dataset.

Frequency distributions including counts and percentages will be used to summarize the qualitative safety data, including AEs, clinically significant changes in vital signs and clinically significant oxygen saturation measurements that fall below 90%. The summary of AEs will include summaries by MedDRA system organ class, relationship to study treatment, and event severity. Serious adverse events also will be summarized separately.

Summary statistics will be provided for all continuous safety data including change in vital signs and oxygen saturations. Paired t-tests will be used to test for statistically significant changes over time.

14 Data Handling and Record Keeping

14.1 Case Report Forms

Electronic CRFs (eCRFs) will be used and clinical trial data will be entered into directly into the electronic data capture (EDC) system. The EDC system will be a 21 Code of Federal Regulations (CFR) Part 11 compliant data capture system. The data system will include password protection, logs to identify individual entering or correcting data and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Any changes, corrections or deletions made in the eCRFs will identify the responsible investigator or other authorized person modifying the data. The investigator will review the completed eCRFs and electronically sign and date them to indicate his/her review, agreement with the data included, and the completeness and accuracy of the data.

Case report forms (CRFs) must be completed for all enrolled subjects, even if the subject fails to complete the study. No section of the CRF is to be left blank without an appropriate explanation by the investigator, since the lack of such explanation may necessitate discarding an otherwise usable observation.

14.2 Completing, Signing and Archiving Case Report Forms

Data collection is the responsibility of the investigator at the investigative site or clinical trial staff under the supervision of the respective site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, timeliness and attributability of the data reported.

Clinical data may be entered directly into the eCRF at the time of data collection or from the source documents. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a study note and maintained in the participant's electronic study record.

To comply with the requirement to maintain accurate case histories investigator(s) should review and electronically sign the completed eCRF for each subject before the data are archived or submitted to FDA. If changes are made to the eCRF after the investigator(s) has already signed, the changes should be reviewed and electronically signed by the clinical investigator(s).

14.2.1 Archiving of Records

The following information must be retained at the investigational site for at least 2 years after the last approval of a marketing application and until there are no pending or contemplated

marketing applications in an ICH region; or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational drug; or for the maximum period of time as required by the study center, whichever is greater:

- Source data (including digital images)
- Source documents
- Copies of protocols
- Protocol amendments
- Correspondence
- Subject identification codes and lists
- Signed informed consent forms
- Any other essential documents pertaining to the conduct of the study

No study document or image should be destroyed without prior written agreement between the sponsor and the investigator(s). Should the investigator(s) wish to assign the study records to another party or move them to another location, advance written notice should be given to the sponsor.

It is the responsibility of the sponsor to inform the investigator(s)/institution(s) when these documents need no longer be retained.

The sponsor will ensure all other study documents (e.g.: protocol, report, all data management documentation) are filed and archived in a secure area in the Trial Master File for at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications in an ICH region; or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product; or for the lifetime of the product, as required by regulation. In addition, the final trial report must be retained by the sponsor, or the subsequent owner, for five years beyond the lifetime of the study agent.

14.3 Direct Access to Source Data/Documents

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial will be made directly available for clinical monitoring activities. Source data are contained in source documents (original records or certified copies). Source documents are original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy

dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negative, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).[13]

All source documents must be accurate, clear, unambiguous, legible, contemporaneous, original, permanent and available for inspection and audit. Paper-based source documents should be made using a permanent form of recording (ink, typing, printing, optical disc, etc.) and they should not be obscured by correcting fluid or have temporary attachments (such as "post-it" notes).

If electronic medical records are used as source data to support trial data, the investigator will authorize the monitor to compare the data stored in the electronic medical records to the CRF data to ensure all data are complete, consistent, and accurate and ensure prior to enrolling a subject that a GCP-compliant method of doing this is available for the monitor.

If electronic medical records are used to support trial data and the monitor is not allowed direct access to the electronic medical records for monitoring and data verification purposes, the source documents that are computer-generated and stored on magnetic support media must be printed and must be certified by the investigator as being an exact duplicate of the original electronic record. The investigator or designee will identify each printed page as a certified copy and will sign and date the printed pages to so indicate.

The minimum requirements for source documents used in clinical trials are that they should contain: the identity of the subject (or trial-related identifiers such as trial enrollment number, treatment number), the subject's participation in the trial (protocol/study title or number), subject's demographic data, the date and time the subject provided informed consent, the subject's medical history, the treatment that the subject received, AEs, SAEs and the dates of the trial visits. The end of the subject's trial participation must be documented. Information recorded in the CRF must be consistent with entries in the source documents.

The following data may be recorded directly in the CRF. If it is, it will be considered as source data:

- Imaging parameters
- Assessment of images for technical adequacy

If other data are recorded directly into the CRF at the time the data are obtained, it will be considered as source data, too. The investigator must document in the study file the use of the CRF as its own source document for any such data.

Source documents in connection with the study, including but not limited to, subject charts, radiology reports and laboratory data, will be made available to the sponsor upon request with due precaution towards protecting the privacy of the subject.

14.4 Monitoring

For this trial, a combination of automated data checks/verification, central (remote, off-site) monitoring of data recording in the eCRFs and data-driven on-site monitoring with targeted source data verification of key data will be used. Automated data checks/verification and centralized monitoring will make most efficient use of limited monitor on-site time and it may allow risks or problems to be identified faster, since some eCRF data will be reviewed centrally prior to an on-site visit. Therefore; it may allow problems to be addressed pro-actively and mitigated instead of being identified and addressed at an on-site visit.

Targeted data verification, using pre-identified data points based on the type of data and its risk to trial integrity (for example informed consent to ensure a subject exists and provided prospective informed consent), or based on the critical nature of the data (for example AE details) or unusual or unexpected data are source data verified, with other data reviewed to the extent necessary to verify CRF completion may reduce the number of data points that are source data verified on-site by a monitor. This will allow the site monitor to focus on the key data that are deemed most important to confirm protocol compliance, subject safety and data validity.

The targeted data include:

- Informed consent
- Eligibility criteria
- Dose administration
- Clinical safety and AEs
- Clinical laboratory assessment
- Concomitant medications
- Unusual or unexpected data

Central monitoring of completed eCRFs will be performed primarily at Certus' offices or other appropriate regional location. It will include a review of targeted data in the completed eCRFs.

On-site monitoring visits will be performed at the investigational site per Certus SOP 403, Site Monitoring Visit, as modified by a project-specific Monitoring Plan. It will include a verification of informed consent and targeted data in the completed eCRFs using comparison to source records.

A closeout visit will be performed at the conclusion of the Investigator's involvement in the

study.

14.4.1 Monitoring of Images and Imaging Data

Images, including imaging parameters, image acquisition and other imaging-related data are verified by the investigator and/or medical physicist or other appropriate staff and they are verified by the imaging Core Lab following SOPs and project-specific methods after receipt of images and supporting data at the Core Lab.

14.5 Final Report

The final report of the trial will be written by the sponsor or its designee and will be submitted to the regulatory authority.

15 Quality Control and Quality Assurance

15.1 Data Quality Assurance

Data entry parameters and automated data checks will be used and implemented by the eCRF system to assist the site investigators and staff in CRF completion. Completed CRFs will be reviewed by clinical research associates (CRAs) or a designee from the sponsor or a Clinical Research Organization representing the sponsor using centralized monitoring and/or on-site monitoring. During monitoring activities, the CRA or designee will check for completion of the entries on the CRFs, site compliance with the study protocol and with GCP, will assess Technegas drug accountability and will evaluate if source data are accurately supports data recorded in the CRF. In addition, the CRA will assess whether all AEs and SAEs have been appropriately reported within the time periods required.

Data Management will also provide services to assure data quality. To ensure the completeness, internal consistency and accuracy of the data in the study database, appropriate validation checks will either be incorporated into the EDC system and will execute at data entry, or they will be performed externally with SAS programs. Details of the checks will be included in a Data Management Plan for the study.

15.2 Auditing

The sponsor or a representative of the sponsor may arrange to visit the investigator in order to audit the performance of the study at the study site and the study documents originating there at any time during the study or following completion of the study. The investigator and designated site staff will cooperate in the scheduling and performance of the investigator/site audit. The auditor(s) may be accompanied by the CRA and/or other the study staff. The investigator will be informed of the results of the audit.

In addition, inspections by the site IRB, by a local site research authority or by health authority representatives, including but not limited to the US FDA, the US Department of Health and Human Services, the US Office of Human Research Protections, the US Nuclear Regulatory Commission or the State regulatory authority are possible at any time. The investigator will notify the sponsor immediately upon being contacted by any local, State or federal regulatory authority for any such inspection.

The investigator will make all pertinent records available including source documentation for inspection by regulatory authorities and for auditing by the sponsor. This information will be considered as confidential.

16 Ethics

16.1 Ethical Considerations

This study will be conducted in accordance with the Declaration of Helsinki and ICH E6 GCP Guideline and in compliance with the protocol and all regulatory requirements including Title 21 CFR § 50, 54, 56 and 312. To ensure compliance the investigator agrees, by written consent to this protocol, to fully cooperate with compliance checks by allowing access to all documentation by authorized individuals.

A copy of the Declaration of Helsinki is provided in Appendix 20.2.

16.2 Institutional Review

This protocol and the informed consent form will be reviewed and approved by the research facility's IRB or IEC. A copy of its letter or certificate of approval will be sent to the sponsor prior to the commencement of the study.

17 Additional Requirements and Procedures

17.1 Regulatory Requirements–Sponsor/Investigator Obligations

This study will be conducted in accordance with the Declaration of Helsinki and ICH E6 GCP Guideline and compliance with the protocol and all regulatory requirements including Title 21 CFR § 50, 54, 56 and 312. To ensure compliance the investigator agrees, by written consent to this protocol, to fully cooperate with compliance checks by allowing access to all documentation by authorized individuals.

17.2 Protocol Amendments

Any changes to the protocol will be made in the form of a protocol amendment. No change to the protocol may be made without the joint agreement of both the investigator and the sponsor. Any amendment to the protocol must be submitted to the FDA and to the IRB/IEC and approved before implementation.

17.3 Protocol Deviations

An investigator may not deviate from the protocol in any way, except when necessary to eliminate an immediate hazard (risk) to the rights, safety or welfare of a subject. The investigator must notify the sponsor immediately and NOT enroll any additional subjects or administer Technegas to any subsequent subjects until the hazard is eliminated from the study protocol or otherwise resolved. The investigator must notify the IRB/IEC of any protocol deviations. The FDA will be notified of all protocol deviations in compliance with federal regulations and GCPs.

17.4 Investigative Agreement

Prior to initiation of the study, the principal investigator must agree to abide by the terms of the Investigative Agreement and sign, date and return the agreement to the sponsor. A copy of this agreement is contained in Appendix 20.1.

17.5 Investigator's Responsibilities

An investigator must comply with all obligations and responsibilities, described in 21 CFR 50, 4, 56, 312, on the completed FDA Form 1571 and other local, state and federal regulations and in ICH GCPs, including but not limited to those responsibilities described in detail in this Section.

17.5.1 Informed Consent

All subjects must sign and personally date an approved Informed Consent Form after receiving detailed written and verbal information about the reason, the nature and the possible risks associated with the administration of the investigational drug prior to enrollment in the study. It is the responsibility of the investigator to obtain that consent. The details of this requirement are explained in 21 CFR 50 Subpart B, the Declaration of Helsinki, and the ICH E6 Guideline for GCP.

The subject must be made aware and agree that personal information may be scrutinized during audit by competent authorities and properly authorized persons. However, personal information will be treated as strictly confidential and will not be publicly available.

By signing the Investigative Agreement, the investigator assures the sponsor that Informed Consent will be obtained for each subject participating in the study.

Prior to IRB/ IEC submission, the investigator must send a copy of the Informed Consent Form to be used at their institution to the sponsor for review to assure compliance with the ICH and CFR requirements.

17.5.2 Curriculum Vitae

The investigator and any sub-investigator(s) must provide the sponsor with a current copy of his/her own curriculum vitae (CV). The CV must include a statement of the investigator's relevant experience.

17.5.3 Financial Disclosure

As required by 21 CFR § 54, all investigators, including sub-investigators and other study staff who perform significant clinical trial responsibilities must provide signed and dated financial disclosure before the study is initiated at the site and at the completion of the study. Any significant changes to the reported financial interests and arrangements must be disclosed for one year after completion of study participation.

The investigator must obtain an original, completed, signed and dated Financial Disclosure Form for any sub-investigator who ends participation in the trial, whether it is due to leaving the research facility or any other reason. The investigator must notify the sponsor and provide the completed Form at the time the sub-investigators ends participation.

17.5.4 Investigator Delegation of Responsibilities

The investigator must complete prior to the start of the study and maintain on an on-going basis until close-out of the study, a Log or other detailed document that identifies all

individuals to who the investigator has delegated significant study-related responsibilities, describes the responsibilities, records personally-completed original signatures and initials of all of the individuals to whom responsibilities have been delegated and documents the individual's acceptance of the delegated responsibilities.

17.5.5 Investigator and Study Staff Training and Documentation

The investigator must supervise and ensure that adequate training is provided for all sub-investigators and study staff to whom study-specific responsibilities and obligations are delegated. The investigator must ensure qualification documentation and training records are completed and available in the study file for the investigator, sub-investigators all pertinent study staff the start of the study and that they are maintained and updated as needed throughout the course of the trial.

17.6 Conditions for Terminating the Study

In the event that the investigator is unable to continue the study, another suitable person may be designated Investigator, and documentation testifying to this will be submitted to the sponsor immediately. The new investigator must be approved by the sponsor and the IRB/IEC before the study can be continued.

If the sponsor and/or the investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted. If the investigator terminates the study, an explanatory letter will be provided to the sponsor.

The sponsor also reserves the right to discontinue this study for administrative reasons at any time. The investigator will be reimbursed for reasonable expenses incurred, if it is necessary to terminate the study or an individual subject's participation. The sponsor will not reimburse the investigator for the evaluation of subjects if the evaluations are not conducted in compliance with the present protocol.

The sponsor may terminate an investigator's participation in this study at any time for any reason, including the investigator's intentional or repeated noncompliance with the study protocol, GCPs, the Investigative Agreement, the FDA Form 1572 or regulatory requirements. If the sponsor terminates an investigator's participation due to noncompliance, the FDA and site IRB or IEC must be notified by the sponsor, as required by 21 CFR 312. 56.

17.7 Warnings, Precautions, Contraindications

For specific information concerning warnings, precautions and contraindications for the study device, the investigator is asked to refer to the appropriate section of the Technegas

Investigator's Brochure and the TechnegasPlus Generator User Manual.

17.8 Information

Before the beginning of the study the investigator will have been given the last updated Investigator's Brochure, TechnegasPlus Generator User Manual and other supporting documents to describe use, maintenance and other pertinent information related to the Technegas. If this information is revised during the study, the investigator will receive a copy of the revised version.

17.9 Confidentiality

All information provided to the investigator dealing with the investigational drug, the protocol and this investigation will be regarded as confidential. Acceptance constitutes the agreement by the recipient that no unpublished information herein contained will be published or disclosed without the sponsor's prior written approval except that this document may be disclosed to appropriate IRB/IEC as long as they are required to keep it confidential. The members of the research team agree not to discuss such information in any way without prior written permission from the sponsor.

18 Financing and Insurance

18.1 Financing

A financial agreement (separate from the protocol) will be made with the investigator or designee. Such agreement will be archived in the relevant file.

Financial support to investigators/sub-investigators other than the cost of conducting the clinical study or other clinical studies will be disclosed in accordance with Title 21 CFR 54.2 to 54.6.

19 Publication Policy

19.1 Use and Publication of Study Results

All unpublished documentation (including the protocol, CRF and Investigator's Brochure) given to the investigator is strictly confidential. All recipients must agree not to disclose the information herein contained to any person without the prior written authorization of the sponsor. The submission of these documents to the IRB/IEC is expressly permitted. The investigator agrees that the sponsor maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and regulatory authorities of any country.

The results of the study may be presented during scientific symposia or published in a scientific journal only after review by the sponsor in accordance with the guidelines set forth in the applicable publication or financial agreement.

19.2 Disclosure of Data

All information obtained during the conduct of this study will be regarded as confidential and written permission from the sponsor is required prior to disclosing any information relative to the study. Manuscripts prepared for publication will be submitted to the sponsor for review and comment prior to submission to the publisher. The sponsor will attempt to provide comments within 30 days. This condition should not be construed as a means of restricting publication but is intended solely to assure mutual concurrence regarding data, evaluations and conclusions and to provide an opportunity to share with the investigator any new and/or unpublished information of which he/she may be unaware.

20 Appendices

20.1 Investigator Agreement

I have read and understand the information in the protocol and attached case report form, the Investigator's Brochure, the TechnegasPlus Generator User Manual and other documents if applicable, understand the information contained and agree that it contains all necessary detail for carrying out this study. I agree to conduct the study in accordance with the Investigator's Agreement, the current protocol, and applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA, and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I have read and understood the provisions of Title 21 of the United States Code of Federal Regulations (CFR) Part 312, Subpart D regarding responsibilities of Sponsors and Investigators; Part 50 and Part 56 regarding the protection of human subjects and informed consent, and Part 54 for financial disclosure. I have read, understood and signed the Statement of Investigator Form FDA1572 which outlines my responsibilities as Principal Investigator.

I agree to personally conduct or supervise the described investigation, including all testing of the investigational drug involving human subjects. I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.

I agree to inform any subjects that Technegas is being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met. I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312. I agree to maintain adequate and accurate records in accordance with 21 CFR 312 and to make those records available for inspection.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

Investigator Agreement (Continued)

Additionally, I warrant and represent that neither I nor anyone else who will be involved in this study has been disqualified or debarred by a U.S. or Australian regulatory body for clinical investigations or any other purpose nor has been convicted of any felony for conduct relating to the development or approval, including the process for the development or approval, of any drug application, or otherwise relating to the regulation of any drug product.

If at any time I or anyone involved in this study should become disqualified or become debarred or is convicted of violations for conduct relating to the development or approval, including the process for development or approval, of any drug application, or otherwise relating to the regulation of any drug product, I will give the sponsor prompt written notice of same. Additionally, I will notify the sponsor at any time in the future if such disqualification or debarment is based in whole or in part on participation in this study.

_____
Printed Name of Principal Investigator

_____, M.D.
Signature of Principal Investigator

Date: _____/_____/_____

20.2 Declaration of Helsinki

DECLARATION OF HELSINKI

RECOMMENDATIONS guiding physicians in biomedical research involving human subjects (adopted by the Eighteenth World Medical Assembly, Helsinki, Finland, 1964; and amended by the Twenty-Ninth World Medical Assembly, Tokyo, Japan, 1975; by the Thirty-Fifth World Medical Assembly, Venice, Italy, 1983; and by the Forty-First World Medical Assembly, Hong Kong, 1989).

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special procedures must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has

prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the principal investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.

10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case, the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

    Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained additionally to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (CLINICAL RESEARCH)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (NON-CLINICAL BIOMEDICAL RESEARCH)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The principal investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

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