STATISTICAL ANALYSIS PLAN Polarean, Inc.

POL-Xe-001

Title: ***Evaluation of Hyperpolarized ^{129}Xe MRI as Compared to ^{133}Xe Scintigraphy for the Assessment of Pulmonary Function in Patients being Evaluated for Possible Lung Resection Surgery***

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LIST OF ABBREVIATIONS AND TERMS DEFINITIONS

Abbreviation	Definition
^{129}Xe	non-radioactive isotope of xenon (hyperpolarized ^{129}Xe is the drug product)
AE	adverse event
ATC	anatomical therapeutic chemical
CI	confidence interval
eCRF	electronic case report form
FEV1	forced expiratory volume in 1 second
Lobectomy	Refers to the removal of a lobe (or lobes).
MedDRA	Medical Dictionary for Regulatory Activities
MR	magnetic resonance
MRI	magnetic resonance imaging
Resection	For this study, the definition of resection surgery includes segmentectomies, lobectomies, and pneumonectomies.
n	Number of observations
PT	preferred term
SAP	statistical analysis plan
SOC	system organ class
SpO_2	peripheral capillary oxygen saturation
SD	standard deviation
TEAE	Treatment-emergent adverse event
Xe	xenon

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Polarean's pivotal Phase 3 study POL-Xe-001.

This document is prepared on the basis of the study protocol version Amendment 3 (dated 26 April 2018). The reader is referred to the study protocol, the electronic case report form (eCRF), general eCRF completion guidelines, and various data collection instruments employed in the study for details of study design, conduct and data collection.

This SAP is to be reviewed, approved, and submitted to FDA prior to study database lock. If any SAP updates are made upon blinded review of study data, or for any other reasons in the course of the study, such modifications and rationale are likewise to be documented and approved prior to unblinding of the study database.

1.1. Study Objectives

1.1.1. Primary Objectives

The primary objective of this study is to demonstrate the equivalence of hyperpolarized ^{129}Xe magnetic resonance imaging (MRI) as compared to ^{133}Xe scintigraphy for the evaluation of pulmonary function.

1.1.2. Secondary Objective

The secondary objectives of this study are to:

- Assess the safety and tolerability of hyperpolarized ^{129}Xe gas;
- Evaluate regional ventilation defects in each of the 6 zones, and
- Demonstrate the equivalence of post-operative forced expiratory volume in 1 second (FEV1) values predicted using hyperpolarized ^{129}Xe as compared to ^{133}Xe scintigraphy.

1.2. Overall Study Design and Plan

This is a multicenter, randomized, open-label, cross-over Phase 3 study evaluating hyperpolarized ^{129}Xe MRI as compared to ^{133}Xe scintigraphy for the evaluation of pulmonary function. This study will enroll male and female subjects being evaluated for possible lung resection surgery (i.e. segmentectomy, lobectomy, or pneumonectomy). This study is comprised of 4 periods.

- Screening: Subjects will be screened for study participation based on inclusion and exclusion criteria. Informed consent will be obtained.

- Imaging: Subjects will undergo both a hyperpolarized ^{129}Xe MRI scan and ^{133}Xe scintigraphy. During the MRI session, one or more conventional proton MRI scans will also be collected to confirm lung anatomical features. Both ^{133}Xe scintigraphy and hyperpolarized ^{129}Xe MRI will be quantified using commercially available software. Images will be interpreted by central readers who are blinded to the subject's medical history and all study assessments. Information related to any adverse events (AEs) will be collected during this period.
- Follow-up: Subjects will be contacted by phone on the day after (+3 days) the completion of all imaging to collect information on any AEs.
- Post-op Follow-up: If the subject has lung surgery, approximately 3 months after surgery the subject will come in for a post-operative FEV1 measurement (spirometry).

Following completion of screening and baseline eligibility assessments, all subjects will receive both a hyperpolarized ^{129}Xe MRI and ^{133}Xe scintigraphy. During the MRI session, one or more proton MRI scans will also be collected to confirm lung anatomical features. If a subject undergoes resection surgery, an additional study visit to record post-operative FEV1 levels (spirometry) will be required approximately 3 months after surgery.

Safety will be monitored after the administration of both hyperpolarized ^{129}Xe and ^{133}Xe (Day 1) and again on Day 2 during the Imaging Follow-up period.

1.3. Randomization and Blinding

All randomized subjects will be divided between 2 treatment sequences in a 1:1 ratio. Subjects will be randomized to receive either ^{129}Xe followed by ^{133}Xe, or ^{133}Xe followed by ^{129}Xe. All subjects will receive at least 1 dose of hyperpolarized ^{129}Xe and 1 dose of ^{133}Xe during study participation.

This is an open-label study. Images generated from this study will be interpreted by a trained central reader, blinded to the subject's medical history and all study assessments. The images will be uploaded in a blinded manner to a computer for review. Both ^{133}Xe scintigraphy and hyperpolarized ^{129}Xe MRI will be quantified using commercially available software.

2. DETERMINATION OF SAMPLE SIZE

The sample size required to demonstrate equivalence is driven by 2 factors: 1) the intra-subject variability of the difference between the predicted post-operative FEV1 from the 2 methods, and 2) the pre-specified equivalence margin. From prior literature, the intra-subject variability for ^{133}Xe scintigraphy leads to an estimated variability in predicted post-operative FEV1 of 0.21 L. Similarly, prior studies have suggested that the equivalence margin between the 2 imaging techniques currently used for resection planning is 0.3 L. Using these assumptions, and based on

the use of a two-sided test at the alpha = 0.05 level of significance, a sample size of 15 subjects is required for 90% power. However, given limited literature on ^{133}Xe variability, we have accounted for the possibility that it could be higher. If true variability is 0.32 L, then a sample size of 32 subjects will provide 90% power to establish equivalence.

3. JUSTIFICATION OF EQUIVALENCE MARGIN

The acceptable equivalence margin between the predicted proportion of remaining function from ^{129}Xe MRI and ^{133}Xe scintigraphy is justified based on literature describing both variability and equivalence margin for the currently available pulmonary function imaging techniques, the ventilation-perfusion scan in the field of lung resection and pneumonectomy (Tulchinsky et al., 2017, Wernly et al., 1980, Win et al., 2006). This literature permits both variability and equivalence margin to be determined by converting the typical predicted post-operative FEV1 values back to their underlying zonal function percentages. From prior literature, the equivalence margin between the 2 imaging techniques currently used for resection planning is 0.3 L (Mariano-Goulart et al., 2006). In this work, the cohort that underwent pneumonectomy, had a mean pre-operative FEV1 of 2.02 L. Assuming the removed lung contributed 50% of total function, the equivalence margin of 0.3 L converts in percentage terms to ±14.7%. This same work, showed that in the pneumonectomy population the intra-subject variability for ^{133}Xe scintigraphy leads to an estimated variability in predicted post-operative FEV1 of 0.17 L. Thus, using similar calculations suggests the intra-subject standard deviation for ^{133}Xe can be estimated in percentage terms to be ±8.3%. We thus seek to demonstrate an equivalence margin of 14.7% between the imaging tests.

4. STATISTICAL METHODS

All final statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released.

All descriptive statistics for continuous variables will be reported using the number of observations (n), mean (arithmetic unless otherwise specified), standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as the number and percentage of subjects.

All inferential statistics will be based on the 5% level of significance (two-sided).

All data from this study will be presented in listings. All listings will be sorted by treatment sequence, subject number, and visit date, as applicable.

4.1. Study Endpoints

4.1.1. Primary Efficacy Endpoint

The primary endpoint is the scan-predicted proportion of pulmonary function that will remain after resection of a pre-specified lung area (predicted proportion of remaining function). The scans will be quantified using commercially available software to report the fraction of activity arising from 6 lung zones. This will be used to predict post-operative percentage of function remaining in the non-operated zones.

4.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints include the post-operative FEV1 value (spirometry) and the percentage function assessments (fraction of ventilation) contributed by each of the individual 6 lung zones.

4.1.3. Exploratory Endpoints

Exploratory endpoints include:

- The difference in scan-predicted proportion of remaining function from the 2 methods standardized to the ^{133}Xe scintigraphy-predicted remaining function. This endpoint is calculated by the following:

$$\Delta fstd = \frac{f_{rem129} - f_{rem133}}{f_{rem133}}$$

Where:

$\Delta fstd =$ standardized difference in predicted proportion of remaining function between the 2 methods;

f_{rem129} = ^{129}Xe MRI predicted proportion of remaining function, and

f_{rem133} = ^{133}Xe scintigraphy predicted proportion of remaining function.

- Proportion of patients with differences between the ^{129}Xe magnetic resonance (MR)-predicted proportion of remaining function and the ^{133}Xe scintigraphy-predicted proportion of remaining function that exceeds the equivalence margin (-14.7%, +14.7%), and
- Proportion of patients with differences between the ^{129}Xe MR-predicted proportion of remaining function and the ^{133}Xe scintigraphy-predicted proportion of remaining function that exceeds each of the following ranges: (-2.5%, +2.5%), (-5%, +5%), (-7.5%, +7.5%), (-10%, +10%), (-12.5%, +12.5%).

4.1.4. Safety Endpoints

Safety and tolerability will be assessed based on the incidence and severity of AEs and serious adverse events. Additionally, subjects will be monitored before, during, and after each dose to monitor for changes in vital signs.

4.2. Study Subjects

4.2.1. Definitions of Analysis Sets

Efficacy Analysis Set: The Efficacy Analysis Set is the group of subjects who had both a ^{129}Xe MRI scan and a ^{133}Xe scintigraphy scan, and for whom both scans met quality control criteria for analysis. The primary and the 6-zone analysis secondary efficacy endpoints will be analyzed using the Efficacy Analysis Set.

Post-operative Analysis Set: The Post-operative Analysis Set is the group of subjects that met the criteria for inclusion in the efficacy analysis set, and had a post-operative FEV1 (spirometry) value. The post-operative secondary endpoint will be analyzed using the Post-operative Analysis Set.

Safety Analysis Set: The Safety Analysis Set is the group of subjects who received at least 1 dose of either hyperpolarized ^{129}Xe or ^{133}Xe. Safety endpoints will be analyzed using the Safety Analysis Set.

Unless otherwise specified, the number and percentage of subjects in each analysis set will be summarized by treatment sequence using descriptive statistics. This and similar summaries will be presented by treatment sequence because the washout period between scans is generally short.

4.2.2. Subject Disposition

Subject disposition will be summarized by treatment sequence for all randomized subjects. The number and percentage of subjects who completed or discontinued prematurely from the study and their reason for discontinuation will be summarized by treatment sequence.

In addition, the number of subjects screened, the number and percentage of screen failures, and their primary reason for screen failure will be summarized.

4.2.3. Protocol Deviations

Protocol deviations will be identified, reviewed and documented by the clinical team prior to database lock. Protocol deviations will be summarized by deviation categories and treatment sequence for all subjects. The listing for protocol deviations, in addition to containing treatment sequence, subject number, visit, and deviations (by categories), will also contain several categories of demographic information.

4.2.4. Demographic and Baseline Characteristics

Demographic and other baseline characteristics for the Efficacy, Post-operative, and Safety Analysis Sets will be summarized for each treatment sequence using descriptive statistics, separately. Continuous demographic and baseline variables include age, height, weight, body mass index, peripheral capillary oxygen saturation (SpO_2) at screening, current cigarettes/day, and pack-years of smoking; categorical variables include sex, race, ethnicity, current smoking status, and Hypothetical Assessment of Resection Location.

4.2.5. Medical History

All medical histories as documented by the Medical and Surgical History eCRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1.

The number and percentage of subjects with any medical history will be summarized by System Organ Class (SOC) and preferred term (PT) for each treatment sequence based on the Safety Analysis Set.

4.2.6. Vital Signs and Physical Examination at Screening

Results of vital signs and physical examinations at screening will be summarized for each treatment sequence using descriptive statistics.

4.2.7. Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded using the World Health Organization Drug Dictionary Version 01 September 2017.

Prior medications are defined as medications that stopped before the first dose of study product. Concomitant medications are defined as medications that (1) started before the first dose of study product and are continuing at the time of the first dose of study product, or (2) started on or after the date of the first dose of study product.

The number and percentage of subjects who take concomitant medications will be summarized using the Safety Analysis Set by treatment sequence, Anatomical Therapeutic Chemical (ATC) class, and PT. If a subject takes the same medication for the same ATC class or PT, the subject will be counted only once for that ATC class or PT. Prior and concomitant medications will be listed separately.

Oxygen flow rate for subjects who used supplemental oxygen will be summarized using descriptive statistics.

Patients who used an inhaler will be summarized using descriptive statistics.

4.2.8. Exposure to Study Treatments

The polarization (%) of ^{129}Xe and the dose amount of ^{133}Xe will be summarized using descriptive statistics. One summary will include data for only those subjects who received only 1 full dose of ^{129}Xe in addition to their dose of ^{133}Xe. A second summary will include data for only those subjects who took 2 full doses of ^{129}Xe in addition to their dose of ^{133}Xe.

The duration between the time of dosing with ^{129}Xe and the time of polarization will be summarized using descriptive statistics. As in the paragraph above, there will be separate summaries for subjects with only 1 full dose of ^{129}Xe and subjects with 2 full doses of ^{129}Xe.

4.3. Data Analysis General Considerations

4.3.1. Handling of Missing Data

Except for the AE causal relationship to the study drug and AE severity (see Section 4.6.1), missing values will not be substituted by estimated values, but treated as missing in the statistical evaluation. Missing efficacy values are not anticipated as all subjects included in the efficacy analysis set must provide acceptable images for both ^{129}Xe MRI and ^{133}Xe scintigraphy. All data from all subjects dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

4.3.2. Visit Windows

There are no visit windows for this study, while time windows are allowable for study assessments as shown in Appendix 11.1. For the statistical analyses, data will be analyzed by their time point of collection.

4.4. Efficacy Analyses

Unless specified otherwise, the efficacy endpoints will be summarized and analyzed using the Efficacy Analysis Set.

4.4.1. Primary Efficacy Analysis

The primary analysis for this study will be to test the mean difference in the predicted proportion of remaining function as measured using hyperpolarized ^{129}Xe MRI relative to the value as measured by ^{133}Xe scintigraphy (reference standard). The primary analysis will be conducted by estimating the two-sided 95% confidence interval (CI) for the mean difference in predicted proportion of remaining function from the 2 methods.

The calculation of the predicted proportion of remaining function will be based on pre-operative imaging and the extent of planned lung resection. The scans will be quantified using commercially available software to report the fraction of activity arising from each of 6 lung

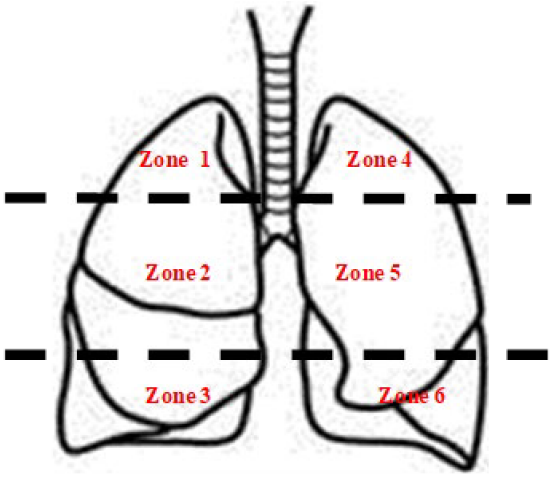
zones, 3 in each lung (refer to Figure 1). On the eCRF, the surgeon will check the zones that are planned for resection.

The predicted proportion of remaining function will be calculated by subtracting the percentage of function contributed by the zone(s) planned for resection from the total percentage of pre-operative function for all 6 zones. The sum of the resected zone(s) plus the non-resected zones equals 100%. For example, assume that the quantified fractions of activity for zone 1 to zone 6 are 15%, 20%, 25%, 10%, 15% and 15%, respectively and the surgeon notes that zone 4 and zone 5 are planned for complete resection. Then, the predicted proportion of remaining function would be:

100% - (zone 4[%] + zone 5[%]) or;

(15%+20%+25%+10%+15%+15%) - (10% + 15%) = 75% remaining

Figure 1 6 Lung Zones



The sample mean ($\overline{d}$) and standard deviation (sd) of the within-subject difference of the predicted remaining proportion of function between the two methods will be estimated and the 95% CI for the mean difference will be computed using the standard formula

$\overline{d} \pm$ t(n-1,0.975)*sd/√(n),

where t(n-1, 0.975) denotes the 97.5th percentile of the t distribution with n-1 decrees of freedom. If the 95% CI for the mean within-subject difference of the predicted remaining proportion of function from each scan is contained within the interval (-14.7%, +14.7%), equivalence will have been demonstrated. In terms of a hypothesis testing framework, let Δ denote the true mean within-subject difference. The null (H_0) and alternative (H_A) hypotheses are:

H0: $|\Delta|>14.7\%$

HA:$|\Delta|<14.7\%$

The listing for the efficacy data will present data for all 6 zones for both imaging methods and indicate the zones expected to be resected.

4.4.2. Secondary Efficacy Analyses

4.4.2.1. By-Zone Analysis

The by-zone secondary analysis for this study will be evaluated by comparing the individual percentage function assessments (fraction of ventilation) from each of the 6 zones as derived from the ^{129}Xe and the ^{133}Xe ventilation images. The equivalence analysis will be conducted using similar methodology to that in the primary efficacy analysis, and the equivalence margin will be ±5 percentage points. Thus, for each of the 6 zones, equivalence will have been demonstrated if the 95% CI for mean difference between the 2 methods is contained within the interval (-5%, +5%).

4.4.2.2. Post-Operative Analysis

The post-operative secondary analyses for this study will be to compare the final measured post-operative FEV1 value (spirometry) to those predicted by both hyperpolarized ^{129}Xe MRI and ^{133}Xe scintigraphy.

The calculation of predicted post-operative FEV1 will be based on pre-operative imaging and the extent of planned lung resection. The scans will be quantified using commercially available software to report the fraction of activity arising from each of 6 lung zones, 3 in each lung. On the eCRF, the surgeon will check the zones that are planned for resection. The predicted post-operative FEV1 will be calculated by multiplying the percentage of function remaining in the non-operated zones by the pre-operative FEV1. For example, assume that the quantified fractions of activity for zone 1 to zone 6 are 15%, 20%, 25%, 10%, 15% and 15%, respectively and the surgeon notes that zone 4 and zone 5 are planned for complete resection. Then, the predicted post-operative FEV1 = pre-operative FEV1 * {(15%+20%+25%) + (15%)}.

For each of these two comparisons, the null hypothesis that the mean difference is equal to zero, will be tested using the one-sample t test. The two-sided 95% CI for the mean difference will also be reported. A third comparison will be to test the null hypothesis that the mean difference between predicted post-operative FEV1 (measured in L) predicted by hyperpolarized ^{129}Xe MRI and ^{133}Xe scintigraphy is equal to zero. This analysis will also be conducted using the one-sample t test and the two-sided 95% CI for the mean difference will be reported.

This analysis will use the Post-operative Analysis Set. Because the final post-operative FEV1 value will be obtained approximately 3 months after surgery, this post-operative secondary analysis will be performed about 3 months after the other planned statistical analyses.

4.5. Exploratory Analyses

As a result of comments and discussion on Version 1.0 of this SAP from the FDA prior to database lock, the following analyses will be included as exploratory analyses.

4.5.1. Difference in Predicted Proportion of Remaining Function Standardized to that Predicted by the Reference Standard (^{133}Xe Scintigraphy)

To standardize each patient's results, predicted remaining function will be expressed as the difference between ^{129}Xe MR and ^{133}Xe scintigraphy predicted proportion of remaining function divided by the ^{133}Xe-predicted proportion of remaining function. The two-sided 95% CI for the mean difference will be estimated and presented as described for the primary endpoint.

4.5.2. Patient-Level Equivalence between ^{129}Xe MR-Predicted Remaining Function and ^{133}Xe Scintigraphy-Predicted Remaining Function

To evaluate the equivalence of the scan methods on a patient level, the proportion of patients will be reported whose difference in scan-predicted proportion of remaining function from ^{129}Xe MRI vs ^{133}Xe scintigraphy exceeds the equivalence margin (-14.7%, +14.7%). These results will also be presented using each of the ranges specified in Section 4.1.3.

4.6. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, where presented by treatment, will be summarized on an "as treated" basis using descriptive statistics (e.g., n, mean, SD, median, minimum, and maximum for continuous variables; n [%] for categorical variables). Safety variables include AEs and change from baseline in vital signs and SpO_2.

4.6.1. Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the MedDRA. AEs will be coded to the MedDRA (Version 20.1) lower level term closest to the verbatim term. The linked MedDRA PT and primary SOC are also captured in the database.

Per CRF design, all reported AEs are treatment-emergent adverse events (TEAEs) and will be included in summary tables. An overview of the TEAEs will be summarized by treatment sequence and overall, including the number and percentage of subjects who experience TEAEs, serious TEAEs, study drug-related TEAEs, TEAEs by maximum severity, and TEAEs leading to

death or to discontinuation from study treatment. This and similar summaries will be provided by treatment sequence because the washout period between scans is generally short, and the hypothetical lag period between a scan and an AE potentially associated with drug product is of unknown duration.

The number and percentage of subjects with TEAEs will be summarized by SOC and PT for each treatment sequence and overall. A subject will be counted only once within a SOC and PT, even if the subject experienced more than one TEAE within that specific SOC and PT.

The number and percentage of subjects with TEAEs will be summarized by maximum severity (mild, moderate, or severe). If severity is missing, the TEAE will be regarded as severe.

The number and percentage of subjects with TEAEs will be summarized by causality to study drug (related/unrelated). AEs recorded as being related to study drug includes all AEs marked as having a reasonable possibility of being related to the study drug. AEs recorded as being unrelated to study drug includes all AEs marked as having no reasonable possibility of being related to study drug. If causality is missing, the TEAE will be regarded as related to study drug.

In addition to the TEAE summaries by relationship to study drug, the number and percentage of subjects with TEAEs will be summarized by the relationship to scan procedure (^{129}Xe or ^{133}Xe), as judged by investigator.

The number and percentage of subjects with TEAEs leading to death will be summarized by SOC and PT for each treatment sequence and overall. A subject data listing of all TEAEs leading to death will also be provided.

The number and percentage of subjects with serious TEAEs will be summarized by SOC and PT for each treatment sequence and overall. A subject data listing of all serious TEAEs will also be provided.

The number and percentage of subjects with TEAEs leading to discontinuation from study treatment will be summarized by SOC and PT for each treatment sequence and overall. A subject data listing of all TEAEs leading to discontinuation from study treatment will also be provided.

The number and percentage of subjects with a subjective sensation of residual anesthesia (e.g., lightheadedness, loss of sensation or awareness, loss of memory, or unconsciousness) will be summarized by PT for each treatment sequence and overall. Any such AEs related to subjective sensation of residual anesthesia will be identified by the sponsor and medical monitor prior to unblinding.

4.6.2. Analysis of Vital Signs and Peripheral Capillary Oxygen Saturation

Descriptive statistics for vital sign parameters (i.e., diastolic and systolic blood pressure, heart rate, respiration rate, and temperature) and SpO_2, and their changes from before each study drug scan to after that study drug scan will be summarized by each treatment (^{129}Xe and ^{133}Xe). Also, if a subject takes a 2nd full dose of ^{129}Xe with accompanying vital sign and SpO_2 assessments, the changes from before the scan with the 2nd dose of ^{129}Xe to after that scan will be summarized separately. In addition, the shifts (normal to abnormal and vice versa) from before study drug scan to after study drug scan of blood pressure and heart rate evaluation will be summarized by each treatment.

5. INTERIM ANALYSES

No interim analyses are planned for this study.

6. SUBGROUP ANALYSIS FOR EFFICACY

Subgroup summaries for the primary efficacy endpoint will be provided separately by the following subgroups using the same methods as described in Section 4.4.1.

- Age group (<65 and ≥65 years old);
- Gender (male and female);
- Race (white and other);
- Current smoking status (current smoker and non-current smoker);
- Inhaler use (Yes and No), and
- Oxygen use (Yes and No).

7. STATISTICAL SOFTWARE

Analysis will be performed using SAS for Windows (release 9.4).

8. MOCK TABLES, LISTINGS AND FIGURES

The study tables, listings and figure shells will be provided in a separate document, which will show the content and format of all tables, listings, and figures in detail.

9. CHANGES FROM THE PROTOCOL

9.1. Analysis Populations

9.1.1. Efficacy Analysis Set

The inclusion criteria for the efficacy analysis set was revised to clarify that both the ^{129}Xe MRI and ^{133}Xe scintigraphy scan images must meet quality control criteria for inclusion in the efficacy analysis set (refer to Section 4.2.1).

9.1.2. Post-operative Analysis Set

The definition of the post-operative population was revised to clarify that that both the ^{129}Xe MRI and ^{133}Xe scintigraphy scan images must meet quality control criteria for inclusion in the efficacy analysis set (refer to Section 4.2.1).

9.2. Primary Efficacy Endpoint

Following discussion of Version 1.0 of the SAP with the FDA, the primary efficacy endpoint was revised. The protocol states that the primary efficacy endpoint is the scan predicted post-operative FEV1. The scan-predicted FEV1 is calculated by multiplying the subject's baseline FEV1 by the proportion of remaining function predicted by each scan. However, inclusion of the baseline FEV1 as part of the endpoint potentially introduces unnecessary variability in the comparison of ^{129}Xe MRI and ^{133}Xe scintigraphy. Thus, the primary efficacy endpoint was revised to directly compare ^{129}Xe MRI to ^{133}Xe scintigraphy without inclusion of the baseline FEV1 (refer to Section 4.1.1).

The primary endpoint is the scan-predicted proportion of pulmonary function that will remain after resection of a pre-specified lung area (predicted proportion of remaining function).

9.3. Primary Efficacy Analysis

The primary efficacy analysis (Section 4.4.1) was revised to account for the comparison of the scan-predicted remaining function from ^{129}Xe MRI and ^{133}Xe scintigraphy without inclusion of the baseline FEV1 in the primary efficacy endpoint. The equivalence margin is expressed in terms of percent remaining function instead of FEV1, measured in L. The revised equivalence margin is (-14.7%, +14.7%).

9.4. Secondary Efficacy Analyses

The post-operative secondary analysis was revised to provide a comparison between the measured post-operative FEV1 and each scan-predicted post-operative FEV1. An additional

analysis was added to compare the difference between predicted post-operative FEV1 from each scan.

9.5. Exploratory Endpoints

As a result of discussion of Version 1.0 of the SAP with the FDA, 2 exploratory endpoints were added.

- The difference in scan-predicted proportion of remaining function from the 2 methods standardized to the ^{133}Xe scintigraphy-predicted remaining function.
- Proportion of patients with differences between the ^{129}Xe MR-predicted proportion of remaining function and the ^{133}Xe scintigraphy-predicted proportion of remaining function that exceeds the equivalence margin (-14.7%, +14.7%).

An additional exploratory endpoint was added by the Sponsor.

- Proportion of patients with differences between the ^{129}Xe MR-predicted proportion of remaining function and the ^{133}Xe scintigraphy-predicted proportion of remaining function that exceeds each of the following ranges: (-2.5%, +2.5%), (-5%, +5%), (-7.5%, +7.5%), (-10%, +10%), (-12.5%, +12.5%).

9.6. Exploratory Analyses

Section 4.5 was added to the SAP to describe the analysis of the added exploratory endpoints.

10. REFERENCES

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Tulchinsky M, Fotos JS, Wechalekar K, Dadparvar S. Applications of ventilation-perfusion scintigraphy in surgical management of chronic obstructive lung disease and cancer. Semin Nucl Med. 2017;47(6):671-9.

Wernly JA, Demeester TR, Kirchner PT, Myerowitz PD, Oxford DE, Golomb HM. Clinical value of quantitative ventilation-perfusion lung scans in the surgical management of bronchogenic carcinoma. J Thorac Cardiovasc Surg. 1980 Oct;80(4):535-43.

Win T, Tasker AD, Groves AM, White C, Ritchie AJ, Wells FC, Laroche CM. Ventilation-perfusion scintigraphy to predict postoperative pulmonary function in lung cancer patients undergoing pneumonectomy. AJR Am J Roentgenol. 2006 Nov;187(5):1260-5.

11. APPENDIX

11.1. Schedule of Events

	Screening[1]	Imaging[1]	Imaging Follow-up[2]	Post-Op Follow-up
Evaluation	**Day -7 to Day 0**	**Day 1**	**Day 2**	**1-2 Months Post-Op**
Informed Consent	X			
Inclusion/Exclusion Criteria	X	X		
Demographics and Medical History[3]	X	X		
Physical Exam	X			
Concomitant Medications Review	X	X		
MRI-suitable Screening	X			
Recording of potential resection location on eCRF	X			
Spirometry (FEV1)[4]		X		X
^{129}Xe Administration[1]		X		
Anatomical proton MRI (MRI session only)		X		
^{133}Xe Administration[1]		X		
Vital Signs[5,6]	X	X		
SpO_2[7]	X	X		
Adverse Events[8]		X	X	
Local Laboratory Tests				
Serum Pregnancy Test[9]	X			

Abbreviations: eCRF = electronic case report form; FEV1 = forced expiratory volume; MRI = magnetic resonance imaging; Op = operative; SpO2 = arterial oxygen saturation.

[1] Screening and Imaging study periods can occur on the same day or on different days, however there should be ≤48 hours between administration of the study drug and reference standard scans.

[2] The Follow-Up period will occur on the day after (+3 days) the completion of all imaging and prior to resection surgery.

[3] Medical history will include any pulmonary function values (i.e. FEV1) from the subject files as well as smoking history.

[4] FEV1 measurement should occur prior to administration of the study drug and reference standard scans.

[5] Vital Signs (including heart rate, respiration rate, temperature, and blood pressure) will be assessed before and after each scanning session (both ^{129}Xe and ^{133}Xe). Subjects will have a 5-minute rest in a supine position before vital signs are assessed.

[6] Changes in heart rate of greater than ±20% are considered significant. If the subject is to receive another dose, the next dose will not be administered until the heart rate is within 20% of its baseline value. If the subject has received their last dose, they will be observed until their heart rate is within 20% of its baseline value. The subject will be monitored for the duration of the MRI exam by a qualified medical professional.

[7] SpO_2 is measured at baseline as well as before and after each scanning session (both ^{129}Xe and ^{133}Xe). An absolute decrease of SpO_2 by greater than 10% is considered significant. If the subject is to receive another dose, the next dose will not be administered until the SpO_2 is within 10% of its baseline value. If the subject has received their last dose, they will be observed until the SpO_2 is within 10% of its baseline value. The subject will be monitored for the duration of the MRI exam by a qualified medical professional.

[8] Subjects will be monitored for any subjective sensation of residual anesthesia (e.g., lightheadedness, loss of sensation or awareness, loss of memory, or unconsciousness). If the subject is to receive another dose, the next dose will not be administered until the sensation has resolved. If the subject has received their last dose, they will be observed until the sensation has resolved. The subject will be monitored for the duration of the MRI exam by a qualified medical professional.

[9] Eligibility assessment will include, if applicable, a negative pregnancy test.