NDA 214375 Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2)
Application Number	214375
Priority or Standard	Standard
Submit Date	March 30, 2022
Received Date	March 30, 2022
PDUFA Goal Date	December 30, 2022
Division/Office	DIRM/ OSM
Review Completion Date	December 22, 2022
Established/Proper Name	xenon Xe 129 hyperpolarized
Trade Name	XENOVIEW/ HPX Hyperpolarization System
Pharmacologic Class	Hyperpolarized contrast agent
Applicant	Polarean Inc.
Dosage form	Gas for inhalation
Applicant proposed Dosing Regimen	Dose equivalent (DE) (b) (4) (b) (4) of hyperpolarized Xe-129 in 250 mL to 750 mL of xenon gas filled to 1 L with nitrogen gas, inhaled with breath hold of up to 15 seconds
Applicant Proposed Indication/Population	(b) (4)
Applicant Proposed SNOMED CT Indication Disease Term	241616006 Magnetic resonance imaging of lungs (procedure)
Regulatory Action	Approval
Recommended Indication/Population	XENOVIEW, prepared from the Xenon Xe 129 Gas Blend, is a hyperpolarized contrast agent indicated for use with magnetic resonance imaging (MRI) for evaluation of lung ventilation in adults and pediatric patients aged 12 years and older. <u>Limitations of Use</u> XENOVIEW has not been evaluated for use with lung perfusion imaging.
SNOMED CT Indication Disease Term	241616006 Magnetic resonance imaging of lungs (procedure)
Recommended Dosing Regimen	Dose equivalent (DE) target range of 75 mL to 100 mL (both adults and children aged 12 years and up) of hyperpolarized Xe-129 in 250 mL to 750 mL of xenon gas filled to 1 L with nitrogen gas, inhaled with breath hold of up to 15 seconds

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CDRH=Center for Devices and Radiological Health
DRH=Division of Radiological Health
DIRM=Division of Imaging and Radiation Medicine
OSM=Office of Specialty Medicine

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OPQ=Office of Pharmaceutical Quality
CDRH=Center for Devices and Radiological Health
DPMH=Division of Pediatrics and Maternal Health
DMEPA=Division of Medication Error Prevention and Analysis
OSE=Office of Surveillance and Epidemiology

1 Executive Summary

Xenon Xe 129 hyperpolarized, tradename XENOVIEW and referred to as hyperpolarized Xe 129 in this review, is the drug component of a combination product. The device components of this product are collectively called the HPX Hyperpolarization System and include the HPX Gas Handling Manifold, HPX Hyperpolarizer, HPX Polarization Measurement Station, and XENOVIEW Dose Delivery Bag.

NDA 214375 was originally submitted on October 5, 2020. Reference is made to the NDA 214375 Multi-Disciplinary Review and Evaluation dated October 5, 2021, and the associated addendum to this review dated December 22, 2022. The benefit of hyperpolarized Xe 129 MRI for evaluation of lung ventilation was found to outweigh its risks in the indicated population. However, due to deficiencies in product quality as well as drug and device facilities and inspection issues, a Complete Response (CR) was issued for the previous NDA review cycle.

NDA 214375 was resubmitted on March 30, 2022, to address approvability issues identified in the CR letter dated October 5, 2021. A major amendment consisting of product quality information was submitted on September 27, 2022, which extended the review period by three months. All CR issues have now been adequately addressed as described in Section 2 below. Updates since the previous review cycle regarding the agreed upon product labeling and postmarketing studies are also included below. Approval of the NDA is recommended.

2 Resolution of Previous Complete Response Issues

As detailed in the separate Office of Pharmaceutical Quality Integrated Quality Assessment dated December 20, 2022, and as summarized below, all previous CR issues have been adequately addressed. All drug and device facilities and inspection/manufacturing issues have been resolved.

2.1. Drug Substance and Drug Product

The active ingredient in XENOVIEW is Xe 129, which is hyperpolarized before administration to patients, meaning that the Xe 129 nuclei are “excited”, having received a transfer of angular momentum from laser-excited rubidium electrons. The drug product administered to patients is hyperpolarized Xe 129 in nitrogen at a strength of 75 mL of 100% hyperpolarized Xe 129 (the equivalent of (b) (4) ml Xe 129 at a target (b) (4)% degree of overall polarization to (b) (4) ml of Xe 129 at a target (b) (4)% degree of overall polarization). The Dose Equivalent (DE) is ≥ 75 mL/1000 mL administered, a calculated value (DE/V_{Amin}) defined as volume of 100% isotopically enriched Xe 129, polarized to 100%.

Hyperpolarized Xe 129 is generated by the HPX Hyperpolarization System, which includes the HPX Hyperpolarizer, QC measurement system, and 1 L dose delivery bag (V_{Amin} of 1000 mL).

Fundamental to production of hyperpolarized Xe 129 is a medical Gas Blend (b) (4) (b) (4) consisting of enriched Xe 129 (1% v/v), nitrogen (N_2, 10% v/v) and helium (He, 89% v/v). After the Gas Blend leaves a laser-irradiated optical cell, frozen and isolated hyperpolarized ^{129}Xe/Xe is collected in a cryotrap (b) (4) nitrogen added, collected in a 1 L bag (to DE of ≥ 75 mL/1000 mL), and then QC measured (percent polarization and DE calculation) before administration to patients as XENOVIEW. XENOVIEW has an expiry of 5 minutes after DE is determined (during QC) at 25^{0}C.

Critical issues regarding the Gas Blend (b) (4) were identified in the (b) (4) DMF impacting cGMP supplier qualification (b) (4) but will be addressed in a postmarketing commitment (PMC # 4324-2). With the PMC in place, the (b) (4) DMF supports the Applicant's NDA and all remaining issues in the NDA are resolved.

2.2. Devices Design Changes and Release

The Applicant provided updated documents that clearly identify the process and acceptance criteria for finished device acceptance for hyperpolarizer Rev D. In addition, the Applicant updated documents related to design requirements, device design validation, manufacturing, and factory acceptance testing. Acceptance testing protocols for the hyperpolarizer report include percent hyperpolarization and DE volume calculated from the polarization measurement. All outstanding concerns related to device design changes and release were acceptably addressed in the resubmission and through interactive review.

2.3. Device Reliability

In response to concerns about device reliability, the Applicant provided a risk-based assessment for reliability of the hyperpolarizer and measurement systems. In addition, historical records from multiple measurement systems were evaluated for long-term stability. The Applicant expects users to perform yearly calibration to ensure that any potential systemic drift in performance is avoided. All outstanding concerns related to device reliability were acceptably addressed in the resubmission.

3 Labeling Recommendation Updates

3.1. Prescription Drug Labeling

Notable revisions to the Prescribing Information that are new relative to those discussed in the NDA 214375 Multi-Disciplinary Review and Evaluation dated October 5, 2021, are mentioned below.

NDA 214375/ xenon Xe 129 hyperpolarized (XENOVIEW)/ HPX Hyperpolarization System: Multi-Disciplinary Review and Evaluation

Section 1. INDICATIONS AND USAGE

Upon further negotiation with the Applicant, it was agreed that the indications would not be specifically restricted to pre-operative evaluation for lung surgery. However, a limitation of use was added to specify that use with lung perfusion imaging has not been evaluated.

The agreed indications statement reads as:

> XENOVIEW, prepared from the Xenon Xe 129 Gas Blend, is a hyperpolarized contrast agent indicated for use with magnetic resonance imaging (MRI) for evaluation of lung ventilation in adults and pediatric patients aged 12 years and older.
>
> Limitations of Use
> XENOVIEW has not been evaluated for use with lung perfusion imaging.

Section 2. DOSAGE AND ADMINISTRATION

The acceptable amount of hyperpolarized Xe 129 contained in each dose delivery bag is ≥ 75 mL DE from the drug product quality aspect. The review team also recommended a DE target range of 75 mL to 100 mL to better align with the dosing used in the clinical trials and to provide guidance on a suitable DE for both the indicated adult and pediatric patient populations. In addition, a statement was added to indicate that DE of greater than 100 mL can be administered to a patient.

Section 5. WARNINGS AND PRECAUTIONS

A warning for risk of bronchospasm, as considered in the previous review cycle, was not added given its applicability to aerosolized rather than gaseous drugs.

Section 8. USE IN SPECIFIC POPULATIONS

The finalized Pediatric Use section reads as follows:

> The safety and effectiveness of XENOVIEW have been established in pediatric patients aged 12 years and older for use with MRI to evaluate lung ventilation. Use of XENOVIEW in this age group is supported by evidence from adequate and well-controlled studies in adults with additional safety data from the scientific literature *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.
>
> Although supportive safety data are available for pediatric patients 6 years to less than 12 years of age *[see Adverse Reactions (6.1)]*, use of XENOVIEW is not approved in this age group because the age-appropriate dose of XENOVIEW cannot be accurately administered.
>
> Safety and effectiveness of XENOVIEW have not been established in pediatric patients less than 6 years of age.

The pediatric use statement aligns with the indications statement, and the second and third paragraphs elucidate the reasons for not approving XENOVIEW in pediatric patients younger than 12 years of age.

Section 17. PATIENT COUNSELING INFORMATION
This section was omitted due to the inapplicability to the safe and effective use of the drug as allowed under 21 CFR § 201.56(d)(4).

3.2. Device Labeling

The revised device labeling aligns with the prescribing information.

4 Postmarketing Requirements and Commitment

As discussed in Section 10 of the previous NDA 214375 Multi-Disciplinary Review and Evaluation dated October 5, 2021, the Applicant agreed to the following postmarketing requirement in accordance with the Pediatric Research Equity Act.

4324-1 Develop an age-appropriate presentation of hyperpolarized Xe 129 that would allow administration of an accurate dose to pediatric patients 6 years to less than 12 years of age.

Submission of Summary Development Plan: 06/2023
Final Report Submission: 07/2024

As discussed in Section 2.1 of the current review, the Applicant agreed to the following postmarketing commitment.

4324-2 Polarean to describe supplier qualifying procedure and (b) (4) acceptance criteria (specification) for (b) (4) Xe 129 (enriched xenon gas) sourced through the (b) (4) supply chain. Include procedure and complete test results on site at (b) (4) and Polarean. Complete test results for 3 batches (b) (4) should be kept on site to qualify (b) (4) and future suppliers.

Amend the NDA post-action with complete test data for at least one batch from (b) (4) After qualification, (b) (4) may be accepted by Polarean (b) (4) from (b) (4) by identity testing and inspection of supplier's CoA per ICH Q7 7.31. Submit a final report of the results as a Changes Being Effected Supplement (CBE-0).

Final Report Submission: 12/2023

5 Division Director Comments

I concur with the findings by the review team that the drug and device quality and manufacturing issues that resulted in a CR action for the initial application have been resolved in the resubmission and that the issues related to the gas blend (b) (4) can be addressed with a PMC. Therefore, I concur that the risk benefit of the product is favorable and approval is warranted.

I also concur with the final labeling including: extending the patient population indicated for hyperpolarized Xe 129 MRI pulmonary ventilation imaging; adding a limitation for use in conjunction with imaging for evaluation of pulmonary perfusion; limiting use to pediatric patients 12 years of age and older and requiring the development of an age-appropriate presentation of the product for use by the 6 to less than 12 years age group.

6 Office Director Comments

I concur with the recommendation of the review team to approve the application with a post-marketing requirement and commitment.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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NDA 214375/ xenon Xe 129 hyperpolarized (XENOVIEW)/ Xeno View System:
Multi-Disciplinary Review and Evaluation

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS	AUTHORED/ APPROVED
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NDA 214375 Multi-Disciplinary Review and Evaluation

Application Type	505(b)(1)
Application Number	214375
Priority or Standard	Standard
Submit Date	October 05, 2020
Received Date	October 05, 2020
PDUFA Goal Date	October 05, 2021
Division/Office	DIRM/ OSM
Review Completion Date	October 05, 2021
Established/Proper Name	xenon-129 hyperpolarized
Trade Name	XENOVIEW/ Xeno View System
Pharmacologic Class	Inhalation Diagnostic Agent
Code name	5081030
Applicant	Polarean Inc.
Dosage form	Gas for inhalation
Applicant proposed Dosing Regimen	Dose equivalent (DE) (b) (4) (b) (4) of hyperpolarized Xe-129 in 250 mL to 750 mL of xenon gas filled to 1 L with nitrogen gas, inhaled with breath hold of up to 15 seconds
Applicant Proposed Indication/Populations	(b) (4)
Applicant Proposed SNOMED CT Indication Disease Term	241616006 Magnetic resonance imaging of lungs (procedure)
Regulatory Action	Complete response
Recommended Indications/Populations	XENOVIEW is a hyperpolarized xenon-129 contrast agent indicated for inhalational use with magnetic resonance imaging (MRI) for preoperative evaluation of lung ventilation prior to lung surgery in adults and pediatric patients aged 12 years and older. (Labeling review is ongoing.)
SNOMED CT Indication Disease Term	241616006 Magnetic resonance imaging of lungs (procedure)
Recommended Dosing Regimen	Dose equivalent (DE) of 75 mL to 100 mL (both adults and children aged 12 years and up) of hyperpolarized Xe-129 in 250 mL to 750 mL of xenon gas filled to 1 L with nitrogen gas, inhaled with breath hold of up to 15 seconds

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OPQ=Office of Pharmaceutical Quality
OSI=Office of Scientific Investigations
DMEPA=Division of Medication Error Prevention and Analysis
DPACC = Division of Pulmonology, Allergy and Critical Care
DPMH = Division of Pediatrics and Maternal Health

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BP	blood pressure
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CF	cystic fibrosis
CFR	Code of Federal Regulations
CGMP	current good manufacturing practice
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CT	computerized tomography
DE	dose equivalent
DRH	Division of Radiological Health
ECG	electrocardiogram
FDA	Food and Drug Administration
FVC	forced vital capacity
GCP	good clinical practice
HR	heart rate
ICH	International Conference on Harmonisation
IND	investigational new drug
MRI	magnetic resonance imaging
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigation
PK	pharmacokinetics
REMS	risk evaluation and mitigation strategy
RR	respiration rate
SAE	serious adverse event
SNR	signal-to-noise ratio
TEAE	treatment emergent adverse event
UHP	ultra-high purity

1 Executive Summary

1.1. Product Introduction

Xenon-129 hyperpolarized, tradename XENOVIEW and hereafter referred to as hyperpolarized Xe-129, is the drug component of a combination product. The device components of this product are collectively called the Xeno View System and include the Gas Handling Manifold, Hyperpolarizer, Polarization Measurement Station, and dose delivery bag.

Hyperpolarized Xe-129 is a non-radioactive gas administered by inhalation to image lung ventilation on magnetic resonance imaging (MRI). No inhaled imaging agents are currently FDA-approved for use with MRI. Xe-129 is a naturally occurring stable isotope of xenon with a nuclear magnetic moment that allows it to be directly detected by MRI using an appropriately tuned coil. Hyperpolarization of Xe-129 greatly increases its magnetization and facilitates its imaging on MRI.

Hyperpolarized Xe-129 is produced by the Hyperpolarizer from a gas blend of helium, nitrogen, and xenon that is isotopically enriched for Xe-129. The Hyperpolarizer (b) (4) removes helium and nitrogen. The resultant hyperpolarized Xe-129 is collected from the Hyperpolarizer device into a dose delivery bag. The administered product contains a total of 250 mL to 750 mL of xenon gas, a fraction of which is Xe-129. A variable degree of this Xe-129 is hyperpolarized. A dose equivalent (DE) calculation accounts for the total volume of xenon, fraction of Xe-129 isotopic enrichment, and fraction of hyperpolarization. The DE result must meet a recommended range to ensure adequate imaging signal. Nitrogen gas is added as an inert buffer to achieve a total dose volume of 1 L. While positioned in the MRI scanner, a patient inhales the entire 1 L dose in a single breath and holds it for up to 15 seconds while lung images are rapidly acquired.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for hyperpolarized Xe-129 MRI was provided by two adequate and well-controlled trials conducted by the Applicant, POL-Xe-001 and POL-Xe-002. These trials were performed with clinically relevant groups of adult patients being evaluated preoperatively for lung surgery. As the primary endpoint in study POL-Xe-001, hyperpolarized Xe-129 MRI was used to predict the percentage of lung ventilation that would remain after planned resection of a portion of the lungs. As the primary endpoint in study POL-Xe-002, hyperpolarized Xe-129 MRI was used to estimate the percentage of ventilation that was contributed by the right lung. In both studies, hyperpolarized Xe-129 MRI results were compared to those obtained in the same patients with the approved alternative, Xenon-133 (Xe-133) scintigraphy.

In both study POL-Xe-001 and study POL-Xe-002, results of the primary endpoint analyses met a pre-specified equivalence margin for hyperpolarized Xe-129 MRI and Xe-133 scintigraphy.

Secondary analyses in both trials further demonstrated reasonable concordance in ventilation measurements between hyperpolarized Xe-129 MRI and Xe-133 scintigraphy at the level of individual lung zones. Supportive exploratory analyses in both trials showed standardized hyperpolarized Xe-129 and Xe-133 results to differ by a relative margin of less than ±20% in the vast majority of patients, and less than ±10% in most patients.

The Applicant's review of published experience in adults and children with hyperpolarized Xe-129 lung imaging only identified studies that were considered to be exploratory in nature. While combining hyperpolarized Xe-129 ventilation imaging with lung perfusion imaging could potentially expand the settings of clinical use, such pairing was not evaluated in the literature review and is of unclear practicality at this time. (b) (4)

Overall, substantial evidence of effectiveness was provided for hyperpolarized Xe-129 MRI for preoperative evaluation of ventilation prior to lung surgery. While studies POL-Xe-001 and POL-Xe-002 only enrolled adult subjects, the relatively simple pharmacokinetics and mechanism of action of inhaled hyperpolarized Xe-129 for ventilation imaging supported extrapolation of efficacy findings to pediatric patients.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Conventional MRI is based on the use of high magnetic fields to introduce a small nuclear polarization in protons that allows them to be detectable. Conventional MRI is of limited utility in evaluating the lungs because the very low concentration of protons and large field gradients in the airspaces result in weak signal. Once hyperpolarized, Xe-129 gas can be directly detected by MRI in the airspaces of the lungs after inhalation.

Xe-129 is a stable, non-radioactive, naturally occurring isotope of the element xenon. Neither isotopic enrichment of Xe-129 nor hyperpolarization of Xe-129 adds safety risk beyond that of xenon gas itself. Xenon gas is approved for use as an anesthetic abroad when administered through steady breathing. For use with MRI, hyperpolarized Xe-129 is inhaled in a single breath that is briefly held while imaging is completed.

Unlike spirometry, hyperpolarized Xe-129 evaluates ventilation at the level of specific lung regions. Such regional ventilation information can be useful in certain clinical settings, such as evaluation of patients prior to lung resection and lung transplant. Available alternatives for imaging of regional ventilation include the approved radiopharmaceuticals, Xe-133 gas and aerosolized Tc99m-DTPA, as well as techniques based on computerized tomography.

The Applicant conducted two adequate and well-controlled trials in two preoperative settings. Study POL-Xe-001 was conducted in 34 adult patients being evaluated for lung resection surgery. As the primary endpoint, hyperpolarized Xe-129 MRI was used to predict the percentage of lung ventilation that would remain after planned resection of a portion of the lungs. Study POL-Xe-002 was conducted in 49 adult patients being evaluated for lung transplant surgery. As the primary endpoint, hyperpolarized Xe-129 MRI was used to estimate the percentage of ventilation that was contributed by the right lung. In both studies, hyperpolarized Xe-129 MRI results were compared to results obtained in the same patients with Xe-133 scintigraphy.

In both study POL-Xe-001 and study POL-Xe-002, results of the primary endpoint analyses met a pre-specified equivalence margin of ±14.7% for hyperpolarized Xe-129 MRI and Xe-133 scintigraphy. In combination with secondary and exploratory analyses, these studies demonstrated reasonable concordance between hyperpolarized Xe-129 MRI and Xe-133 scintigraphy in adult preoperative patients. The relatively simple pharmacokinetics and mechanism of action of inhaled hyperpolarized Xe-129 for ventilation imaging supported

extrapolation of these efficacy findings to pediatric patients.

The safety database was adequate and included information from 147 adults in trials submitted by the Applicant as well as published experience with hyperpolarized Xe-129 MRI in 204 adults and 120 pediatric subjects aged 6 years and older. Adverse reactions were non-serious, transient, and generally consistent with those expected from brief exposure to an anesthetic or anoxic gas.

Overall, the benefit of hyperpolarized Xe-129 MRI for preoperative evaluation of ventilation prior to lung surgery outweighs its risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Unlike spirometry, certain types of imaging can assess regional ventilation in the lungs. • Regional ventilation information has potential advantages in certain clinical settings. • For example, regional ventilation information can be used in preoperative evaluation of patients before lung resection and lung transplant.	• In patients who are being evaluated for potential lung resection, particularly those with reduced baseline pulmonary function, imaging of regional ventilation can be used to help assess operative risk by predicting the proportion of ventilation that will remain postoperatively. • In patients who are being evaluated for lung transplant, imaging of regional ventilation can contribute to procedure planning by identifying the more dysfunctional lung.
Current Treatment Options	• Conventional proton MRI results in weak signal in the lungs due to very low concentration of protons and large field gradients in the airspaces. • Computerized tomography (CT) methods can be used to evaluate predicted postoperative pulmonary ventilation following lung resection. • Available imaging agents approved for evaluation of lung ventilation	• Conventional MRI is currently not useful for evaluating ventilation due to technical limitations. • CT methods can contribute to evaluation of regional ventilation in limited clinical settings. • Radiopharmaceuticals approved for

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	are Xe-133 gas and aerosolized Tc99m-DTPA.	evaluation of ventilation are most commonly used with the two dimensional technique of scintigraphy to provide regional information.
Benefit	• Two adequate and well-controlled trials were conducted by the Applicant, studies POL-Xe-001 and POL-Xe-002. • Study POL-XE-001 was conducted in 34 adult patients being evaluated for lung resection surgery. As the primary endpoint, hyperpolarized Xe-129 MRI was used to predict the percentage of lung ventilation that would remain after planned resection of a portion of the lungs. • Study POL-Xe-002 was conducted in 49 adult patients being evaluated for lung transplant surgery. As the primary endpoint, hyperpolarized Xe-129 MRI was used to estimate the percentage of ventilation that was contributed by the right lung. • In both studies, hyperpolarized Xe-129 MRI results were compared to results obtained in the same patients using Xe-133 scintigraphy. • A review of published experience with hyperpolarized Xe-129 in adults and children was also provided by the Applicant.	• In both study POL-Xe-001 and study POL-Xe-002, results of the primary endpoint analyses met a pre-specified equivalence margin of ±14.7% for hyperpolarized Xe-129 MRI and Xe-133 scintigraphy. • Secondary analyses in both trials further demonstrated reasonable concordance in regional ventilation measurements between hyperpolarized Xe-129 MRI and Xe-133 scintigraphy at the level of individual lung zones. • Supportive exploratory analyses in both trials showed standardized hyperpolarized Xe-129 and Xe-133 results to differ by a relative margin of less than ±20% in the vast majority of patients, and less than ±10% in most patients. • The Applicant's review of published experience in adults and children with hyperpolarized Xe-129 lung imaging only identified exploratory studies (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		(b) (4) • The relatively simple pharmacokinetics and mechanism of action of inhaled hyperpolarized Xe-129 for ventilation imaging supported extrapolation of efficacy findings to pediatric patients. • Potential expansion of the uses of hyperpolarized Xe-129 MRI may be possible through future clinical trials.
Risk and Risk Management	• Xe-129 is a stable, non-radioactive, naturally occurring isotope of the element xenon. • Neither isotopic enrichment of Xe-129 nor hyperpolarization of Xe-129 adds safety risk beyond that of xenon gas itself. • Xenon is approved for use as an anesthetic abroad when administered through steady breathing. • Hyperpolarized Xe-129 for MRI is administered in a single breath of up to 750 mL of xenon that is held for up to 15 seconds while imaging is completed. • The safety database included 147 adults from trials submitted by the Applicant: POL-Xe-001 (n=34), POL-Xe-002 (n=49), POL-Xe-003 (n=20), and GE-141-001 (n=44). In the most relevant trials, POL-Xe-001 and POL Xe-002, the most common adverse reactions were oropharyngeal pain (n = 4), headache (n = 2), and dizziness (n = 2). • A total of 13 publications reported safety information in 204 adult subjects, and 5 publications described safety information in 120 pediatric subjects aged 6 years and older. In both populations,	• Adequate safety information was available in adults and pediatric subjects aged 6 years and older. • Adverse reactions in the Applicant's submitted trials and review of the literature were non-serious, transient, and generally consistent with those expected from brief exposure to an anesthetic or anoxic gas. • A warning is recommended in Section 5 of the prescribing information to monitor for hypoxia and treat accordingly.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	transient numbness, tingling, euphoria, and dizziness were described. In pediatric patients, transient and non-serious blood oxygen desaturation and heart rate elevation were described. • No serious adverse events or deaths related to hyperpolarized Xe-129 were identified. • One event consistent with a non-serious allergic reaction occurred in study POL-Xe-001.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☒	**Patient experience data was not submitted as part of this application and was not needed.**			

2 Therapeutic Context

2.1. Analysis of Condition

Techniques such as spirometry are well established for evaluating pulmonary function through measurement of various ventilatory parameters. Unlike spirometry, which provides information on the lungs as a whole, certain types of lung imaging can assess ventilation within particular lung regions. Regional ventilation information has potential advantages in some clinical settings. For example, regional imaging of ventilation is commonly used in the evaluation of pulmonary embolism when paired with lung perfusion imaging.

Another clinical setting in which regional imaging of ventilation can be used is in the preoperative evaluation of patients for lung surgery. In patients who are being evaluated for potential lung resection, particularly those with reduced baseline pulmonary function, regional imaging of lung ventilation can be used to help assess operative risk by predicting the proportion of ventilation that will remain postoperatively. In patients who are being evaluated for lung transplant, preoperative ventilation imaging can contribute by identifying the more dysfunctional lung. In the case of single lung transplant, the more dysfunctional lung is typically targeted for transplant. In the case of bilateral lung transplant, the more dysfunctional lung is typically removed first by sequential technique to reduce chances of requiring cardiac bypass during the procedure.

2.2. Analysis of Current Treatment Options

Conventional proton MRI results in a weak signal in the lungs due to a very low concentration of protons and large field gradients in the air spaces. As such, conventional MRI is currently not useful for evaluation of ventilation.

Chest computerized tomography (CT) can be used to estimate predicted postoperative pulmonary ventilation following lung resection through an anatomic method in which the number of unobstructed lung segments that are expected to be removed are identified and divided by the total number of unobstructed lung segments. More quantitative volumetric CT approaches are also under development for this purpose.

Available imaging agents that are FDA-approved for ventilation imaging, including in the preoperative setting, are Xe-133 gas and aerosolized Tc99m-DTPA. Both agents are radioactive and therefore involve ionizing radiation whereas hyperpolarized Xe 129 gas does not. Radiopharamaceuticals for ventilation imaging are administered through multiple successive breaths and are typically imaged scintigraphically, although cross-sectional imaging with single-photon emission computerized tomography is possible. Xenon-127 and Krypton-81m are other radioactive gases that are FDA-approved for ventilation imaging but have been withdrawn from the market for reasons unrelated to safety or efficacy.

Intravenously injected Tc99m-macroaggregated albumin is FDA-approved for lung perfusion imaging and is also used to assess preoperative lung function and predict postoperative lung function, often in conjunction with one of the approved ventilation agents.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

XENOVIEW is a new molecular entity. There is no prior U.S. regulatory action or marketing history.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 075010 for hyperpolarized Xe-129 by Polarean Inc. was allowed to proceed in May 2006.

In June 2014, the FDA completed a request for designation and determined the Applicant's product to be a combination product. Hyperpolarized Xe-129 gas was determined to be a drug constituent part while the other product components were determined to be device constituent parts. The primary mode of action was attributed to the hyperpolarized Xe-129 gas, and CDER was assigned as the lead center for premarket review and regulation. A subsequent request for reconsideration affirmed the above determination in July 2014.

The first meeting between the Applicant and the FDA was held in May 2015. An NDA was agreed upon as the future marketing application. The FDA also advised the Applicant that sensitivity and specificity would not be appropriate efficacy endpoints.

An end-of-phase 2 meeting was held in March 2016. At the meeting, the FDA suggested the Applicant use the approved product, Xe-133, as an active comparator to demonstrate agreement with hyperpolarized Xe-129. The FDA also recommended including localization of ventilation defects as part of study endpoints and analyses. As a result, both phase 3 studies included analysis of six lung zones.

A Type C Meeting was held in August 2016. The FDA recommended postoperative FEV1 obtained by spirometry as a reference standard for the estimates derived by Xe-133 and hyperpolarized Xenon-129 imaging. This recommendation was further discussed at a follow-up meeting in September 2016. Since many patients with poor ventilation who are evaluated for lung resection would have Xe-133 scintigraphy results that contraindicate surgery and therefore would have no postoperative FEV1 for comparison, the FDA recommended obtaining postoperative FEV1 by spirometry for use as a reference standard in a subset of patients as an exploratory analysis. Ultimately, postoperative FEV1 was included as a secondary endpoint in a subset of patients who underwent lung resection surgery in study POL-Xe-001. FDA again recommended region-level (lung zone) comparisons be conducted. Both pivotal studies included a secondary endpoint to compare regional (six lung zone) ventilation results between hyperpolarized Xe-129 MRI and Xe-133 scintigraphy.

The FDA Advice Letter and follow-up teleconference in December 2019 discussed the phase 3 statistical analysis plan. The FDA recommended primary analysis of within-subject differences between hyperpolarized Xe-129 MRI and Xe-133 scintigraphy. Additionally, it was agreed that

both phase 3 studies would include exploratory analyses to determine the number of patients exceeding an equivalence margin and to evaluate within-subject differences between Xe-129 MRI and Xe-133 scintigraphy with standardization to Xe-133 scintigraphy results.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

While no specific data quality issues were suspected, an audit by the Office of Scientific Investigations was requested for studies POL-Xe-001 and POL-Xe-002 because these studies provided primary effectiveness and safety results to support this NDA. Good clinical practice (GCP) inspections were performed for two representative sites including a contract research organization where the primary efficacy analysis data were generated and a clinical investigator site where secondary efficacy analysis data and safety data were generated. No significant GCP violations were identified through either inspection. The clinical data generated by the inspected sites appeared to be acceptable for purposes of NDA support.

4.2. Product Quality

Xe-129 (at least 80% enriched) in a gas blend with high purity nitrogen and helium is hyperpolarized in the presence of rubidium vapor (b) (4) Cryogenic collection in a dewar vessel isolates Xe-129 from the gas blend, removing nitrogen and helium. After thawing, the Xe-129 is diluted with NF grade nitrogen to provide a product dose to be inhaled by patients of 1 L total volume of gas in a dose delivery bag containing 250 ml to 750 mL of xenon. The portion of xenon that consists of hyperpolarized Xe-129 corresponds to a dose equivalent volume of 75 mL to 100 mL, as calculated by accounting for the total volume of xenon, the fraction of Xe-129 isotopic enrichment, and the fraction of hyperpolarization (see Section 6.2.2).

The Office of Pharmaceutical Quality (OPQ) recommends a Complete Response for this NDA, taking into account withhold CGMP recommendations for (b) (4) (proposed commercial manufacturer) and Polarean Inc. (Applicant, specifications developer, tester), as further described in Section 4.5. The preapproval inspection of (b) (4) was classified as Official Action Indicated. Manufacturing record deficiencies (b) (4) include lack of measurements of the degree of Xe-129 polarization. Specification and acceptance criteria must be developed and adequately justified by Polarean (b) (4) for this critical quality attribute.

4.3. Clinical Microbiology

This section is not applicable to this NDA.

4.4. Devices and Companion Diagnostic Issues

This combination product includes the Xeno View System which consists of multiple device components that together generate, quantify, and store hyperpolarized Xe-129 doses that are inhaled for the purpose of imaging lung ventilation with MRI. CDER sought input from CDRH/DRH

on device components and any regulatory issues associated with MR systems/accessories. DRH reviewed the device description, device-related risk analysis, software documentation, device-related nonclinical testing, human factors testing, and labeling. The anesthesia devices team reviewed the dose bag for performance and mitigation of pressure-related risks. The device sterility team reviewed the biocompatibility information of Xeno View System, categorized as a skin-contacting and externally communicating device through humidified and dry gas pathways.

During the review, CDRH requested clarification concerning the overall workflow/MR acquisition protocol, additional information about the provided risk management, additional validation of the Polarization Measurement Station, supporting biocompatibility information for the humidified and dry gas pathways, dose bag pressure validations and risk assessments, other testing of the dose bag, testing and evaluation of the particulate matter in the gas, and cytotoxicity, sensitization, and irritation testing on the final finished mouthpiece. Outstanding deficiencies were communicated interactively to the Applicant to ensure the device components functioned as intended with sufficient accuracy, device-related risks were reduced to the minimum amount, and device labeling had sufficient instructions for use. The Applicant provided additional information about the testing procedures and the particulate matter, irritation, sensitization, and cytotoxicity results were acceptable. In addition, the Applicant responded with an improved clinical workflow description and additional information about hardware/software mechanisms for risk control. CDRH found the Applicant's responses to be adequate and had no outstanding concerns. See Section 4.5 for discussion of device manufacturing issues identified upon facilities inspection.

Device Components

The production, measurement, and administration of hyperpolarized Xe-129 are accomplished by the following device components of the Xeno View System:

- Gas Handling Manifold – an ultra-high purity (UHP) gas pressure regulation and purification system that allows connecting up to two XENOVIEW gas blend cylinders, one NF-grade ultra-high purity nitrogen (UHP N2 NF) cylinder, and one industrial nitrogen (STD N2) cylinder to the Hyperpolarizer.

- Hyperpolarizer – the device used to hyperpolarize the Xe-129 from the (b) (4) gas blend. The device consists of an inert gas laser optical pumping system, a cryogenic Xe accumulator, and various electrical and fluid controls.

- XENOVIEW Dose Delivery Bag – a one-liter (1 L) dose delivery bag that provides the means to store and transport XENOVIEW from the Hyperpolarizer to the Polarization Measurement Station, and subsequently to the patient. The dose delivery bag features a mouthpiece for administration to the patient.

- Polarization Measurement Station – the device used to measure the (b) (4) polarization of XENOVIEW no more than 5 minutes prior to patient administration to ensure the dose equivalent (DE) volume is greater than or equal to 75 mL (b) (4) - (b) (4)

FDA-Recognized Voluntary Consensus Standards and Guidance

The NDA complied with the following FDA-recognized voluntary consensus standards:

- Polarean's risk management process complied with ISO 14971:2019.
- Xenon Hyperpolarizer complied with both IEC 61010-1 (Edition 3.1) and IEC 61010-2-010 (4th Edition) requirements.
- Polarization Measurement Station complied with IEC 61010-1 (Edition 3.1) requirements.
- Xenon Hyperpolarizer and Polarization Measurement Station complied with IEC 60601-1-2 (4th Edition) requirements.
- Dose delivery bag and gas pathways of the Xenon Hyperpolarizer complied with the requirements of the biocompatibility-related standards ISO 10993-12 (2021), ISO 10993-10 (2010), ISO 10993-5 (2009), and ISO 18562-2 (2017).

CDRH guidance documents referred to during the NDA review:

- Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (May 11, 2005)
- Guidance for Industry, FDA Reviewers and Compliance on Off-The-Shelf Software Use in Medical Devices (September 27, 2019)

4.5. Facilities Inspection Issues

Polarean Inc. (FEI:3010132318) is the Applicant and design and specification developer for the Xeno View System and is also responsible for manufacturing of all the device components for the Xeno View System. Polarean has contracted (b) (4) for commercial production of the device components which include the Xe-129 Hyperpolarizer, Measurement Station and the dose delivery bags. (b) (4) will be responsible for providing the medical gas blend with the approved quality specifications under this NDA application.

The preapproval inspection (b) (4) was classified as Official Action Indicated due to several product specific deficiencies (b) (4)

The preapproval inspections at (b) (4) and Polarean Inc. are recommended for withhold by the Office of Process and Facility and CDRH (b) (4) Deficiencies were noted in several of the device specific process and procedures required for commercial manufacturing, testing, quality assurance, final product release, and shipping/distribution. Polarean (b) (4) has also failed to (b) (4)

(b) (4)

Satisfactory resolution of the manufacturing deficiencies identified upon inspection at Polarean Inc, (b) (4) is required before this application may be approved.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Xenon is a noble gas. Neither isotopic enrichment of Xe-129 nor hyperpolarization of Xe-129 alters the pharmacologic or toxicologic properties of xenon gas. Hyperpolarized Xe-129 has been imaged by MRI in the lungs in several nonclinical models. In a rat central nervous system (CNS) safety pharmacology study, inhalation for up to 20 minutes of a gas blend containing 80% Xe/20% O_2 produced transient analgesia, reduced activity, and reduced capacity to learn escape/avoidance behavior during the inhalation period. These are expected pharmacology findings since 80% Xe/20% O_2 inhalation can be used as an anesthetic agent. There were no drug-related effects on carbon monoxide diffusing capacity, quasistatic cord capacity (a mechanical measurement of lung compliance), or lung vital capacity in a dog respiratory safety pharmacology study performed in combination with a dog expanded single-dose inhalation toxicity study; additionally, no adverse effects on electrocardiogram (ECG) parameters were observed. Nonclinical absorption, distribution, metabolism, excretion (ADME)/pharmacokinetic (PK) study reports were not submitted or needed given the available nonclinical and clinical reports in the scientific literature. These reports were adequately summarized by the Applicant in Section 2.4 of the NDA submission.

The Applicant submitted what they consider an expanded single-dose toxicity study in rats and an expanded single-dose toxicity study in dogs. Apnea was induced in anesthetized animals, 2 to 3 pulses of 100% Xe gas were administered via endotracheal tube, the animal was allowed to resume normal breathing, and this procedure was repeated until 20 insufflations had been administered. There were no drug-related adverse effects observed in these toxicity studies.

Genetic toxicology study reports were not submitted or needed. Carcinogenicity data were also not submitted or needed since Xe gas is not administered chronically. Nonclinical reproductive and developmental toxicology study reports were not submitted. The Applicant did summarize the nonclinical reproductive and developmental toxicology data available in the public literature. The inhalation of 70-80% Xe/20-30% O_2 had no adverse effects on reproduction and fetal development in rat studies. However, the nonclinical reviewer is unable to confirm that the above studies were adequately designed and well-controlled. Nonetheless, additional reproductive and developmental toxicity studies are not needed for this application based on the fact that Xe gas exhibits significant anesthetic properties only at high doses and on the absence of adverse effects in the above studies where much greater volumes of Xe were used relative to the maximum volume of Xe proposed in this NDA.

The nonclinical review discipline recommends approval.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

In a pharmacology study report, male hamsters were administered either 0 (saline control), 1, or 3 units of intratracheal elastase. Hyperpolarized Xe-129 and helium-3 (He-3) apparent diffusion coefficient measurements were performed four weeks later with a 15 minute washout period between administration/imaging sessions. Animals were sacrificed after imaging and lungs were removed and fixed for histological measurement of alveolar dimensions. Elastase administration induced mostly mild emphysema in animals that received 1 unit and mostly moderate emphysema in animals that received 3 units (confirmed by histology and measuring tidal volumes and total lung capacities). Mean apparent diffusion coefficient values for both hyperpolarized gases were highly correlated with elastase-induced changes on histological measures of alveolar dimensions. Results from this study suggested that hyperpolarized Xe-129 (as well as hyperpolarized He-3) diffusion imaging may be a useful technique for detecting lung parenchyma damage resulting from emphysema.

The Applicant also cited additional nonclinical pharmacology data from the publicly available literature. Overall, the cited data supported the proposed indication.

In a CNS safety pharmacology study, rats were administered via inhalation 80% Xe/20% O_2 for up to 20 minutes. The tail-flick analgesia test was performed immediately prior to and during the last minute of gas exposure. Locomotor activity was evaluated for first 5 minutes immediately following exposure to the Xe gas blend and an active avoidance test was performed after that. The results were compared to animals exposed to air from a cylinder containing what was labeled as breathing air. Inhalation of 80% Xe/20% O_2 for up to 20 minutes produced transient analgesia, reduced activity, and reduced capacity to learn escape/avoidance behavior. These are expected pharmacology findings; Xe gas inhalation is approved outside the US for use as an anesthetic. The Applicant evaluated a number of respiratory parameters and performed ECGs in a dog expanded single-dose inhalation toxicity study. Methods and results from these safety pharmacology-related parameters are reviewed in the General Toxicology section below.

5.4. ADME/PK

Nonclinical pharmacokinetic (absorption, distribution, metabolism, excretion) study reports were not submitted. The Applicant provided a summary of the nonclinical and clinical reports in the scientific literature. Following inhalation, a small amount of Xe is known to rapidly diffuse from the lungs into the blood and a small portion is further distributed to other tissues. The solubility of Xe is higher in fat than in blood and other tissues. Xe is not metabolized and is primarily eliminated via the lungs once the alveolar concentration decreases. Most absorbed Xe is eliminated rapidly once uptake via inhalation ceases. Given these findings, ADME/PK preclinical studies are not needed.

5.5. Toxicology

5.5.1. General Toxicology

The Applicant submitted study reports for expanded single-dose inhalation toxicity studies in rat and dog. No drug-related adverse effects were observed in these studies.

Study title/ number: Expanded Single-Dose Toxicity Study in Rats with NC100674 (test article comprised of Xe gas with 50% Xe-129)/ Study number FY01-019

- No drug-related adverse effects were observed in this study.

Conducting laboratory and location: (b) (4) (b) (4)

GLP compliance: Yes

Methods:	
Dose and frequency of dosing:	Each rat was exposed to 20 total pulses of NC100674 or breathing air on Day 0. The mean volume per group was approximately 0.123 L/kg for male groups and 0.141 L/kg for female groups. Individual values ranged from 0.094 to 0.165 L/kg for males and 0.096 to 0.222 L/kg for females.
Route of administration:	Inhalation. Anesthetized rats were intubated with an endotracheal tube. Twenty insufflations (1 to 2.5 mL/insufflation) were then administered by inducing apnea, administering 2 to 3 gas pulses through the tube using gas filled glass syringes, allowing normal respiration to resume, and then repeating until a total of 20 pulses had been administered.
Formulation/ Vehicle:	100% Xe gas reportedly containing 50% Xe-129/ breathing air was used as the control article.
Species/ Strain:	Rat/ Sprague Dawley
Number/ Sex/ Group:	5/ sex/ group for main study (sacrificed on Day 3) and recovery (sacrificed on Day 14) groups
Age:	8 to 9 weeks at initiation of dosing
Satellite groups/ unique design:	None
Deviations from study protocol affecting interpretation of results:	None. There were several flaws with the conduct of this study. Several animals died or required oxygen due to poor breathing rates following anesthesia but prior to Xe administration.

	Animals that died were replaced with extra animals. Revived animals continued in the study. Additionally, there was a large variation in the amount of Xe administered to individual rats. Nonetheless, these flaws were not severe enough to change the overall study conclusion.

Observations and Results: Changes from Control

Parameters	Major findings
Mortality	There were no deaths following Xe administration.
Clinical Signs	There were no drug-related clinical signs.
Body Weights	There were no drug-related effects on mean body weights.
Ophthalmoscopy	There were no drug-related ophthalmic findings.
Hematology	There were no biologically significant drug-related adverse effects on mean hematology parameters.
Clinical Chemistry	There were no biologically significant drug-related adverse effects on mean clinical chemistry parameters.
Gross Pathology	There were no macroscopic findings mentioned in the study report. However, it was unclear if animals were examined for macroscopic findings.
Organ Weights	There were no biologically significant drug-related effects on mean organ weights.
Histopathology Adequate battery: Yes	There were no drug-related adverse microscopic findings observed in this study.
Other Evaluations	There were no drug-related effects on mean feed consumption.

Study title/ number: Toxicity and Safety Pharmacology Assessment of Inhaled NC100674 in Beagle Dogs/ Study number FY01-15

- Animals treated with NC100674 experienced prolonged periods of apnea. Some animals failed to resume normal breathing and were administered oxygen until breathing returned to normal. A male dog died due to misdosing and was replaced in the study with an extra animal. No other drug-related adverse effects were observed in this study.
- The study report concluded that there were no drug-related adverse effects observed in this study. The study report considered the observed apnea to be due to the anesthetic effect of Xe gas (normal pharmacology) and not an adverse effect. The nonclinical review team agrees that the anesthetic properties of Xe likely contributed to the development of apnea but that the use of a model that induces apnea just prior to insufflation and that incorporated anesthesia prior to Xe gas administration also likely contributed. Overall, the nonclinical review team agrees that the observed apnea was likely due to exaggerated pharmacology and agrees that there were no drug-related adverse effects observed in this study.

Conducting laboratory and location: (b) (4)
(b) (4)

GLP compliance: Yes

Methods:

Dose and frequency of dosing:	Each dog was exposed to a total of 20 pulses of NC100674 or air on Day 0. The mean volume per group ranged from 1.14 to 1.24 L/kg. Individual values ranged from 1.00 to 1.43 L/kg.
Route of administration:	Inhalation. Dogs were anesthetized with acepromazine. Anesthetized dogs were intubated with an endotracheal tube. Xe or ambient air was then administered by inducing apnea, administering 2 to 3 gas pulses through the tube using gas filled glass syringes, allowing normal respiration to resume, and then repeating until a total of 20 pulses had been administered.
Formulation/ Vehicle:	100% Xe gas reportedly containing 50% 129 Xe/ breathing air was used as the control article.
Species/ Strain:	Dog/ Beagle
Number/ Sex/ Group:	2/ sex/ group main study (Sacrificed on Day 3) and 3/ sex/ group recovery (Sacrificed on Day 14)
Age:	6 to 7 months at initiation of dosing
Satellite groups/ unique design:	Pulmonary function tests (and ECG recordings) were performed twice prior to dosing and immediately after NC100674 dosing as well as on Days 3 and 14.
Deviation from study protocol affecting interpretation of results:	No. Two animals were misdosed (one of the animals died) and subsequently replaced.

Observations and Results: Changes from Control

Parameters	Major findings
Mortality	A male dog died after accidently being administered 22 insufflations instead of 20 with the key factor being that the animal received 5 pulses instead of 3 during the final round of insufflations. This animal was replaced with an extra animal. The cause of death was considered due to misdosing and was not considered drug-related.
Clinical Signs	Inhalation of NC100674 caused prolonged periods of apnea with 5 of 11 treated dogs requiring oxygen therapy until they resumed normal breathing. No other clinical signs were noted in this study.

Body Weights	There were no drug-related effects on body weights.
Ophthalmoscopy	There were no drug-related ophthalmic findings.
ECG	There were no obvious drug-related effects on ECG parameters.
Hematology	There were no biologically significant drug-related adverse effects on mean hematology parameters.
Clinical Chemistry	There were no biologically significant drug-related adverse effects on mean clinical chemistry parameters.
Gross Pathology	There were no macroscopic findings mentioned in the study report. However, it was unclear if animals were examined for macroscopic findings.
Organ Weights	Mean absolute and relative thymus weights were significantly increased by ~80% in Day 14 treated females compared to Day 14 control females. This finding was not considered adverse since correlating microscopic findings were not observed.
Histopathology Adequate battery: Yes	There were no drug-related adverse microscopic findings noted in this study.
Other evaluations	There were no drug-related effects on carbon monoxide diffusing capacity, quasistatic cord capacity, or lung vital capacity.

General toxicology; additional studies

No adverse effects were reported in a number of published non-GLP toxicity studies in various species that used repeated dosing of 70-80% Xe/20-30% O_2, with the gas being administered for a minimum of 2 hours per dose. Repeat-dose toxicology studies are not required for drug approval of this NDA. However, the data from the repeat-dose toxicology studies available in the public literature suggest that Xe gas inhalation is relatively nontoxic.

5.5.2. Genetic Toxicology

Genetic toxicology study reports were not submitted and were not needed.

5.5.3. Carcinogenicity

Carcinogenicity data were not submitted and were not needed.

5.5.4. Reproductive and Developmental Toxicology

Nonclinical reproductive and developmental toxicology study reports were not submitted. The Applicant summarized the nonclinical reproductive and developmental toxicology data available in the scientific literature. No effects on fertility or pregnancy indices were observed in male and female rats administered 80% Xe/20% O_2 for 2 hours daily twice a week for 2 and 10 weeks. No adverse effects on embryo-fetal development were observed in rats administered 70-75% Xe/20-25% O_2 for 24 hours on the ninth day of gestation and rats administered 80% Xe/20% O_2 2 hours twice a week from the first to the nineteenth day of gestation. A subset of the rats from the above study were allowed to go to labor, delivery, and postnatal care of offspring. No adverse effects were noted regarding neonatal and postnatal development for this part of the study.

The nonclinical reviewer is unable to confirm that the above studies were adequate and well-controlled. However, from a nonclinical perspective the typically recommended battery of

reproductive and developmental toxicity studies are not needed for this application based on: 1) the absence of adverse effects in the above studies in which much greater volumes of Xe were used relative to the maximum volume of Xe proposed under this NDA; and 2) the fact that Xe gas only exhibits significant analgesic/anesthetic properties at high doses.

5.5.5. Other Toxicology Studies

No other nonclinical toxicology study reports were submitted or were needed.

6 Clinical Pharmacology

6.1. Executive Summary

Hyperpolarized Xe-129 is a gas that is inhaled and in one breath-hold disperses into ventilated spaces in the lungs. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below.

6.2. Summary of Clinical Pharmacology Assessment

Recommendations and Comments for Review Issues in NDA 214375

Review Issue	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	The primary evidence of effectiveness is provided by Study POL-Xe-001 and Study POL-Xe-002.
General dosing instructions	XENOVIEW (hyperpolarized Xe-129) is prepared by the Xeno View System from the XENOVIEW gas blend. The recommended dose for both adults and pediatric patients aged 12 years and older is 75 to 100 mL dose equivalent (DE) of hyperpolarized Xe-129 gas (in 250 mL to 750 mL total Xe) with nitrogen, NF (99.999% purity) added to 1 L total volume for inhalation from the XENOVIEW dose delivery bag. DE is defined as (P_{129}) X (F_{129}) X (V_{Xe}), where P_{129} is the fraction of hyperpolarization, F_{129} is the fraction of isotopic enrichment of Xe-129 in the Xe gas, and V_{Xe} is the total volume of Xe in mL. DE equates to the volume of 100% isotopically enriched Xe-129 with 100% hyperpolarization that would be required to produce the equivalent MRI signal of a clinical dose.
Dosing in patient subgroups (intrinsic and extrinsic factors)	A study on the effect of hepatic impairment or renal impairment on hyperpolarized Xe-129 pharmacokinetics is not needed as the drug is exhaled by the lungs within 1 to 2 minutes.

Drug-drug interactions	No dedicated drug interaction study is necessary as the drug is exhaled by the lungs within 1 to 2 minutes. The drug is not metabolized. However, patients with compromised pulmonary function often receive inhaler-based medications such as bronchodilators for management of asthma and COPD exacerbations. As expected, 60% of patients in Study POL-Xe-001 and 31% of patients in Study POL-Xe-002 reported concomitant inhaler use. However, hyperpolarized Xe-129 MRI was found to be similarly comparable to Xe-133 scintigraphy in patients regardless of whether they were on concomitant inhaler medication. There is potential for oxygen to hasten depolarization of hyperpolarized Xe-129, thus decreasing the MR signal strength. Roughly half of the patients in Study POL-Xe-001 (46.9%) and nearly all patients in Study POL-Xe-002 (89.7%) regularly used supplemental oxygen. During administration of hyperpolarized Xe-129, supplemental oxygen was only withheld during the two breaths preceding hyperpolarized Xe-129 inhalation and the subsequent 10 to 15 seconds of the breath hold during which images were acquired. Hyperpolarized Xe-129 MRI was found to be similarly comparable to Xe-133 scintigraphy in patients regardless of whether they regularly used supplemental oxygen.
Labeling	The recommended DE is 75 to 100 ml for both adults and pediatric patients aged 12 years and older. DE exceeding 100 mL is acceptable.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable.

6.2.1. Pharmacology and Clinical Pharmacokinetics

Upon inhalation, hyperpolarized Xe-129 disperses to the ventilated areas of the lung including the small airways and distal alveoli. Neither isotopic enrichment of Xe-129 nor hyperpolarization of Xe-129 alters the clinical pharmacologic properties of xenon gas itself. A small amount of inhaled hyperpolarized Xe-129, and inhaled xenon in general, diffuses through cell membranes, enters the pulmonary vessels, and distributes to more distal organs. At high doses, xenon has analgesic/anesthetic properties.

In a published modeling study, the pharmacokinetics of xenon gas was compared among humans, pigs, and rats (Katz et al. 2015). It was found that during a 60-minute administration of 50% xenon, the arterial blood xenon concentration reached a plateau (equilibrium) after 1 minute for all three species. After 5 minutes, the arterial blood xenon concentration was 2-fold greater in rats (0.004 mol/L) than in pigs (0.002 mol/L), and 1.6-fold greater in rats than in humans (0.0025 mol/L). The solubility of hyperpolarized Xe-129, and xenon in general, is higher in fatty tissues than in aqueous tissues/body compartments such as plasma.

Changes in chemical shift as hyperpolarized Xe-129 diffuses into the interstitial barrier space and red blood cells allow it to be distinguished by MRI in these compartments from hyperpolarized Xe-129 remaining in the airways. Although such dissolved-phase techniques are not utilized for the current indication of ventilation imaging, they are being further studied and might support additional clinical applications in the future.

The Applicant conducted a Phase 1, single-center, open-label, cross-over study designed to evaluate the exhalation kinetic parameters of inhaled, isotopically enriched (Xe-129) but non-hyperpolarized gas as a primary objective. Healthy subjects were randomly assigned to either of two treatment orders: 250 mL (25%) Xe-129 gas with 750 mL nitrogen gas (Treatment 1) followed by 750 mL (75%) Xe-129 gas with 250 mL nitrogen gas (Treatment 2), or Treatment 2 followed by Treatment 1. The gas mixtures were administered via inhalation in a single breath from the intended commercial dose delivery bag. Subjects were instructed to hold their breath for 10 to 15 seconds following inhalation of the gas mixture and then to exhale directly into air-tight collection bags at prescribed intervals. Results from this study showed that Xe-129 was rapidly eliminated ($t_{1/2}$ = 14.3 seconds) following inhalation of a gas mixture containing 25% Xe-129. Similar results were obtained ($t_{1/2}$ = 14.5 seconds), with a 75% Xe-129 gas mixture.

Hyperpolarized Xe-129, like xenon, does not undergo any metabolism. Following a single breath hold, the majority of hyperpolarized Xe-129 is immediately eliminated upon exhalation. The portion of hyperpolarized Xe-129 that is absorbed by the blood and tissues is also ultimately eliminated by exhalation from the lungs. The effect of hepatic impairment and renal impairment does not apply to hyperpolarized Xe-129 as the drug is exhaled completely within 2 minutes.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

XENOVIEW (hyperpolarized Xe-129) is prepared by the Xeno View System from the XENOVIEW gas blend. The recommended dose for both adults and pediatric patients aged 12 years and older is 75 to 100 mL dose equivalent of hyperpolarized Xe-129 gas (in 250 mL to 750 mL total Xe) with nitrogen, NF (99.999% purity) added to 1 L total volume for inhalation from the XENOVIEW dose delivery bag.

Dose equivalent (DE) = (P_{129}) X (F_{129}) X (V_{Xe})

P_{129} = fraction of hyperpolarization
F_{129} = fraction of isotopic enrichment of Xe-129 in the Xe gas
V_{Xe} = total volume of Xe in mL

DE equates to the volume of 100% isotopically enriched Xe-129 with 100% hyperpolarization that would be required to produce the equivalent MRI signal of a clinical dose.

Therapeutic Individualization

No therapeutic individualization is needed.

Outstanding Issues

No outstanding issues are identified from a clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant conducted a Phase 1, single-center, open-label, cross-over study designed to evaluate the exhalation kinetic parameters of inhaled, isotopically enriched Xe-129 gas as a primary objective. The secondary objective was to assess the safety and tolerability of inhaled, Xe gas that is isotopically enriched in Xe-129.

A total of 20 healthy subjects were enrolled in the study, of whom 10 (50%) were male and 10 (50%) were female. One subject was excluded from the analysis due to incomplete pulmonary function testing. Subjects ranged in age from 29 to 64 years old.

Subjects were randomly assigned to either of two treatment orders: 250 mL (25%) Xe-129 gas with 750 mL nitrogen gas (Treatment 1) followed by 750 mL (75%) Xe-129 gas with 250 mL nitrogen gas (Treatment 2), or Treatment 2 followed by Treatment 1. The gas mixtures were

administered via inhalation in a single breath from the intended commercial dose delivery bag. Subjects were instructed to hold their breath for 10 to 15 seconds following inhalation of the gas mixture and then to exhale directly into air-tight collection bags at specified intervals.

The first exhaled Xe measurement was performed at 0 minutes using Collection Bag #1. Exhalations were collected in additional air-tight gas collection bags at 1, 1.5, 2, 2.5, 3, 4, 5, 10, 15, and 20 minutes. Gas in the collection bags was analyzed by gas chromatography-mass spectroscopy (GC-MS) using a validated method that measures Xe-129 selectively.

To obtain a concentration versus time elimination curve, the concentration (ppm) of Xe-129 was measured directly from exhaled gas over a period of 5 minutes for Treatment 1 and Treatment 2. Pulmonary function testing such as forced vital capacity (FVC), forced expiratory volume in 1 second, (FEV1), FVC/FEV1 ratio, tidal volume, and functional residual capacity were performed after the second treatment. Using these data, the overall clearance of Xe was determined and compared to predicted excretion curves based on the subject's tidal volume and functional residual capacity.

Results from this study showed that Xe-129 was rapidly eliminated (half-life of 14.3 seconds [relative standard deviation of 18.6%]) following inhalation of a gas mixture containing 25% Xe-129 (Treatment 1). Similar results were obtained (half-life of 14.5 seconds [relative standard deviation of 24.9%]) with a 75% Xe-129 gas mixture (Treatment 2). Relative to the concentration at time 0, the average concentration in exhaled breath dropped approximately 200- and 160-fold in the 3-minute samples from subjects that inhaled the 25% and 75% Xe-129 gas mixtures, respectively.

ADME and Clinical PK Information for XENOVIEW

Pharmacology	
Mechanism of action	Hyperpolarized Xe-129 is a readily diffusible gas. When inhaled, hyperpolarized Xe-129 distributes in the ventilated areas of the lungs including the small airways and alveoli and provides an MRI signal to allow imaging evaluation of lung ventilation. The MRI signal is dependent on volume of xenon gas inhaled, degree of Xe-129 isotopic enrichment, and extent of hyperpolarization.
Active Moieties	Hyperpolarized Xe-129
Dose Equivalent	75 to 100 mL
QT/QTc prolongation	Not applicable
General Information	
Bioanalysis	Exhaled gas in the collection bags was analyzed by GC-MS using a validated method that directly measures Xe-129.

Healthy volunteers vs. patients	Not applicable

Parameter	Information
Distribution	
Volume of distribution	When inhaled, hyperpolarized Xe-129 disperses to the ventilated areas of the lung. A small amount of inhaled hyperpolarized Xe-129 diffuses through cell membranes, enters the pulmonary vessels, and distributes to more distal organs. The solubility of hyperpolarized Xe-129 is higher in fatty tissues than in aqueous tissues/body compartments such as plasma.
Plasma protein binding	Not studied
Blood to plasma ratio	Not studied
Elimination	
Half-life	The elimination half-life (exhalation) is approximately 15 seconds.
Clearance	Hyperpolarized Xe-129 is exhaled by the lungs. There is minimal absorption.
Metabolism	
Primary metabolic pathway(s)	Not studied
Inhibitor/inducer	Not studied
Excretion	
Primary excretion pathways	Exhaled

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The optimal amount of hyperpolarized Xe-129 (dose equivalent, a pharmacodynamic surrogate) must be inhaled by patients to provide clinically meaningful images.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes.

Dose Equivalent

Polarean conducted two phase 3 trials (POL-Xe-001 and POL-Xe-002) that evaluated the efficacy of hyperpolarized Xe-129 for the evaluation of pulmonary ventilation:

The Applicant's proposed DE was 75 mL. The administered mean DE and mean xenon gas volumes with ranges were as follows in the two phase 3 studies:

POL-Xe-001: mean 99 mL DE (range 41 to 163 mL), total xenon gas mean 369 mL (220 to 750 mL)
POL-Xe-002: mean 102 mL DE (range 56 to 132 mL), total xenon gas mean 324 mL (220 to 580 mL)

The phase 3 trial protocols specified a DE of 75 mL. However, the clinical sites conducting the trials tended to achieve higher hyperpolarization than specified and therefore, on average, delivered a higher DE than specified.

The Applicant stated that the justification for the recommended DE of 75 mL was derived from several published studies briefly described here. First, (He et al. 2015), established the simple, linear relationship between DE and image signal-to-noise ratio (SNR) for fast gradient echo ventilation imaging, the same pulse sequence as used in the phase 3 studies. Subsequently, (Tan et al. 2018), used this approach to estimate the SNR required for 6-zone analysis of hyperpolarized Xe-129 MRI acquired at a resolution of 3.1 × 3.1 × 12.5 mm^3. (Tan et al. 2018), evaluated both reader-based and automated 6-zone analysis of hyperpolarized Xe-129 MRI as image SNR was progressively degraded. Using the highest SNR image as a gold standard and reader-based analysis as the worst-case scenario, the authors found that activity measured within a given zone deviated by more than 5% from the high-SNR measurement when image SNR decreased below a value of 4.4 ± 5.8. The authors suggested conservatively setting an SNR threshold that was two standard deviations higher than this limit, and thus recommended images be acquired with SNR of greater than 16. Using the formalism of (He et al. 2015), this SNR threshold translated into a DE requirement of 89.2 mL. However, this estimate was based on an image resolution that was higher than the 4 × 4× 15 mm^3 used for the Applicant's phase 3 trials. The phase 3 trials used a voxel volume that was two-fold larger than the (Tan et al. 2018), study. Thus, the Applicant estimated a required DE of 44.6 mL, half that estimated by (Tan et al. 2018). Ultimately, the Applicant used 50 mL as the conservative minimum cutoff for DE and 75 mL as the target DE.

To assess if DE affected imaging efficacy in the Applicant's phase 3 trials, the Applicant pooled data and divided patients into quartiles based on the DE administered (approximately 60-80, 81-105, 106-119, 120-162 mL). Primary efficacy results (i.e., the difference between the Xe-129 measurement and the Xe-133 measurement) were calculated for within each DE quartile. As illustrated in Table 1 below, there was no appreciable relationship among DE quartiles and the primary efficacy results.

Table 1. Primary Efficacy Results Within Each Dose Equivalent Quartile

	Dose Equivalent Quartile			
	1st	2nd	3rd	4th
Mean Diff. ^{129}Xe-^{133}Xe (%) (95% CI)	-0.20 (-2.05, 1.64)	-1.03 (-5.31, 3.25)	-0.50 (-3.09, 2.10)	-0.00 (-2.72, 2.71)
Median Diff. ^{129}Xe-^{133}Xe (%)	-0.675	-1.75	-1.29	0.18

Abbreviations: CI = confidence interval; Diff = difference.
Source: Applicant's Response to Clinical Pharmacology Information Request June 21, 2021

Thus, it appears that a large range of DE starting at approximately 50 mL and extending to over 100 mL can be used without compromising efficacy. Of additional note, higher DE is not expected to increase safety risk given the 750 mL limit on total xenon volume per dose. In order to better align with the dosing of the Applicant's phase 3 trials as well as to allow for a single recommended dose range for both adult and pediatric patients, as further discussed below, a dose range of 75 to 100 mL DE is recommended. Labeling will also note that higher DE is acceptable.

Number of Doses

The Applicant's submitted phase 1 safety trial, GE-141-001, administered up to four doses containing 1L of xenon in addition to a calibration dose of at least 200 mL of xenon. As discussed in Section 8.2.8 of this review, adverse events were more frequent in this trial compared to the Applicant's phase 3 trials in which almost all patients received a single dose.

Multiple studies reported in the literature provided repeat dosing during a single imaging session. Often, the doses provided were 1 L of xenon, compared with the maximum recommended dose of 750 mL of xenon for XENOVIEW. For example, (Dregely et al. 2011) and (Ebner et al. 2017), reported administering two doses while (Shukla et al. 2012), reported administering two to four doses, and others reported administration of an even greater number of doses. For example, (Patz et al. 2008), administered up to 18 doses to the same patient. These doses were typically repeated within 10 to 20 minutes of one another. Unlike the GE-141-001 trial, the cited studies generally reported no adverse events or mild and transient adverse events consistent with the experience in the Applicant's phase 3 trials (e.g., dizziness, headache).

For the ventilation imaging indications being proposed, it is not expected that more than one or two doses would be necessary, as confirmed in the Applicant's phase 3 trials. In any event, the frequency of dosing is also limited by the expected time needed to produce additional doses of hyperpolarized Xe-129 (approximately 10 to 20 minutes). As such, it does not seem necessary to specify a maximum dose number in the prescribing information.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The relatively simple pharmacokinetics and mechanism of action of hyperpolarized Xe-129 inhaled for the purpose of ventilation imaging with MRI support extrapolation of adult efficacy to pediatric patients. Through responses to FDA requests, the Applicant provided information relevant to pediatric dosing.

Regarding device compatibility and total dose volume, the Applicant stated that the currently available 1 L dose delivery bag and associated mouthpiece would be compatible for use with patients aged 12 years and older. (b) (4)

(b) (4)

Regarding DE, the Applicant proposed (b) (4) While seemingly intuitive, no specific supporting information was otherwise provided by the Applicant for this assertion.

In consideration of the above information and through consultation with the Division of Pediatric and Maternal Health and the Division of Pulmonology, Allergy, and Critical Care at the FDA, a recommended DE of 75 mL to 100 mL was determined to be reasonable for both adults as well as pediatric patients aged 12 and over. Similarly, a total xenon gas dose of 250 mL to 750 ml with additional nitrogen gas to reach an overall dose volume of 1 L was determined to be acceptable for both of these populations.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Patients with compromised pulmonary function often receive inhaler-based medications such as inhaled bronchodilators for management of asthma and chronic obstructive pulmonary disease (COPD) exacerbations. As expected, 60% of patients in Study POL-Xe-001 and 31% of patients in Study POL-Xe-002 reported concomitant inhaler use. However, hyperpolarized Xe-129 MRI was found to be similarly comparable to Xe-133 scintigraphy in patients regardless of whether they were on concomitant inhaler medication.

There is potential for oxygen to hasten depolarization of hyperpolarized Xe-129, thus decreasing the MR signal strength. Roughly half of the patients in Study POL-Xe-001 (46.9%) and nearly all patients in Study POL-Xe-002 (89.7%) regularly used supplemental oxygen. During administration of hyperpolarized Xe-129, supplemental oxygen was only withheld during the two breaths preceding hyperpolarized Xe-129 inhalation and the subsequent 10 to 15 seconds of the breath hold during which images were acquired. Hyperpolarized Xe-129 MRI was found to be similarly comparable to Xe-133 scintigraphy in patients regardless of whether they regularly used supplemental oxygen.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 2: Listing of Clinical Trials Relevant to This NDA

Study number	Trial Design	Study population	Primary endpoints	Number of subjects dosed	Dosing	No. of Centers and Countries
POL-Xe-001	Prospective, open-label, cross-over phase 3 protocol comparing hyperpolarized Xe-129 MRI to approved Xe-133 scintigraphy	Patients with various lung diseases being evaluated for lung resection surgery	Scan predicted proportion of remaining pulmonary function	34	Target dose equivalent of 75 mL of hyperpolarized Xe-129 in up to 750 mL of xenon gas filled to 1 L with nitrogen gas, inhaled with 10 to 15 second breath hold	3 (USA)
POL-Xe-002	Prospective, open-label, cross-over phase 3 protocol comparing hyperpolarized Xe-129 MRI to approved Xe-133	Patients with various lung diseases being evaluated for lung transplant surgery	Scan predicted contribution of the right lung to overall lung function	49	Target dose equivalent of 75 mL of hyperpolarized Xe-129 in up to 750 mL of xenon gas filled to 1 L with nitrogen gas,	2 (USA)

	scintigraphy				inhaled with 10 to 15 second breath hold	
GE-141-001	Prospective, open-label phase 1 safety and feasibility study	Healthy volunteers and patients with emphysema	Safety and imaging feasibility	44	3 to 4 doses of 1 L of isotopically enriched and hyperpolarized Xe-129, plus a calibration dose of 200mL to 1 L hyperpolarized Xe-129 , each inhaled with approximately 15 second breath hold, at least 15 minutes between doses	1 (USA)
POL-Xe-003	Prospective, open-label pharmacokinetic study	Healthy volunteers	Exhalation pharmacokinetic parameters of inhaled Xe-129	20	One of each low and high doses in randomized order: Low dose: 250 mL of isotopically enriched Xe-129 with 750 mL nitrogen gas, inhaled with 10 to 15 second breath hold	1 (USA)

					High dose: 750 mL of isotopically enriched Xe-129 with 250 mL nitrogen gas, inhaled with 10 to 15 second breath hold	

7.2. Review Strategy

Clinical evidence was obtained from two phase 3 studies, a phase 1 safety study, a clinical pharmacology study, and supportive clinical literature. Primary evidence of efficacy was provided by the phase 3 studies (POL-Xe-001 and POL-Xe-002). These two studies had similar design and endpoints but different pre-operative patient populations, with patients evaluated for lung resection enrolled in the POL-Xe-001 study and patients evaluated for lung transplant enrolled in the POL-Xe-002 study. A literature review in adult and pediatric populations was also provided by the Applicant for efficacy evaluation.

The data from the phase 1 safety study were limited due to use of a higher dosing regimen than proposed for use. Safety evaluation instead relied on more relevant data from the phase 3 efficacy studies, clinical pharmacology study, and Applicant's literature review conducted in adult and pediatric populations.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study POL-Xe-001

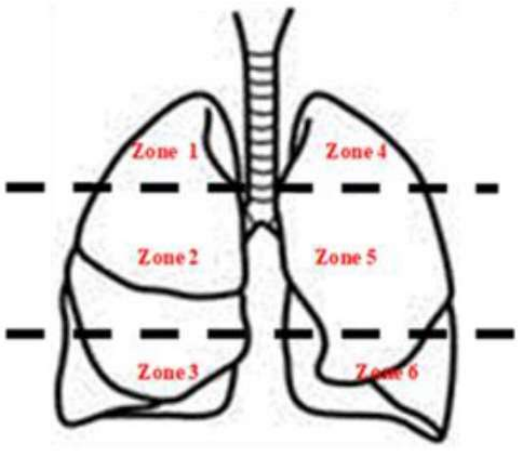
Trial Design

Study POL-Xe-001 was a randomized, open-label, cross-over, multicenter, phase 3 study designed to demonstrate the equivalence of hyperpolarized Xe-129 MRI compared to Xe-133 scintigraphy for the evaluation of pulmonary ventilation and to assess the safety of hyperpolarized Xe-129 gas. The study enrolled male and female patients being evaluated for possible lung resection surgery including segmentectomy, lobectomy, or pneumonectomy. The study consisted of a screening period, imaging period (during which patients underwent hyperpolarized Xe-129 MRI and Xe-133 scintigraphy), phone follow-up period, and postoperative follow-up period (approximately 3 months after surgery, for patients who underwent lung surgery). A total of 32 patients were planned to be randomized in a 1:1 ratio to receive hyperpolarized Xe-129 followed by Xe-133 (referred to hereafter as Xe-129/Xe-133) or Xe-133 followed by hyperpolarized Xe-129 (referred to hereafter as Xe-133/Xe-129).

Study Endpoints

The primary efficacy endpoint was the scan-estimated percentage of pulmonary ventilation predicted to remain after resection of a pre-specified lung area (predicted percentage of remaining ventilation). On each hyperpolarized Xe-129 and Xe-133 scan, commercially available software was used to calculate the percentage of total lung ventilation contributed by each of six lung zones consisting of upper, mid, and lower regions on each side, as displayed in Figure 1. Regions of interest corresponding to these zones were verified by central readers blinded to patient medical history and study assessments. The predicted postoperative percentage of remaining ventilation was calculated by subtracting the percentage of ventilation contributed by the lung zone(s) planned for resection from 100%.

Figure 1. Illustration of Lung Zones



Source: Figure 3 in the clinical study report

Secondary efficacy endpoints included the scan-estimated percentage of overall pulmonary ventilation contributed by each of the six individual lung zones and the scan-predicted postoperative forced expiratory volume in 1 second (FEV1) value.

Statistical Analysis Plan

The analysis of the primary and six zone secondary efficacy endpoints was based on the efficacy analysis set, defined as the group of patients who had both a hyperpolarized Xe-129 MRI scan and a Xe-133 scintigraphy scan, and for whom both scans met quality control criteria for analysis.

The secondary analysis of the postoperative FEV1 value was based on the postoperative analysis set, defined as the group of patients in the efficacy analysis set who underwent surgery and had a postoperative FEV1 value.

The primary efficacy endpoint was planned to be analyzed using the two-sided 95% CI for the mean of the intra-patient differences in the predicted percentage of remaining ventilation determined on the hyperpolarized Xe-129 MRI scan and Xe-133 scintigraphy scan. The statistical analysis plan pre-specified that equivalence would be demonstrated if the 95% CI was contained within -14.7% to +14.7%. The Applicant relied mainly on published data that compared scintigraphic techniques for evaluation of pulmonary function in a pre-pneumonectomy population as the basis for this equivalence margin (Mariano-Goulart et al. 2006).

For individual lung zones, the statistical analysis plan pre-specified that equivalence would be demonstrated if the 95% CI for the mean of the within-patient differences for the hyperpolarized Xe-129 MRI scan and Xe-133 scintigraphy scan was contained within -5% to +5%. The Applicant rationalized this margin as an approximate third of the above 14.7% margin,

given derivation of the 14.7% margin from a pneumonectomy setting in which three analyzed lung zones would remain.

Protocol Amendments

There were three protocol amendments following the original protocol dated October 20, 2017, with the last amendment completed on April 26, 2018. The study was initiated on September 4, 2018 and completed on November 1, 2019.

Compliance with Good Clinical Practices

The Applicant reported that this study was conducted in accordance with the Declaration of Helsinki, the ICH guideline for GCP, FDA regulations, and other applicable local laws and regulations.

Financial Disclosure

No relevant financial disclosures were reported by the Applicant.

Patient Disposition

A total of 44 patients were screened and 38 randomized at the three trial sites, all of which were in the United States. Among the randomized patients, 18 patients (47%) were randomized to receive Xe-129/Xe-133 and 20 patients (53%) to receive Xe-133/Xe-129. A total of 13 patients in the Xe-129/Xe-133 group and 19 patients in the Xe-133/Xe-129 group were included in the efficacy analysis set. The following lists summarize the reasons that some randomized patients were not included in the efficacy analysis set:

For Xe-129/Xe-133:

- One patient was excluded prior to imaging according to inclusion/exclusion criteria.
- One patient was discontinued due to an adverse event prior to imaging.
- One patient withdrew consent prior to completion of imaging.
- One patient did not complete study procedures.
- One patient did not undergo imaging because enrollment goal was met.

For Xe-133/Xe-129:

- Image quality was inadequate for analysis for one patient.

Protocol Deviations

Table 3 summarizes the protocol deviations for all randomized patients. These protocol

deviations were considered to be minor and unlikely to affect safety or efficacy evaluation.

Table 3. Study POL-Xe-001 Protocol Deviations For All Randomized Patients

Protocol Deviation	Treatment Order		Total
	$^{129}Xe/^{133}Xe$ N=18 n (%)	$^{133}Xe/^{129}Xe$ N=20 n (%)	N=38 n (%)
Subject with any protocol deviation	4 (22.2)	10 (50.0)	14 (36.8)
Informed consent procedure	0	2 (10.0)	2 (5.3)
Assessment not performed	0	1 (5.0)	1 (2.6)
Assessment out of time window	0	1 (5.0)	1 (2.6)
Investigational product	2 (11.1)	0	2 (5.3)
Other	2 (11.1)	7 (35.0)	9 (23.7)

Abbreviations: N = total number of subjects; n = number of subjects in a specific group.
Source: Section 14.1.2 in the clinical study report

Table of Demographic Characteristics

Table 4 shows the demographic characteristics of the 32 patients in the efficacy analysis set. There were more males (69%) than females in the efficacy analysis set. The average age was 62 years (SD = 9.75). The majority of the patients (78%) were white. Sex, age, race, and ethnicity of the patient subgroups that received the two treatment sequences were similar.

Table 4. Study POL-Xe-001 Summary of Demographic Characteristics in the Efficacy Analysis Population

Demographic Parameters	Xe-129/Xe-133 (N = 13)	Xe-133/Xe-129* (N = 19)	Total (N = 32)
Sex			
Female n(%)	4 (31%)	6 (32%)	10 (31%)
Male n(%)	9 (69%)	13 (68%)	22 (69%)
Age			
Mean years (SD)	58.5 (11.93)	64.3 (7.39)	62.0 (9.75)
Median (years)	59	63	62
Min, max (years)	25, 75	51, 77	25, 77
Race			
Asian n (%)	0	1 (5%)	1 (3%)
Black or African American n (%)	2 (15%)	4 (21%)	6 (19%)
White n (%)	11 (85%)	14 (74%)	25 (78%)
Ethnicity			
Hispanic or Latino n (%)	0	0	0
Not Hispanic or Latino n (%)	13 (100%)	19 (100%)	32 (100%)

Source: Selected from 14.1.3.1 in the clinical study report
*Patient (b) (6), a 71 years of age, white male, was excluded from the primary efficacy analysis because the planned area of lung

resection was not recorded in the eCRF.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

POL-Xe-001 enrolled patients with various lung diseases who were being evaluated for lung resection surgery. Patients reported medical histories including pulmonary mass (44%), COPD (35%), asthma (12%), and emphysema (9%).

A spurious negative baseline FEV1 was recorded in one patient due to a data entry error involving the patent's height. Out of the other 31 patients in the efficacy analysis set, 21 patients (68%) had baseline FEV1 below 80% predicted.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study drug was administered at the clinical sites. There were no restrictions with respect to concomitant therapies. See Section 6.3.2 for information regarding concomitant medication inhaler and supplemental oxygen use.

Dose/Dose Response

A total of 33 patients received a single dose of hyperpolarized Xe-129 gas. One additional patient received two doses of hyperpolarized Xe-129, as well as a small calibration dose containing 100 mL of xenon.

Mean dose equivalent was 99 mL (range 41 to 163 mL) in patients receiving one dose. The mean percentage of Xe-129 hyperpolarization for all patients dosed was 36.8% (minimum = 13.8% and maximum = 57%), mean total volume of Xe administered per dose was 369 mL (SD = 152 mL), and mean breath hold time was 10.4 seconds (SD = 1.1 seconds). For patients receiving both hyperpolarized Xe-129 and Xe-133, the mean time between administration was 1.8 hours (minimum = 0.7 and maximum = 4.9 hours).

Data Quality and Integrity

The statistical reviewer was able to perform independent review using the Applicant's submitted datasets to confirm the Applicant's analysis results.

Efficacy Results – Primary Endpoint

Table 5 presents the analysis results of the primary endpoint. The Applicant excluded one patient (patient (b) (6) receiving Xe-133/Xe-129) from the primary efficacy analysis because the planned area of lung resection was missing.

Table 5. Study POL-Xe-001 Analysis of the Primary Endpoint (Scan-Estimated Percentage of Pulmonary Ventilation Predicted to Remain After Resection of a Pre-Specified Lung Area)

	^{129}Xe N=31	^{133}Xe N=31	Within-Subject Difference (^{129}Xe - ^{133}Xe)
Mean % (SD)	73.4 (13.0)	71.9 (12.1)	1.4 (5.9)
Median %	75.8	72.0	1.7
Min, Max %	34.3, 94.2	47.3, 91.3	-21.4, 14.2
95% CI %			-0.75, 3.60

Abbreviations: CI = confidence interval; Max = maximum; Min = minimum; N = total number of subjects; SD = standard deviation.
Source: Table 7 in the clinical study report

Considerable variability was observed across patients: the within-patient differences of the predicted percentage of remaining ventilation calculated by subtracting Xe-133 scintigraphy results from hyperpolarized Xe-129 MRI results demonstrated a range of -21.5% to 14.2%. The mean of the within-patient differences of predicted percentage of remaining ventilation calculated in the same manner was 1.4% (95% CI -0.75%, 3.6%). The pre-specified equivalence criterion was met since the 95% CI of the mean within-patient differences was contained in the pre-specified equivalence interval of -14.7% to +14.7%.

By the intent-to-image principle, excluded patient (b) (6) should be included in the primary efficacy analysis via imputation, perhaps with the assumption that the unknown area of planned lung resection was missing at random. However, given that the primary efficacy endpoint results met the equivalence criterion by a reasonable margin, success of the primary analysis is expected to hold even with random imputation of this single patient. Of note, patient (b) (6) was included in the individual zone secondary efficacy analysis discussed later.

Efficacy Results – Secondary and Other Relevant Endpoints

Table 6 presents an analysis of the within-patient differences of predicted remaining ventilation as performed for the results in Table 5 but with standardization to the predicted remaining ventilation results of Xe-133 scintigraphy. The mean standardized within-patient difference was 0.02 (95% CI -0.02, 0.06) indicating that, on average, the percentage of remaining ventilation predicted by hyperpolarized Xe-129 MRI was 2% higher than the percentage of remaining ventilation predicted by Xe-133 scintigraphy.

Table 6. Study POL-Xe-001 Analysis of the Standardized Within-Patient Difference

	$(^{129}Xe - ^{133}Xe)/^{133}Xe$[1] N=31
Mean (SD)	0.02 (0.10)
Median	0.02
Min, Max	-0.4, 0.3
95% CI	(-0.02, 0.06)

Abbreviations: CI = confidence interval, Max = maximum; Min = minimum; N = total number of subjects; SD = standard deviation

[1] Standardized predicted remaining function = (^{129}Xe MRI predicted proportion of remaining function – ^{133}Xe scintigraphy predicted proportion of remaining function)/^{133}Xe scintigraphy predicted proportion of remaining function.

Source: Selected from 14.2.2.1 in the clinical study report

Table 7 presents an analysis of the within-patient differences of the estimated ventilation contributions in each of the six lung zones.

Table 7. Study POL-Xe-001 Analysis of Within-Patient Difference of Estimated Ventilation Contributions by Lung Zone

Lung Zone	Within-Subject Mean Difference ($^{129}Xe - ^{133}Xe$) Mean % (SD) [95% CI] N=32
Lower Left	3.71 (4.39) [2.12, 5.29]
Lower Right	-1.76 (3.96) [-3.19, -0.34]
Middle Left	1.35 (3.22) [0.18, 2.51]
Middle Right	-2.72 (3.82) [-4.10, -1.35]
Upper Left	0.39 (2.40) [-0.48, 1.26]
Upper Right	-0.96 (3.16) [-2.10, 0.18]

Abbreviations: CI = confidence interval; N = total number of subjects; SD = standard deviation.

Source: Table 8 in the clinical study report

Considerable patient variability (i.e., standard deviation) within individual lung zones was observed. The 95% CIs for the mean of the within-patient differences of the estimated ventilation contributions were contained within the -5% to +5% equivalence interval for all lung zones, except the lower left lung which narrowly exceeded the upper limit of the interval. The Applicant hypothesized that the results in the lower left lung might be related to underestimation of ventilation in this region by Xe-133 scintigraphy due to photon attenuation by the left ventricle of the heart, as previously described in a publication by (Schembri et al. 2015). There was no pre-specified multiplicity procedure to formally assess statistical conclusions for this secondary analysis.

Table 8 presents the secondary analysis results of predicted versus measured postoperative FEV1 measured in liters (L). In the 12 patients who underwent lung resection, had an intended area of lung resection recorded, and had both baseline and postoperative FEV1 measured by

spirometry, the predicted postoperative FEV1 was calculated by multiplying the predicted percentages of remaining ventilation, as determined using hyperpolarized Xe-129 MRI or Xe-133 scintigraphy, by the baseline FEV1 measurements.

Table 8. Study POL-Xe-001 Analysis of Predicted Versus Measured Postoperative FEV1

	^{129}Xe MRI Predicted FEV1 (L) N=13	^{133}Xe Scintigraphy Predicted FEV1 (L) N=13	Measured Post-Operative FEV1 (L)	Within-Subject Difference ^{129}Xe Predicted – Measured FEV1 (L)	Within-Subject Difference ^{133}Xe Predicted – Measured FEV1 (L)
n	12[a]	12[a]	13	12[a]	12[a]
Mean (SD)	1.60 (0.76)	1.61 (0.76)	2.16 (0.99)	-0.65 (0.60)	-0.65 (0.66)
Min, Max	0.74, 3.04	0.68, 3.03	1.01, 3.67	-1.91, 0.05	-1.89, 0.25
95% CI				-1.03, -0.27	-1.10, -0.23

Abbreviations: CI = confidence interval; eCRF = electronic case report form; FEV1 = forced expiratory volume in 1 second; Max = maximum; Min = minimum; N = total number of subjects; n = number of subjects in a specific group; SD = standard deviation.

[a] One subject was excluded because the intended area of lung resection was not recorded on the eCRF.

Source: Table 9 in the clinical study report

The mean within-patient difference between the postoperative FEV1 predicted by hyperpolarized Xe-129 MRI and actual FEV1 measured by spirometry after surgery was -0.65L (95% CI: -1.03L, -0.27L); the mean within-patient difference between the FEV1 predicted by Xe-133 scintigraphy and actual FEV1 measured postoperatively was -0.65L (95% CI: -1.10L, -0.23L). While the observed mean differences between the predicted versus measured postoperative FEV1 were similar for both hyperpolarized Xe-129 and Xe-133, the predicted FEV1 using imaging was less than measured FEV1, as evidenced by the 95% CIs for the mean differences that excluded 0 L.

Since mean measured postoperative FEV1 was 2.2 L (SD=1.0), both imaging techniques appear to have underestimated postoperative FEV1 considerably. However, as noted by the Applicant, any conclusions regarding accuracy of these imaging techniques for this purpose are limited since planned resection areas were confined to one or more of the six whole lung zones while actual surgical resection was not. The Applicant reasonably hypothesizes that some surgical resections may have not involved the entirety of one or more of the six imaging lung zones, potentially accounting for the observed underestimation of postoperative FEV1.

Additional Analyses Conducted on the Individual Trial

An exploratory analysis was performed on the within-patient differences of the predicted percentage of remaining ventilation with standardization to Xe-133 scintigraphy results. While Table 6 presented such data as mean and median results for all analyzed patients, the additional exploratory analysis determined the number of patients who had standardized results for hyperpolarized Xe-129 and Xe-133 that differed by less than fractions of ± 0.1, ±

0.15, and ± 0.2 (i.e., ± 10%, ± 15%, and ± 20%). The percentages of patients within each margin were 81% (25/31) , 94% (29/31) , and 94% (29/31), respectively. Unlike analyses described above that focused on mean results for all patients, this exploratory analysis did not allow relative positive and negative intra-patient differences between hyperpolarized Xe-129 and Xe-133 results to effectively cancel out.

Since patients with FEV1 or diffusing capacity for carbon monoxide below 80% predicted would most likely benefit from preoperative evaluation of ventilation, the Applicant was asked to identify these patients for exploratory subgroup analyses. While baseline diffusing capacity for carbon monoxide data were not available, 20 evaluable patients were identified with FEV1 below 80% predicted. Using the same approach as above, the proportions of these patients whose standardized within-patient differences for predicted remaining ventilation were within ± 0.1, ± 0.15, and ± 0.2 were determined to be 70% (14/20), 90% (18/20), and 90% (18/20), respectively.

8.1.2. Study POL-Xe-002

Trial Design

Study POL-Xe-002 was a randomized, open-label, cross-over, multicenter, phase 3 study designed to demonstrate the equivalence of hyperpolarized Xe-129 MRI as compared to Xe-133 scintigraphy for the evaluation of pulmonary ventilation and to assess the safety of hyperpolarized Xe-129 gas. The study enrolled male and female patients being evaluated for possible lung transplant surgery. The study consisted of the screening period, imaging period (during which patients underwent hyperpolarized Xe-129 MRI and Xe-133 scintigraphy), and phone follow-up period. A total of 48 patients were planned to be randomized in a 1:1 ratio to receive Xe-129/Xe-133 or Xe-133/Xe-129.

Study Endpoints

The primary efficacy endpoint was the scan-estimated percentage of overall pulmonary ventilation contributed by the right lung. Secondary efficacy endpoints included the scan-estimated percentage of overall pulmonary ventilation contributed by each of the individual six lung zones. Regions of interest corresponding to these zones were verified by central readers blinded to patient medical history and study assessments.

Statistical Analysis Plan

The analysis of the primary and six zone secondary efficacy endpoints were based on the efficacy analysis set, defined as the group of patients who had both a hyperpolarized Xe-129 MRI scan and a Xe-133 scintigraphy scan, and for whom both scans met quality control criteria for analysis.

The primary efficacy endpoint was planned to be analyzed using the two-sided 95% CI for the mean of the intra-patient differences in predicted percentage of remaining ventilation determined on the hyperpolarized Xe-129 MRI scan and Xe-133 scintigraphy scan. The statistical analysis plan pre-specified that equivalence would be demonstrated if the 95% CI was contained within -14.7% to +14.7%, the same margin as rationalized for Study POL-Xe-001 primary analysis.

For individual lung zones, the statistical analysis plan pre-specified that equivalence would be demonstrated if the 95% CI for the mean within-patient differences for the hyperpolarized Xe-129 MRI scan and Xe-133 scintigraphy scan was contained within -5% to +5%. This margin was again the same as that rationalized for Study POL-Xe-001.

Protocol Amendments

There were three protocol amendments following the original protocol dated October 20, 2017, with the last amendment completed on April 27, 2018. The study enrolled the first patient on August 21, 2018 and the last patient visit was November 5, 2019.

Compliance with Good Clinical Practices

The Applicant reported that this study was conducted in accordance with the Declaration of Helsinki, the ICH guideline for GCP, Food and Drug Administration (FDA) regulations, and other applicable local laws and regulations.

Financial Disclosure

No relevant financial disclosures were reported by the Applicant.

Patient Disposition

A total of 57 patients were randomized at two trial sites, both of which were in the United States. Among the randomized patients, 29 patients (51%) were randomized to receive Xe-129/Xe-133 and 28 patients (49%) to receive Xe-133/Xe-129. A total of 27 patients in the Xe-129/Xe-133 group and 22 patients in the Xe-133/Xe-129 group were included in the efficacy analysis set. The following lists summarize the reasons that some randomized patients were not included in the efficacy analysis set:

For Xe-129/Xe-133:

- One patient was excluded prior to imaging according to inclusion/exclusion criteria.
- One patient withdrew consent prior to completion of imaging.

For Xe-133/Xe-129:

- Two patients were excluded prior to imaging according to inclusion/exclusion criteria.
- Four patients withdrew consent prior to completion of imaging.

Protocol Deviations

Table 9 summarizes the protocol deviations of all patients in the efficacy analysis set. These protocol deviations were considered to be minor and unlikely to affect safety or efficacy evaluation.

Table 9. Study POL-Xe-002 Protocol Deviations for All Patients in the Efficacy Analysis Set

Protocol Deviations	Treatment Order		Total
	$^{129}Xe/^{133}Xe$ N=27 n (%)	$^{133}Xe/^{129}Xe$ N=22 n (%)	N=49 n (%)
Subject with any protocol deviation	7 (25.9)	5 (22.7)	12 (24.5)
Inclusion/Exclusion criteria	1 (3.7)	0	1 (2.0)
Informed consent procedures	1 (3.7)	0	1 (2.0)
Assessment not performed	1 (3.7)	2 (9.1)	3 (6.1)
Assessment out of window	5 (18.5)	2 (9.1)	7 (14.3)
Investigational Product	0	0	0
Other	0	1 (4.5)	1 (2.0)

Abbreviations: N = total number of subjects; n = number of subjects in specific group.

Some subjects may have multiple deviation reasons.

Source: section 14.1.2 in the clinical study report

Table of Demographic Characteristics

Table 10 shows the demographic characteristics of the 49 patients in the efficacy analysis set. There were more males (69%) than females in the efficacy analysis set. The average age was 62 years (SD = 10.5). The majority of the patients (94%) were white. There was a trend towards fewer females in the Xe-133/Xe-129 treatment sequence than the Xe-129/Xe-133 treatment sequence. Age, race, and ethnicity of the patient subgroups that received the two treatment sequences were similar.

Table 10. Study POL-Xe-002 Summary of Demographic Characteristics in the Efficacy Analysis Population

Demographic Parameters	Xe-129/Xe-133 (N= 27)	Xe-133/Xe-129 (N= 22)	Total (N= 49)
Sex			
Female n(%)	12 (44%)	3 (14%)	15 (31%)
Male n(%)	15 (56%)	19 (86 %)	34 (69%)
Age			
Mean years (SD)	62.1 (9.6)	60.8 (11.7)	61.5 (10.5)
Median (years)	64	65	64
Min, max (years)	40, 77	19, 74	19, 77
Race			
Black or African American n (%)	2 (7%)	1 (5%)	3 (6%)
White n (%)	25 (93%)	21 (95%)	46 (94%)
Ethnicity			
Hispanic or Latino n (%)	0 (0%)	1 (5%)	1 (2%)
Not Hispanic or Latino n (%)	27 (100.0)	21 (95.5)	48 (98.0)

Source: Selected from 14.1.4.1 in the clinical study report

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Study POL-Xe-002 enrolled patients with various lung diseases being evaluated for lung transplant surgery (either single or bilateral). All subjects (100%) reported medical history events within the system organ class of respiratory, thoracic, and mediastinal disorders. The study population included a high proportion of subjects reporting chronic pulmonary conditions including interstitial lung disease (49.0%), idiopathic pulmonary fibrosis (28.6%), COPD (22.4%), pulmonary fibrosis (14.3%), and asthma (8.2%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study drug was administered at the clinical sites. There were no restrictions with respect to concomitant therapies. See Section6.3.2 for information regarding concomitant medication inhaler and supplemental oxygen use.

Dose/Dose Response

A total of 48 patients received a single dose of hyperpolarized Xe-129 gas. One additional patient received two doses of hyperpolarized Xe-129, as well as a small calibration dose containing 100 mL of xenon.

Mean dose equivalent was 102 mL (range 56 to 132 mL) in patients receiving one dose. The mean percentage of Xe-129 hyperpolarization for all patients dosed was 37.1% (minimum = 12.4% and maximum = 53.0%), mean total volume of Xe administered per dose was 324 mL (SD = 45 mL), and mean breath hold time was 10 seconds (SD = 1.2 seconds). For patients receiving both hyperpolarized Xe-129 and Xe-133, the mean time between administration was 1.9 hours (minimum = 0.6 and maximum = 26.8 hours).

Data Quality and Integrity

The statistical reviewer was able to perform independent review using Applicant's submitted datasets and confirm the Applicant's analysis results.

Efficacy Results – Primary Endpoint

Table 11 presents the analysis results of the primary endpoint.

Table 11. Study POL-Xe-002 Analysis of the Primary Endpoint (Scan-Estimated Percentage of Overall Pulmonary Ventilation Contributed by the Right Lung)

	Hyperpolarized ^{129}Xe N=49	^{133}Xe N=49	Within-Subject Difference (^{129}Xe-^{133}Xe)
Mean % (SD)	52.76 (8.26)	54.35 (10.24)	-1.59 (7.28)
Median %	51.99	53.43	-2.18
Min, Max %	38.8, 80.7	5.9, 72.0	-16.3, 32.9
95% CI %			-3.69, 0.50

Abbreviations: CI = confidence interval; Max = maximum; Min = minimum; N = total number of subjects; SD = standard deviation.

Source: Table 6 in the clinical study report

Considerable variability was observed across patients: the within-patient differences of the estimated percentage of overall ventilation contributed by the right lung calculated by subtracting Xe-133 scintigraphy results from hyperpolarized Xe-129 MRI results demonstrated a range of -16.3% to 32.9%. The mean of the within-patient differences of the estimated percentage of overall ventilation contributed by the right lung calculated in the same manner was -1.59% (95% CI was -3.69%, 0.50%). The pre-specified equivalence criterion was met since the 95% CI of the mean within-patient differences was contained in the pre-specified equivalence interval of -14.7% to +14.7%.

Of note, the Applicant explained that the most extreme within-patient difference of 32.9% in the primary analysis was related to low MRI signal suspected to be due to depolarization caused by the patient's continued inhalation of 6L of supplemental oxygen during hyperpolarized Xe-129 administration. This patient was the first scanned at one of the study sites and led to a procedural change to interrupt supplemental oxygen during hyperpolarized Xe-129 administration, as will be reflected in the prescribing information.

Efficacy Results – Secondary and other relevant endpoints

Table 12 presents an analysis of the within-patient differences of estimated percentage of overall ventilation contributed by the right lung as performed for the results in Table 11 but with standardization to the estimated right lung contribution results of Xe-133 scintigraphy. The mean standardized within-patient difference was 0.08 (95% CI -0.16, 0.31), indicating that on average, the percentage of overall ventilation contributed by the right lung as estimated by hyperpolarized Xe-129 MRI was 8% higher than that estimated by Xe-133 scintigraphy.

Table 12. Study POL-Xe-002 Analysis of the Standardized Within-Patient Difference

Statistics	$(^{129}Xe\text{-}^{133}Xe)/^{133}Xe$[1] N=49
Mean (SD)	0.076 (0.8079)
Median	-0.040
Min, Max	-0.26, 5.58
95% CI	(-0.156, 0.308)

Abbreviations: CI = confidence interval; Max = maximum; Min = minimum; N = total number of subjects; SD = standard deviation.

[1] Standardized Contribution of the Right Lung Function = (^{129}Xe MRI contribution of the right lung function - ^{133}Xe scintigraphy contribution of the right lung function)/ ^{133}Xe scintigraphy contribution of the right lung function.

Source: Selected from 14.2.3.1 in the clinical study report

Table 13 presents the analysis of the within-patient differences of estimated contributions of the six lung zones to overall ventilation.

Table 13. Study POL-Xe-002 Analysis of Within Patient Difference of Estimated Contributions by Lung Zone

Lung Zone	Within-Subject Mean Difference ($^{129}Xe\text{-}^{133}Xe$) Mean % (SD) [95% CI] N=49
Lower Left	1.49 (4.11) [0.31, 2.67]
Lower Right	-1.89 (4.83) [-3.28, -0.51]
Middle Left	0.34 (5.10) [-1.12, 1.81]
Middle Right	0.12 (4.10) [-1.06, 1.30]
Upper Left	-0.23 (3.33) [-1.19, 0.72]
Upper Right	0.18 (3.61) [-0.86, 1.22]

Abbreviations: CI = confidence interval; ; N = total number of subjects SD = standard deviation.

Source: Table 7 in the clinical study report

Considerable patient variability (i.e., standard deviation) within individual zones was observed. The 95% CIs of for the mean of the within-patient differences of the estimated ventilation contributions were contained within the -5% to +5% equivalence interval for all six lung zones. Although there was no pre-specified multiplicity procedure requiring all six lung zones to be

within a pre-specified equivalence interval, this analysis provides supportive evidence to the results of the primary analysis.

Additional Analyses Conducted on the Individual Trial

An exploratory analysis was performed on the within-patient differences of estimated contribution of the right lung to overall ventilation with standardization to Xe-133 scintigraphy results. While Table 12 presented such data as mean and median results for all analyzed patients, the additional exploratory analysis determined the number of patients who had standardized results for hyperpolarized Xe-129 and Xe-133 that differed by less than fractions of ± 0.1, ± 0.15, and ± 0.2 (i.e., ± 10%, ± 15%, and ± 20%). The percentages of patients within each margin were 65% (32/49) for ± 0.1 , 80% (39/49) for ± 0.15, and 96% (47/49) for ± 0.2. Unlike analyses described above that focused on mean results for all patients, this exploratory analysis did not allow relative positive and negative intra-patient differences between hyperpolarized Xe-129 and Xe-133 results to effectively cancel out.

8.1.3. Review of the Published Literature

The Applicant submitted a review of published experience with hyperpolarized Xe-129 MRI in adult and pediatric settings. A total of 21 published studies with adult subjects and 10 published studies with pediatric patients were cited. These published studies typically were small in sample size and involved patients with various known pulmonary disorders or a history of smoking. Hyperpolarized Xe-129 MRI results were often compared between such patients and healthy subjects. Comparisons among hyperpolarized Xe-129 MRI results and results of pulmonary function tests or other imaging tests were also often reported. In some studies, changes in hyperpolarized Xe-129 MRI results were described following certain treatments.

Upon FDA review, all the published studies cited by the Applicant were not considered to be adequate and well-controlled for purposes of providing additional efficacy support. Rather, these studies were considered to be exploratory in nature with various study design weaknesses, including lack of pre-specified primary analyses and success criteria needed to confirm clinically relevant hypotheses.

Although the published studies did not contribute to either adult or pediatric efficacy support, certain publications provided safety information in both populations, as discussed in Section 8.2 of this review.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

For both Study POL-Xe-001 and Study POL-Xe-002, the pre-specified equivalence criterion was met for the mean of the within-patient differences of the primary endpoints obtained with hyperpolarized Xe-129 MRI and Xe-133 scintigraphy.

Subpopulations

Table 14, Table 15, and Table 16 present subgroup analyses of the primary endpoints by age, sex, and race, respectively, for Study POL-Xe-001. Table 17, Table 18, and Table 19 present subgroup analyses of the primary endpoint by age, sex, and race, respectively, for Study POL-Xe-002. There is no compelling evidence that hyperpolarized Xe-129 MRI is unlikely to be equivalent to Xe-133 scintigraphy for a specific subgroup.

Table 14. Study POL-Xe-001 Analysis of the Primary Endpoint by Age Group

	<65 Years			≥65 Years		
	^{129}Xe N=22	^{133}Xe N=22	^{129}Xe – ^{133}Xe[1] N=22	^{129}Xe N=9[2]	^{133}Xe N=9[2]	^{129}Xe - ^{133}Xe[1]
Mean, % (SD)	73.5 (14.3)	72.5 (13.6)	1.0 (6.2)	72.9 (9.8)	70.6 (8.2)	2.3 (5.3)
Median, %	76.9	72.2	1.5	70.4	65.4	1.7
Min, Max, %	34.3, 94.2	47.3, 91.3	-21.4, 14.2	57.0, 91.8	62.7, 82.9	-7.9, 8.8
95% CI, %			(-1.72, 3.82)			(-1.73, 6.42)

Abbreviations: CI = confidence interval; Max = maximum; Min = minimum; N = total number of subjects; SD = standard deviation.

[1] Within-subject difference of the proportion of remaining function measured by ^{129}Xe and ^{133}Xe. The 95% CI is based on the paired t-test.

[2] Predicted remaining function could not be calculated for subject (b) (6) because the planned area of resection was not recorded on the eCRF.

Source: Selected from 14.2.1.2 in the clinical study report

Table 15. Study POL-Xe-001 Analysis of the Primary Endpoint by Sex

	Male			Female		
	^{129}Xe N=21[1]	^{133}Xe N=21[1]	^{129}Xe - ^{133}Xe[2]	^{129}Xe N=10	^{133}Xe N=10	^{129}Xe - ^{133}Xe[2]
Mean (SD)	75.5 (10.8)	74.3 (11.1)	1.2 (3.5)	68.8 (16.6)	66.9 (13.3)	1.9 (9.5)
Median	76.8	72.1	1.1	67.8	64.5	3.4
Min, Max	50.2, 94.2	47.3, 91.3	-7.9, 7.4	34.3, 91.8	50.5, 90.7	-21.4, 14.2
95% CI			(-0.39, 2.77)			(-4.86, 8.69)

Abbreviations: CI = confidence interval; eCRF = electronic case report form; Max = maximum; Min = minimum; N = total number of subjects; SD = standard deviation.

[1] Predicted remaining function could not be calculated for subject (b) (6) because the planned area of resection was not recorded on the eCRF.

[2] Within-subject difference of the proportion of remaining function measured by ^{129}Xe and ^{133}Xe. The 95% CI is based on the paired t-test.

Source: Selected from 14.2.1.3 in the clinical study report

Table 16. Study POL-Xe-001 Analysis of the Primary Endpoint by Race

	Race					
	White			Other		
	^{129}Xe N=24[2]	^{133}Xe N=24[2]	^{129}Xe - ^{133}Xe[1]	^{129}Xe N=7	^{133}Xe N=7	^{129}Xe - ^{133}Xe[1]
Mean (SD)	72.8 (14.2)	71.6 (12.3)	1.2 (6.1)	75.4 (8.1)	73.1 (12.4)	2.3 (5.8)
Median	74.3	70.3	2.0	76.8	72.1	-0.4
Min, Max	34.3, 94.2	47.3, 90.8	-21.4, 8.8	64.7, 90.3	50.5, 91.3	-2.0, 14.2
95% CI			(-1.39, 3.72)			(-3.06, 7.72)

Abbreviations: CI = confidence interval; eCRF = electronic case report form; Max = maximum; Min = minimum; N = total number of subjects; SD = standard deviation.

[1] Within-subject difference of the proportion of remaining function measured by ^{129}Xe and ^{133}Xe. The 95% CI is based on the paired t-test.

[2] Predicted remaining function could not be calculated for subject (b) (6) because the planned area of resection was not recorded on the eCRF.

Source: Selected from 14.2.1.4 in the clinical study report

Table 17. Study POL-Xe-002 Analysis of the Primary Endpoint by Age Group

	<65 Years			≥65 Years		
	^{129}Xe N=24	^{133}Xe N=24	^{129}Xe-^{133}Xe[1]	^{129}Xe N=25	^{133}Xe N=25	^{129}Xe-^{133}Xe[1]
Mean (SD)	53.19 (8.962)	52.23 (11.776)	0.96 (8.533)	52.34 (7.679)	56.39 (8.254)	-4.05 (4.841)
Median	51.87	52.12	-0.41	51.99	54.60	-2.56
Min, Max	38.8, 80.7	5.9, 72.0	-9.5, 32.9	40.2, 67.2	39.4, 71.4	-16.3, 3.4
95% CI			(-2.64, 4.57)			(-6.05, -2.05)

Abbreviations: CI = confidence interval; Max = maximum; Min = minimum; N = total number of subjects; SD = standard deviation.

[1] Within-subject difference of the fraction of ventilation contributed by the right lung measured by ^{129}Xe and ^{133}Xe. The 95% CI is based on the paired t-test.

Source: selected from 14.2.1.1 in the clinical study report

Table 18. Study POL-Xe-002 Analysis of the Primary Endpoint by Sex

	Male			Female		
	^{129}Xe N=34	^{133}Xe N=34	^{129}Xe-^{133}Xe[1]	^{129}Xe N=15	^{133}Xe N=15	^{129}Xe-^{133}Xe[1]
Mean (SD)	53.50 (8.075)	56.24 (7.187)	-2.74 (5.195)	51.08 (8.698)	50.08 (14.485)	1.00 (10.379)
Median	52.30	54.65	-2.42	50.18	52.15	-1.26
Min, Max	40.2, 80.7	39.4, 72.0	-16.3, 8.7	38.8, 72.6	5.9, 71.4	-13.9, 32.9
95% CI			(-4.55, -0.93)			(-4.74, 6.75)

Abbreviations: CI = confidence interval; Max = maximum; Min =minimum; N = total number of subjects; SD = standard deviation.

[1] Within-subject difference of the fraction of ventilation contributed by the right lung measured by ^{129}Xe and ^{133}Xe. The 95% CI is based on the paired t-test.

Source: Selected from 14.2.1.2 in the clinical study report

Table 19. Study POL-Xe-002 Analysis of the Primary Endpoint by Race

	Race					
	White			Other		
	^{129}Xe N=46	^{133}Xe N=46	^{129}Xe-^{133}Xe[1]	^{129}Xe N=3	^{133}Xe N=3	^{129}Xe-^{133}Xe[1]
Mean (SD)	52.71 (8.523)	54.01 (10.463)	-1.30 (7.376)	53.50 (0.759)	59.60 (3.324)	-6.09 (3.987)
Median	51.50	52.88	-1.99	53.37	58.07	-4.70
Min, Max	38.8, 80.7	5.9, 72.0	-16.3, 32.9	52.8, 54.3	57.3, 63.4	-10.6, -3.0
95% CI			(-3.49, 0.89)			(-16.00, 3.81)

Abbreviations: CI = confidence interval; Max = maximum; Min = minimum; N = total number of subjects; SD = standard deviation.

[1] Within-subject difference of the fraction of ventilation contributed by the right lung measured by ^{129}Xe and ^{133}Xe. The 95% CI is based on the paired t-test.

Source: Selected from 14.2.1.3 in the clinical study report

8.1.5. Integrated Assessment of Effectiveness

Studies POL-Xe-001 and POL-Xe-002 were considered to be adequate and well-controlled for purposes of providing evidence of effectiveness. Since image interpretation essentially consisted of placement of regions of interest for subsequent quantitative analysis, lack of multiple blinded readers for each scan was acceptable. Given the difficulty in devising a reliable truth standard for regional ventilation in the lung that was not imaging-based, comparison to the established standard of Xe-133 scintigraphy was acceptable. Although sample sizes were small in both trials, primary analyses met pre-specified success criteria with statistical robustness.

Overall, studies POL-Xe-001 and POL-Xe-002 provided substantial evidence of effectiveness for hyperpolarized Xe-129 MRI for preoperative evaluation of ventilation prior to lung surgery. The successful primary analyses of studies POL-Xe-001 and POL-Xe-002 demonstrated relative equivalence of hyperpolarized Xe-129 MRI and Xe-133 scintigraphy in preoperative settings. Secondary analyses in both trials further demonstrated reasonable concordance in ventilation measurements between hyperpolarized Xe-129 MRI and Xe-133 scintigraphy at the level of individual lung zones. Supportive exploratory analyses in both trials showed standardized hyperpolarized Xe-129 and Xe-133 results to differ by a relative margin of less than ±20% in the vast majority of patients, and less than ±10% in most patients. While studies POL-Xe-001 and POL-Xe-002 only enrolled adult patients, the relatively simple pharmacokinetics and mechanism of action of inhaled hyperpolarized Xe-129 for ventilation imaging support extrapolation of efficacy findings to pediatric patients.

The Applicant's provided review of the published experience with hyperpolarized Xe-129 lung imaging only identified studies that were considered to be exploratory in nature. While combining hyperpolarized Xe-129 ventilation imaging with lung perfusion imaging could potentially expand the settings of clinical use, such pairing was not evaluated in the literature and is of unclear practicality at this time.

8.2. Review of Safety

8.2.1. Safety Review Approach

Safety data from the Applicant's submitted efficacy trials (POL-Xe-001 and POL-Xe-002), pharmacokinetic study (POL-Xe-003), phase 1 study (GE-141-001), and adult and pediatric literature were reviewed. Supportive safety data from published adult and pediatric studies are discussed separately from the trials conducted by the Applicant since safety monitoring and adverse event information were variable.

Neither isotopic enrichment of Xe-129 nor hyperpolarization of Xe-129 adds safety risk beyond that of xenon gas itself. Thus, safety review focused on the volume of xenon administered per dose and number of doses administered rather than degree of Xe-129 isotopic enrichment,

extent of hyperpolarization, or calculated dose equivalent.

Previous FDA findings of safety for the approved drug, Xe-133, were not considered to be supportive for hyperpolarized Xe-129 since recommended dosing of Xe-133 delivers a maximum of only 6 mL of xenon gas.

8.2.2. Review of the Safety Database

Overall Exposure

The safety database included 147 adults from studies submitted by the Applicant: POL-Xe-001 (n=34), POL-Xe-002 (n=49), POL-Xe-003 (n=20), and GE-141-001 (n=44).

Study POL-Xe-001 and POL-Xe-002 enrolled only patients who were being evaluated for potential lung resection or lung transplant surgery. All patients except one from each study received a single dose of hyperpolarized Xe-129. The two patients who were exceptions received two full doses of hyperpolarized Xe-129, as well as a small calibration dose containing 100 mL of xenon. In POL-Xe-001, mean total volume of Xe administered per dose (excluding the single calibration dose) was 369 mL (SD = 152 mL, range = 220 to 750 mL) and mean breath hold time was 10.4 seconds (SD = 1.1 seconds). In POL-Xe-002, mean total volume of Xe administered per dose (excluding the single calibration dose) was 324 mL (SD = 45 mL, range = 220 to 580 mL) and mean breath hold time was 10.0 seconds (SD = 1.2 seconds).

Study POL-Xe-003 enrolled only healthy subjects, all of whom received both 250 mL and 750 mL doses of Xe gas that was isotopically enriched in Xe-129 without hyperpolarization, as detailed in Section 6.2.1 of this review. Subjects were instructed to breath hold for 10 to 15 seconds, but actual timing was not recorded.

Study GE-141-001 enrolled 34 healthy subjects and 10 patients with COPD. As discussed further in Section 8.2.8 of this review, up to four doses containing 1 L of xenon were administered to each participant in addition to a calibration dose of at least 200 mL of xenon. At least 15 minutes elapsed between doses.

The safety database was supplemented with supportive scientific literature, particularly in the pediatric population, as the Applicant's submitted trials did not include pediatric subjects. A total of 13 publications reported safety information in 204 adult subjects, and 5 publications described safety information in 120 pediatric subjects. An additional 17 publications studied hyperpolarized Xe-129 MRI in 319 adult and pediatric subjects, but safety information was not reported in these publications and they were not considered for review purposes.

Adequacy of the Safety Database:

The adult safety database derived from the Applicant's submitted trials and the published

literature as well as the pediatric safety database derived from the published literature are adequate.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Adverse Events Monitoring

In studies POL-Xe-001, POL-Xe-002, and POL-Xe-003, adverse events were monitored on the day of study drug administration and at a follow-up phone call on the day after dosing. In the GE-141-001 study, adverse events (AEs) were collected continually from the time of initial dosing until a visit at 24 ± 6 hours following the last dose. Adverse event monitoring was variable in the published literature as further described in Section 8.2.6 and 8.2.7.

Routine Clinical Tests

In studies POL-Xe-001 and POL-Xe-002, vital signs were assessed during the screening period as well as before and after each scanning session for both hyperpolarized Xe-129 and Xe-133. Vital signs included blood pressure (BP), heart rate (HR), respiration rate (RR), blood oxygen saturation (SpO2), and temperature. SpO2 was assessed during the screening period as well as before (within 5 minutes) and after (within 1 minute) each scanning session for both hyperpolarized Xe-129 and Xe-133. An absolute decrease of SpO2 by >10% was considered significant. Changes in HR of >20% were considered significant. ECG and clinical laboratory evaluations were not collected in POL-Xe-001 and POL-Xe-002.

In study POL-Xe-003, vital signs (HR, RR, BP, and temperature) were collected before and after each dose. ECG and clinical laboratory evaluations were not collected in POL-Xe-0003.

In the GE-141-001 study, vital signs (HR, RR, BP, SpO2) were assessed prior to study drug administration and at 2 minutes, 4 minutes, 5 minutes, 10 minutes, 30 minutes, 1 hour, and 24 ± 6 hours after study drug administration. ECG was performed prior to and at 0 minutes, 10 minutes, 1 hour, and 24 ± 6 hours after the last dose. Clinical laboratory hematology and biochemical tests were collected at screening and 24 ± 6 hours after the last dose. Both physical and neurological examinations were performed at screening and 24 ± 6 hours after the last dose, with additional neurological examinations at 10 minutes following every dose and 30 minutes after the last dose. Later phase subjects in the GE-141-001 study underwent spirometric evaluation at screening and 24 ± 6 hours after the last dose.

Safety monitoring with clinical tests was variable in the published literature as further described in Section 8.2.6 and 8.2.7.

8.2.4. Safety Results

Deaths

Across the four trials submitted by the Applicant, only one death was reported (Patient (b) (6)

in Study POL-Xe-002). The patient's death and related petechial rash, thrombocytopenia, and progressive anemia were considered by the Applicant to be unrelated to hyperpolarized Xe-129.

The patient was a 52 year-old male with alcoholic cirrhosis, portal hypertension, ascites, esophageal varices, portal vein thrombosis, hepatopulmonary syndrome, pulmonary fibrosis, and pulmonary hypertension who was on the waiting list for lung and liver transplant. The patient received hyperpolarized Xe-129 and Xe-133 as well as hepatitis B and pneumococcal vaccines on the same day and developed petechial rash on the feet and back that night. The investigator believed the rash was secondary to an allergic reaction to the hepatitis B vaccination.

The patient was hospitalized the following day for rash in addition to worsening of thrombocytopenia and anemia that were present at baseline due to chronic liver disease. An acute gastrointestinal bleed was treated during the hospitalization. Weeks later, the patient developed acute hypotension and tachycardia requiring resuscitation. The patient was transitioned to comfort care only and expired the same day.

According to the hepatitis B vaccine labeling, thrombocytopenia is an adverse reaction identified in the postmarketing experience, and petechial rash can be caused by thrombocytopenia. The review team agrees that the patient's death and adverse events were unrelated to hyperpolarized Xe-129.

Serious Adverse Events

Two study patients reported three serious adverse events (SAEs).

In Study POL-Xe-001, one patient with sigmoid colon cancer metastatic to the lung, status post sigmoid colectomy had nausea, vomiting, and abdominal pain reasonably attributed to colonic ileus and segmental colitis and unrelated to study drug.

In Study POL-Xe-002, progressive anemia and thrombocytopenia in the above described patient who died were recorded as SAEs unrelated to hyperpolarized Xe-129.

No SAEs were reported in the POL-Xe-003 or the GE-141-001 studies.

Dropouts and/or Discontinuations Due to Adverse Effects

Across the four trials submitted by the Applicant, only one discontinuation was reported (Patient (b) (6) in Study POL-Xe-001). This 58 year-old female experienced several AEs within 30 minutes of hyperpolarized Xe-129 administration that were considered by the investigator to be related to the exposure and led to discontinuation from the study.

The patient was being evaluated for resection of a lung neoplasm and had an extensive history

of hypersensitivity reaction to several drugs, adhesive tape, latex (causing nausea, vomiting, and hives, and foods (including anaphylaxis . Approximately 25 minutes after administration of hyperpolarized Xe-129 the patient experienced pruritus, followed by left eye itching and watering, patchy erythema, and transient numbness of the tongue. The patient was given oral diphenhydramine and symptoms and signs resolved by 90 minutes post administration of hyperpolarized Xe-129. There was no shortness of breath, wheezing, or angioedema. A follow up visit documented no residual issues. The event was considered possibly or probably related to hyperpolarized Xe-129 by the investigator.

The patient's episode is consistent with a hypersensitivity reaction. It should be noted that hyperpolarized Xe-129 is a single atom that itself is unlikely to cause allergy. This patient's episode is considered to be a hypersensitivity reaction associated with the study drug and its related procedures although the exact mechanism is unclear.

Significant Adverse Events

Aside from the above described case of allergic reaction, no adverse events were considered to be significant in studies POL-Xe-001, POL-Xe-002, POL-Xe-003, and GE-141-001.

Treatment Emergent Adverse Events and Adverse Reactions

An overall summary of AEs reported in the trials submitted by the Applicant clinical is presented in Table 20.

Table 20. Treatment-Emergent Adverse Events by Study

	POL-Xe-001 N=34 n (%)	POL-Xe-002 N=49 n (%)	POL-Xe-003 N=20 n (%)	GE-141-001 N=44 n (%)
Subjects with any TEAE	5 (14.7)	10 (20.4)	1 (5.0)	40 (91)
Subjects with any serious TEAE	1 (2.9)	1 (2.0)	0	0
Subjects with any TEAE related to study drug	4 (11.8)	8 (16.3)	0	40 (91)
Subjects with any TEAE by maximum severity[1]				
Mild	3 (8.8)	8 (16.3)	1 (5.0)	40 (91)
Moderate	1 (2.9)	1 (2.0)	0	2 (5)
Severe	1 (2.9)	1 (2.0)	0	0
Subjects with any TEAE leading to discontinuation	1 (2.9)	0	0	0
Deaths	0	1 (2.0)	0	0

Abbreviations: N = total number of subjects; TEAE = treatment emergent adverse event.

[1] Subject reporting multiple events of the same TEAE were counted once by maximum severity reported.

Source: POL-Xe-001 Clinical Study Report (CSR) Table 11, POL-Xe-002 CSR Table 10, POL-Xe-003 CSR Section 12.2.1, GE-141-001 CSR Table 15 and Section 12.1.1

A total of 38% (56/147) of subjects reported one or more treatment-emergent adverse events (TEAEs). The majority (93%; 52/56) of subjects reporting TEAEs had events that were mild. As discussed in the sections above, the patient who died had two TEAEs that were classified as severe and the patient with a hypersensitivity reaction had a TEAE that lead to discontinuation.

Adverse events were rated by the investigator as related to hyperpolarized Xe-129 in 93% (52/56) of subjects reporting TEAEs. Of important note, the majority (40/52; 77%) of these subjects with related TEAEs were from Study GE-141-001 in which three to four doses of hyperpolarized Xe-129 with 1 L volumes of xenon per dose were administered to each subject in a single visit along with a calibration dose containing at least 200 mL of xenon. The most commonly reported AEs in this study (> 10% of subjects overall) included dizziness (59%), paresthesia (34%), hypoethesia (30%), euphoric mood (30%), oral hypoesthesia (18%), and oral paresthesia (16%). All events were considered at least possibly related to hyperpolarized Xe-129 by the investigator. Most AEs were mild and transient with a mean resolution time of 1.6 ± 0.9 minutes without treatment or clinical intervention. There were no SAEs.

Since ventilation imaging with hyperpolarized Xe-129 is anticipated to require only one or two doses containing 250 mL to 750 mL of xenon per dose, as demonstrated in the Applicant's phase 3 trials, the AE data from Study GE-141-001 has limited relevance to the intended use and dosing of this drug. As such, the most meaningful summary AE data focuses on studies POL-Xe-001, POL-Xe-002, and POL-Xe-003 in which clinically applicable dosing was used. Of the 83 exposed patients in POL-Xe-001 and POL-Xe-002, 12 patients (14%) reported adverse reactions that included oropharyngeal pain, cough, pulmonary pain, headache, dizziness, flushing, hot flush, oral hypoesthesia, dyspepsia, and hypersensitivity reaction. Adverse reactions reported by more than one patient were oropharyngeal pain (4 patients), headache (2 patients), and dizziness (2 patients). No adverse reactions were reported in the 20 healthy subjects in Study POL-Xe-003.

Laboratory Findings

Clinical laboratory evaluations from Study GE-141-001 revealed minor, but no clinically significant changes in serum biochemistry and hematology and no safety signals.

Vital Signs

In Study POL-Xe-001 and Study POL-Xe-002, changes from baseline in SpO2, BP, HR, RR, and temperature were not clinically meaningful and were similar between hyperpolarized Xe-129 gas and Xe-133 gas. In Study POL-Xe-003 minimal changes in vital signs compared to pre-dose and 5-minutes post first and second dose were within the expected normal variability for the study population. No clinically meaningful changes in vital signs were consistently noted in Study GE-141-001.

Physical/Neurological Examination

No clinically significant shifts from baseline to post-dosing assessment on physical and neurological examinations in Study GE-141-001 were noted.

Spirometry

In Study GE-141-001, mean FVC, FEV1, and FEV1/FVC were similar at baseline and 24 hours after final dosing. No safety signal was identified in the collected spirometry data.

Electrocardiograms (ECGs)

ECG evaluations pre- and post- hyperpolarized Xe-129 administration were conducted only in Study GE-141-001. There were fluctuations in mean 12-lead ECG parameter values at pre- and post-dose time points for all subject groups, but no noticeable trends. Post-administration ECG changes from baseline that qualified as outlying results compared to baseline were as follows: QRS changes in 2 (5%) subjects overall at 1-hour after the final dose and QTc interval (Fridericia) changes in 2 (5%) subjects overall at 1-hour and at 24-hours after the final dose. All other changes that qualified as outlying results occurred in 1 subject each. No clear safety signal was identified through the ECG data.

QT

See above for ECG findings. No formal QT study was needed or performed for this drug.

Immunogenicity

Dedicated immunogenicity evaluation was not needed and was not performed for this drug that consists of a single element.

8.2.5. Safety Analyses by Demographic Subgroups

There were no clear differences in safety data between subjects less than 65 years of age and greater than 65 years or among racial and gender groups, although the number of subjects in the trials and the number of adverse reactions were not large enough to allow definitive comparisons.

8.2.6. Adult Safety Data from the Scientific Literature

In the scientific literature cited by the Applicant, the number of hyperpolarized Xe-129 doses administered to adult subjects varied widely. Since ventilation imaging with hyperpolarized Xe-129 is anticipated to require only one or two doses, as evidenced in the Applicant's phase 3 trials, safety review of the scientific literature was narrowed to eight studies cited by the Applicant in which adult subjects received only one to two doses of hyperpolarized Xe-129. These relevant studies included a total of 123 subjects including those with respiratory

conditions such as asthma and cystic fibrosis and those who were healthy. Xenon gas volumes per dose were approximately 500 mL to 1 L, similar to the range for the proposed clinical use. While the types of adverse reactions reported in these publications are described below, their overall frequency could not be determined from the available information.

In (Dregely et al. 2011) certain subjects reported mild transient neurological effects such as numbness or tingling following hyperpolarized Xe-129 administration. In (Ebner et al. 2017) mild reactions including tingling, euphoria, and dizziness were experienced by certain subjects following hyperpolarized Xe-129 administration, with all reactions resolving within 3 minutes. In (Rao et al. 2018) some subjects reported mild dizziness following hyperpolarized Xe-129 administration with resolution within a few seconds of breathing room air. In (Wang et al. 2018) mild side effects including euphoria and tingling were reported in certain subjects following hyperpolarized Xe-129 administration with resolution within 2 minutes. In (Kirby et al. 2012) there was a single unrelated adverse event of headache 7 hours after completion of MR imaging with hyperpolarized He-3 and hyperpolarized Xe-129 with resolution without treatment. The other three identified publications that studied one to two doses of hyperpolarized Xe-129 reported no related AEs. As noted in Section 6.3.2, published studies with more than two doses of hyperpolarized Xe-129 often reported few or no adverse events.

8.2.7. Pediatric Safety Data from the Scientific Literature

The Applicant cited five published studies that reported safety information following exposure of hyperpolarized Xe-129 in a total of 120 pediatric subjects 6 to 18 of years of age who were either healthy or had respiratory conditions such as asthma and cystic fibrosis. All subjects received one to two doses of hyperpolarized Xe-129 with a typical xenon volume of 10% to 17% of total lung capacity, up to a maximum volume of 1 L. The overall frequency of the events could not be determined from the available information.

(Walkup et al. 2016) reported mild heart rate elevation and oxygen desaturation following hyperpolarized Xe-129 administration. In this study, the majority of 12 healthy children and 11 children with cystic fibrosis (CF) experienced oxygen desaturation with a mean difference of SpO2% from baseline of -6.0% following hyperpolarized Xe-129 administration. Mean change in heart rate from baseline was +6.6 beats per minute following hyperpolarized Xe-129 administration. Oxygen desaturation and heart rate elevation resolved by 2 minutes post-dose without intervention.

(Rayment et al. 2019) reported a drop in SpO2 to less than 88% in half of hyperpolarized Xe-129 administrations performed in 15 patients with CF. These events resolved without intervention within 10 seconds and did not affect completion of successful scans. (Thomen et al. 2017), reported transient oxygen desaturations following hyperpolarized Xe-129 administration in both healthy children and children with CF which resolved within 60 seconds.

(Walkup et al. 2016) reported mild neurologic effects consisting of peripheral numbness, tingling, dizziness, and euphoria following hyperpolarized Xe-129 administration. These reactions resolved after beathing room air for 2 minutes. The other two publications reported no AEs related to hyperpolarized Xe-129 administration.

8.2.8. Safety in the Postmarket Setting

Hyperpolarized Xe-129 has not been marketed.

8.2.9. Integrated Assessment of Safety

Xenon is approved for use as an anesthetic abroad. As such, pharmacologic effects occur during periods of prolonged, continuous inhalation. For the proposed imaging use, a single breath of hyperpolarized Xe-129 is expected to be sufficient to evaluate ventilation in most patients, as was the case in the Applicant's phase 3 efficacy trials. In the event that a second dose is needed, approximately 10 to 20 minutes is expected to elapse as the second dose is prepared on site. Thus, for imaging purposes, xenon exposure will not approach that required for significant anesthetic effect.

Neither isotopic enrichment of Xe-129 nor hyperpolarization of Xe-129 adds safety risk beyond that of xenon gas. Of note, hyperpolarized Xe-129 MRI does not carry potential risk associated with ionizing radiation, unlike Xe-133.

In the trials submitted by the Applicant, the few observed SAEs and a single death are considered unrelated to hyperpolarized Xe-129. Discontinuation of a single patient from a trial was due to events consistent with a non-serious hypersensitivity reaction, although the exact mechanism is unclear given the simple atomic composition of hyperpolarized Xe-129.

Adverse reactions in the Applicant's submitted trials and review of the literature are consistent with reactions expected from brief exposure to an anesthetic or anoxic gas. As discussed above, AE data from Study GE-141-001 were considered to have limited relevance to the proposed clinical use.

While the trials submitted by the Applicant did not evaluate pediatric patients, sufficient safety data in children aged 6 years and older were identified in the literature. Reports of drops in oxygen saturation and increase in heart rate were described in pediatric patients, although non-serious, transient, and requiring no intervention. Transient drops in oxygen saturation might be expected after inhalation of any anoxic gas, and heart rate elevation is a known response to acute hypoxia. As a risk-mitigation step, a warning is planned in Section 5 of the prescribing information to monitor for hypoxia and treat accordingly.

8.3. Statistical Issues

In studies POL-Xe-001 and POL-Xe-002, the order of administration of hyperpolarized Xe-129 and Xe-133 was randomly assigned to patients. Analyses were conducted to assess whether the order of drug administration impacted study results.

Table 21 presents analysis of the standardized within-patient differences ((Xe-129– Xe-133)/(Xe-133)) of predicted remaining ventilation for each treatment order in Study POL-Xe-001. The 95% CIs for the means of the standardized within-patient differences were similar between treatment order Xe-129/Xe-133 (-0.06, 0.09) and treatment order Xe-133/Xe-129 (-0.02, 0.06).

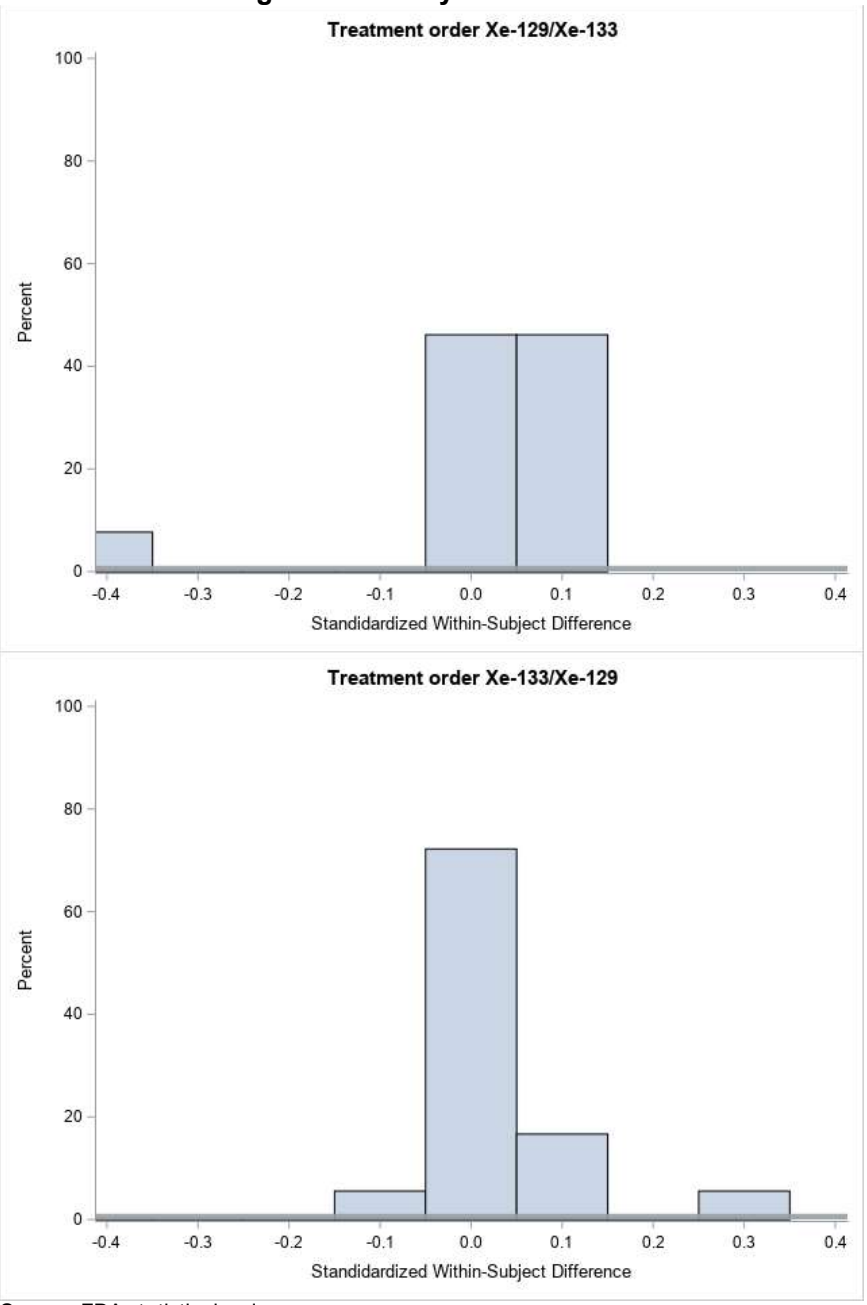
Table 21. Study POL-Xe-001 Analysis by Treatment Order of the Standardized Within-Patient Differences of Predicted Remaining Ventilation

Standardized within-patient difference of predicted remaining ventilation*	Xe-129/Xe-133 N = 13	Xe-133/Xe-129 N = 18
Mean	0.02	0.03
Median	0.04	0.00
Min, Max	-0.38, 0.11	-0.12, 0.28
95% CI	(-0.06, 0.09)	(-0.02, 0.06)

* Standardized within-patient difference of predicted remaining ventilation = (hyperpolarized Xe-129 MRI predicted proportion of remaining ventilation– Xe-133 scintigraphy predicted proportion of remaining ventilation)/ (Xe-133 scintigraphy predicted proportion of remaining ventilation).
Source: FDA statistical reviewer

Figure 2 presents the distributions of the standardized within-patient differences of predicted remaining ventilation by treatment order for Study POL-Xe-001. For the treatment order Xe-129/Xe-133, the proportions of patients whose standardized within-patient differences within ± 0.1, ± 0.15, and ±0.2 were 85% (11/13), 92% (12/13), and 92% (12/13), respectively. For the treatment order Xe-133/Xe-129, the proportions of patients whose standardized within-patient differences were within ± 0.1, ± 0.15, and ±0.2 were 78% (14/18), 94% (17/18), and 94% (17/18), respectively. The results of these subgroup analyses were generally consistent with the previously noted proportions of all evaluated patients in Study POL-Xe-001 whose standardized within-patient differences of predicted remaining ventilation were within ± 0.1 (81%), ± 0.15 (94%), and ±0.2 (94%).

Figure 2. Study POL-Xe-001 Histograms of the Standardized Within-Patient Differences of Predicted Remaining Ventilation by Treatment Order



Source: FDA statistical reviewer

Table 22 presents an analysis of the standardized within-patient differences ((Xe-129 – Xe-133)/(Xe-133)) of estimated contribution of the right lung to overall ventilation for each treatment order in Study POL-Xe-002. The 95% CIs for the means of the standardized within-patient differences were similar between treatment order Xe-129/Xe-133 (-0.26, 0.60) and treatment order Xe-133/Xe-129 (-0.07, 0.00).

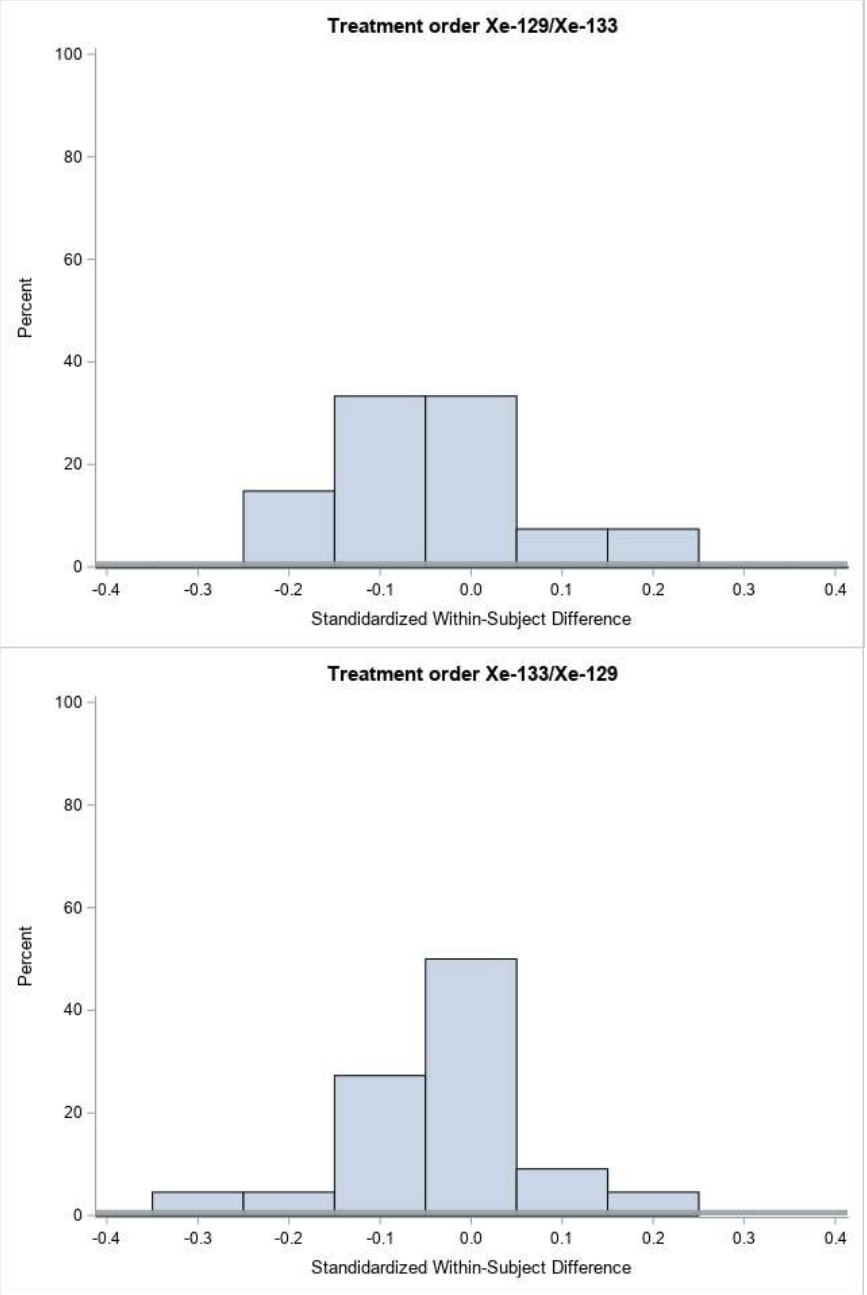
Table 22. Study POL-Xe-002 Analysis by Treatment Order of the Standardized Within-Patient Differences of Estimated Contribution of the Right Lung to Overall Ventilation

Standardized within-patient difference of estimated contribution of the right lung to overall ventilation	Xe-129/Xe-133 N = 27	Xe-133/Xe-129 N = 22
Mean	0.17	-0.04
Median	-0.04	-0.04
Min, Max	-0.20, 5.58	-0.26, 0.16
95% CI	(-0.26, 0.60)	(-0.07, 0.00)

* Standardized within-patient difference of estimated contributions of the right lung to overall ventilation = (hyperpolarized Xe-129 MRI estimated contr bution of the right lung – Xe-133 scintigraphy estimated contribution of the right lung)/(Xe-133 scintigraphy estimated contribution of the right lung).
Source: FDA statistical reviewer

Figure 3 presents the distributions of the standardized within patient differences of estimated contribution of the right lung to overall ventilation by treatment order for Study POL-Xe-002. For treatment order Xe-129/Xe-133, the proportions of patients whose standardized within-patient differences were within ± 0.1, ± 0.15, and ±0.2 were 52% (14/27), 74% (20/27), and 96% (26/27), respectively; for treatment order Xe-133/Xe-129, the proportions of patients whose standardized within-patient differences were within ± 0.1, ± 0.15, and ±0.2 were 82% (18/22), 86% (19/22), and 95% (21/22), respectively. The results of these subgroup analyses were generally consistent with the previously noted proportions of all evaluated patients in Study POL-Xe-002 whose standardized within-patient differences of estimated contribution of the right lung to overall ventilation were within ± 0.1 (65%), ± 0.15 (80%), and ±0.2 (96%).

Figure 3. Study POL-Xe-002 Histograms of the Standardized Within-Patient Differences of Estimated Contributions of the Right Lung to Overall Ventilation by Treatment Order*



*The patient who had a standardized within-patient difference of 5.58 in sequence Xe-129/Xe-133 was not included in the histogram.
Source: FDA statistical reviewer

For both studies, there was no compelling evidence from the above exploratory analyses that the demonstration of equivalence between hyperpolarized Xe-129 MRI and Xe-133 scintigraphy relied on treatment order.

There are no statistical issues with Study POL-Xe-001 and Study POL-Xe-002 that affect the approval of this NDA.

8.4. Conclusions and Recommendations

Upon clinical and statistical review, studies POL-Xe-001 and POL-Xe-002 provide substantial evidence of effectiveness for hyperpolarized Xe-129 MRI for evaluation of ventilation prior to lung resection or lung transplant surgery. While these trials were conducted only in adults, the relatively simple pharmacokinetics and mechanism of action of inhaled hyperpolarized Xe-129 for ventilation imaging support extrapolation of efficacy findings to pediatric patients, as discussed further in Section 10 of this review.

Clinical review of data from the Applicant's submitted trials in adults and review of publications in both adults and children aged 6 years and older revealed a benign safety profile for hyperpolarized Xe-129 in the clinical setting of ventilation imaging. Adverse reactions in both adults and children were non-serious and transient, and generally were consistent with those expected from brief exposure to an anesthetic or anoxic gas. As discussed in Section 10 of this review, certain of the Applicant's device components such as the dose delivery bag are currently suitable only for use by children aged 12 years and older.

In conclusion, the benefit of hyperpolarized Xe-129 MRI for preoperative evaluation of ventilation prior to lung surgery outweighs its risks. Approval of these indications is warranted in adults as well as children aged 12 years and older. However, given deficiencies in device manufacturing noted during inspections, as summarized in Section 4.5, a Complete Response will be issued for this NDA.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting or other external consultation was needed for this NDA.

10 Pediatrics

In November 2016, agreement was reached between the Applicant and FDA on the pediatric study plan. The plan included a partial waiver of study requirements under Pediatric Research Equity Act for pediatric patients less than 6 years of age because necessary studies are impossible or highly impracticable due to potential inability of children of such age to follow instructions to inhale and breath hold hyperpolarized Xe-129 or undergo MRI without sedation. The plan also included a deferral of pediatric studies in patients 6 years to less than (b) (4) years. At the time of NDA submission, the Applicant requested a full waiver of pediatric studies because the Applicant could not identify a pediatric population equivalent to the adult population studied with sufficient numbers to support a pediatric study.

During review of this NDA, FDA worked with the Applicant to define a path for extrapolation of efficacy from adults to pediatric patients with additional data to support pediatric dosing and safety. Efficacy was extrapolated from trials in adults to pediatric patients given the simple pharmacokinetics and mechanism of action of hyperpolarized Xe-129 when inhaled and imaged during a single breath to visualize distribution in the airspaces. The recommended dose for pediatric patients is the same as for adults, as discussed in Section 6.3.2 of this review. In addition to adult patients, hyperpolarized Xe-129 is recommended to be indicated in pediatric patients aged 12 years and older for preoperative evaluation of ventilation by MRI prior to lung surgery.

Upon future NDA approval, the Applicant will need to develop an age-appropriate presentation of hyperpolarized Xe-129 that would allow administration of an accurate dose to pediatric patients 6 years to less than 12 years of age through a postmarketing requirement.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Section 1. INDICATIONS AND USAGE

- The Applicant's proposed broad indication should be narrowed to the preoperative settings that were supported by adequate and well-controlled trials.
- Pediatric patients should be indicated through extrapolation of adult efficacy results and the collected pediatric safety data from the literature.

Section 2. DOSAGE AND ADMINISTRATION

- As discussed in Section 6 of this review, a single DE range of 75 mL to 100 mL is recommended for both adult and pediatric patients aged 12 years and older with 250 to 750 mL of xenon and nitrogen added to reach a total volume of 1 L.

Section 5. WARNINGS AND PRECAUTIONS

- As initially suggested by the Applicant, risk of decreased image quality from supplemental oxygen should be described, as was noted in study POL-XE-002. Instructions to temporarily withhold supplemental oxygen during hyperpolarized Xe-129 inhalation and breath holding should be provided.
- Risk of transient hypoxia should be described, as noted in the pediatric literature.
- Risk of bronchospasm should be described in a fashion similar to other inhaled drugs.

Section 6. ADVERSE REACTIONS

- Clinical trials experience should include pooled data from patients in POL-Xe-001 and POL-Xe-002 and separately describe experience in healthy subjects in POL-Xe-003.
- Safety data from study GE-141-001 should not be included in labeling since the dosing regimen was not relevant to the indicated use and dosage.
- Safety data in adult and pediatric subjects from scientific publications should be summarized separately.

Section 8. USE IN SPECIFIC POPULATIONS

- Subsection 8.4 Pediatric Use in should describe the rationale for indicating pediatric patients aged 12 years and older as follows:

  The safety and effectiveness of XENOVIEW have been established in pediatric patients 6 years of age and older. Use of XENOVIEW is supported by evidence from adequate and well-controlled studies in adults and safety data in pediatric patients. Use of XENOVIEW in pediatric patients 6 years to less than 12 years is not recommended due to the lack of availability of an appropriately sized delivery device. Safety and effectiveness of XENOVIEW have not been established in pediatric patients less than 6 years of age.

Section 14. CLINICAL STUDIES

- Design and results of the Applicant's adequate and well-controlled trials, POL-Xe-001 and POL-Xe-002, should be described.

11.2. Device Labeling

DRH identified several inconsistencies between the Applicant's proposed device labeling and prescribing information and recommended alignment. DRH recommended consolidation of the device manuals into a single manual with clarifications to facilitate a more intuitive step-by-step procedure for the entire clinical procedure. The Applicant combined the three device manuals into a single comprehensive device operator's manual and highlighted all necessary steps for the core clinical workflow.

12 Risk Evaluation and Mitigation Strategies (REMS)

A Risk Evaluation and Mitigation Strategy is not needed for hyperpolarized Xe-129.

13 Postmarketing Requirements and Commitment

As mentioned in Section 10, upon future NDA approval, the Applicant will need to develop an age-appropriate presentation of hyperpolarized Xe-129 that would allow administration of an accurate dose to pediatric patients 6 years to less than 12 years of age through a postmarketing requirement.

14 Division Director (Clinical) Comments

I concur with the findings and the recommendation by the NDA review team to indicate hyperpolarized xenon 129 for inhalational use in adults and pediatric patients 12 years of age and older for pre-operative evaluation of lung ventilation prior to lung surgery.

I concur with a complete response action for the NDA given the manufacturing deficiencies identified by the facility inspections.

15 Office Director Comments

I concur with the review team interpretation of the data submitted with this application. I concur with the recommendation of the review team and division to issue a complete response action based on the manufacturing deficiencies.

16 Appendices

16.1. References

Dregely, I, JP Mugler, 3rd, IC Ruset, TA Altes, JF Mata, GW Miller, J Ketel, S Ketel, J Distelbrink, FW Hersman, and K Ruppert, 2011, Hyperpolarized Xenon-129 gas-exchange imaging of lung microstructure: first case studies in subjects with obstructive lung disease, J Magn Reson Imaging, 33(5):1052-1062.

Ebner, L, M He, RS Virgincar, T Heacock, SS Kaushik, MS Freemann, HP McAdams, M Kraft, and B Driehuys, 2017, Hyperpolarized 129Xenon Magnetic Resonance Imaging to Quantify Regional Ventilation Differences in Mild to Moderate Asthma: A Prospective Comparison Between Semiautomated Ventilation Defect Percentage Calculation and Pulmonary Function Tests, Invest Radiol, 52(2):120-127.

He, M, SH Robertson, SS Kaushik, MS Freeman, RS Virgincar, J Davies, J Stiles, WM Foster, HP McAdams, and B Driehuys, 2015, Dose and pulse sequence considerations for hyperpolarized (129)Xe ventilation MRI, Magn Reson Imaging, 33(7):877-885.

Katz, I, J Murdock, M Palgen, J Pype, and G Caillibotte, 2015, Pharmacokinetic analysis of the chronic administration of the inert gases Xe and Ar using a physiological based model, Med Gas Res, 5:8.

Kirby, M, S Svenningsen, A Owrangi, A Wheatley, A Farag, A Ouriadov, GE Santyr, R Etemad-Rezai, HO Coxson, DG McCormack, and G Parraga, 2012, Hyperpolarized 3He and 129Xe MR imaging in healthy volunteers and patients with chronic obstructive pulmonary disease, Radiology, 265(2):600-610.

Mariano-Goulart, D, E Barbotte, C Basurko, F Comte, and M Rossi, 2006, Accuracy and precision of perfusion lung scintigraphy versus 133Xe-radiospirometry for preoperative pulmonary functional assessment of patients with lung cancer, Eur J Nucl Med Mol Imaging, 33(9):1048-1054.

Patz, S, I Muradian, MI Hrovat, IC Ruset, G Topulos, SD Covrig, E Frederick, H Hatabu, FW Hersman, and JP Butler, 2008, Human pulmonary imaging and spectroscopy with hyperpolarized 129Xe at 0.2T, Acad Radiol, 15(6):713-727.

Rao, MR, NJ Stewart, PD Griffiths, G Norquay, and JM Wild, 2018, Imaging Human Brain Perfusion with Inhaled Hyperpolarized (129)Xe MR Imaging, Radiology, 286(2):659-665.

Rayment, JH, MJ Couch, N McDonald, N Kanhere, D Manson, G Santyr, and F Ratjen, 2019, Hyperpolarised (129)Xe magnetic resonance imaging to monitor treatment response in children with cystic fibrosis, Eur Respir J, 53(5).

Schembri, GP, PJ Roach, DL Bailey, and L Freeman, 2015, Artifacts and Anatomical Variants Affecting Ventilation and Perfusion Lung Imaging, Semin Nucl Med, 45(5):373-391.

Shukla, Y, A Wheatley, M Kirby, S Svenningsen, A Farag, GE Santyr, NA Paterson, DG McCormack, and G Parraga, 2012, Hyperpolarized 129Xe magnetic resonance imaging: tolerability in healthy volunteers and subjects with pulmonary disease, Acad Radiol, 19(8):941-951.

Tan, F, M He, L Rankine, RS Virgincar, JC Nouls, S Shipes, and B Driehuys, 2018, SNR and Dose Requirements for Quantitative 6-Zone Analysis of Hyperpolarized (129)Xe Ventilation MRI, Proceedings of the International Society for Magnetic Resonance in Medicine, Paris, France.

Thomen, RP, LL Walkup, DJ Roach, ZI Cleveland, JP Clancy, and JC Woods, 2017, Hyperpolarized (129)Xe for investigation of mild cystic fibrosis lung disease in pediatric patients, J Cyst Fibros, 16(2):275-282.

Walkup, LL, RP Thomen, TG Akinyi, E Watters, K Ruppert, JP Clancy, JC Woods, and ZI Cleveland, 2016, Feasibility, tolerability and safety of pediatric hyperpolarized (129)Xe magnetic resonance imaging in healthy volunteers and children with cystic fibrosis, Pediatr Radiol, 46(12):1651-1662.

Wang, JM, SH Robertson, Z Wang, M He, RS Virgincar, GM Schrank, RM Smigla, TG O'Riordan, J Sundy, L Ebner, CR Rackley, P McAdams, and B Driehuys, 2018, Using hyperpolarized (129)Xe MRI to quantify regional gas transfer in idiopathic pulmonary fibrosis, Thorax, 73(1):21-28.

16.2. Financial Disclosure

Covered Clinical Studies: POL-Xe-001, POL-Xe-002, POL-Xe-003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 9		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Ronald Honchel, PhD Dr. Cohen signing on behalf of Dr. Honchel	OND/ORDPURM	Section: 5	X Authored ___ Approved
	Signature: Jonathan E. Cohen -S Digitally signed by Jonathan E. Cohen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011434936, cn=Jonathan E. Cohen -S Date: 2021.10.04 09:14:29 -04'00'			
Nonclinical Supervisor	Jonathan Cohen, PhD	OND/ORDPURM	Section: 5	___ Authored X Approved
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Clinical Pharmacology Reviewer	Christy S. John, PhD	OTS/OCP/DCPII	Section: 6	X Authored ___ Approved
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Statistical Primary Reviewer	Xiangmin Zhang, PhD	OB/DBI	Sections: 8.1, 8.3	X Authored ___ Approved
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Statistical Secondary Reviewer	Jyoti Zalkikar, PhD	OB/DBI	Sections: 8.1, 8.3	___ Authored X Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Deputy Division Director	Sue-Jane Wang, PhD	OB/DBI	Sections: 8, 8.1, 8.3	___ Authored _X_ Approved
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CDRH Device Reviewer	Ningzhi Li, PhD	CDRH/OPEQ/OIDRH/DRH/MREPB	Sections: 4.4, 11.2	_X_ Authored ___ Approved
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CDRH Device Reviewer	LT Nam To	CDRH/OPEQ/THT1C1	Sections: 4.4	_X_ Authored ___ Approved
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CDRH Biocompatibility Device Reviewer	Kiros Hailemariam, PhD	CDRH/OPEQ/OHT4/DHT4B	Sections: 4.4	_X_ Authored ___ Approved
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CDRH Device Team Lead	Dan Krainak, PhD	CDRH/OPEQ/OIDRH/DRH/MREPB	Sections: 4.4, 11.2	_X_ Authored _X_ Approved
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CDRH/DRH Deputy Director	Michael O'Hara, PhD	CDRH/OPEQ/OHT7/DRH	Sections: 4.4, 11.2	___ Authored _X_ Approved
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Clinical Reviewer	Amy Taylor, MD, MSH	OND/ORDPURM/DPMH	Sections: 10, 13	_X_ Authored ___ Approved
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OPQ Application Technical Lead	Eldon Leutzinger, PhD	OND/OPQ/ONDP /DNDPIII/NDPB6	Sections: 4.2	X Authored X Approved
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NDA 214375/ xenon-129 hyperpolarized (XENOVIEW)/ Xeno View System:
Multi-Disciplinary Review and Evaluation

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Lead Medical Officer	Shetarra Walker, MD, MSCR	OND/ORDPURM /DPMH	Sections: 10, 13	___ Authored _X_ Approved
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Clinical Reviewer	Brenda Ye, M.D.	OSM/DIRM	Sections: 8	_X_ Authored ___ Approved
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Clinical Team Leader and Cross-Disciplinary Team Leader	August Hofling, MD, PhD	OSM/DIRM	Sections: All	_X_ Authored _X_ Approved
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Division Director	Louis Marzella, MD, PhD	OSM/DIRM	Sections: All	___ Authored _X_ Approved
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Office Director	Charles Ganley, M.D.	OND/OSM	Sections: All	___ Authored _X_ Approved
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