Clinical Investigation Plan

Final v3.0 – 01 June 2017

A Pivotal Multi-Center, Randomized, Controlled, Single-Blinded Study Comparing the Silver Nitrate-Coated Indwelling Pleural Catheter (SNCIPC) to the Uncoated PleurX® Pleural Catheter for the Management of Symptomatic, Recurrent, Malignant Pleural Effusions

Study Number:	CS-IP-VH-14-009
Study Phase:	Pre-market device study
Investigational Product:	Silver Nitrate-Coated Indwelling Pleural Catheter
IDE/Eudamed Number:	G150146 / CIV-GB-16-07-016364
Indication:	Intermittent, long term drainage of symptomatic, recurrent, malignant pleural effusion. The device is indicated for 1) palliation of dyspnea due to pleural effusions and 2) providing pleurodesis (resolution of pleural effusion).
Sponsor:	CareFusion 2200, Inc. 75 North Fairway Drive Vernon Hills, Illinois 60061

For this study, the protocol and subsequent amendments were released as follows:

Original Protocol:	Final Version 1.0, dated 03JUN2015
Previous Version:	Final Version 2.0, dated 08OCT2015
Current Version:	Final Version 3.0, dated 01JUN2017

Compliance Statement: This study will be conducted in accordance with the Declaration of Helsinki, the clinical research guidelines established by the US Code of Federal Regulations (CFR) (Title 21, Parts 50, 54, 56, and 812; and Title 45 Part 46), the regulations and guidelines of the Therapeutic Goods Administration, the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and International Organization for Standardization (ISO) 14155 (Clinical Investigation of Medical Devices for Human Subjects - Part 1: General Requirements and Part 2: Clinical Investigational Plans). Study documents will be maintained in accordance with applicable regulations.

Sponsor's Representatives

09 JUN 2017
Kevin Burroughs, PhD — Date
Director, Research & Development
CareFusion 2200, Inc.

12 June 2017
John Ray — Date
VP, Research & Development
CareFusion 2200, Inc.

9 Jun 2017
John Roberts — Date
Associate Director, Regulatory Affairs
CareFusion 2200, Inc.

12-Jun-2017
Jim Bornick — Date
Director, Quality Assurance
CareFusion 2200, Inc.

Shayna Massi for Christine Kearney 12 Jun 2017
Christine Kearney Shayna Massi — Date
Sr. Principal Engineer, Research & Development
CareFusion 2200, Inc.

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Bruce Culleton, M.D. — Date
VP WW Medical Affairs, MPS
CareFusion 2200, Inc.

Biostatistician

Qin Pan
Associate Director, Biostatistics
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14 Jun 2017 8:34 AM -07:00

Qin Pan, PhD — Date
Associate Director, Biostatistics
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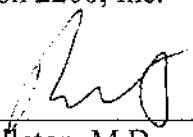

June 13, 2017

Bruce Culleton, M.D.
VP WW Medical Affairs, MPS
CareFusion 2200, Inc.

Date

Biostatistician

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Qin Pan, PhD
Associate Director, Biostatistics
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Date

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Protocol Synopsis

Sponsor:	Name of Medical Device:
CareFusion 2200, Inc.	Silver Nitrate-Coated Indwelling Pleural Catheter (SNCIPC)

Study Title: A Pivotal Multi-Center, Randomized, Controlled, Single-Blinded Study Comparing the Silver Nitrate-Coated Indwelling Pleural Catheter (SNCIPC) to the Uncoated PleurX® Pleural Catheter for the Management of Symptomatic, Recurrent, Malignant Pleural Effusions

Study Centers: This study will be conducted at approximately 17 investigational centers in the United States (US) and 3 investigational centers in the United Kingdom (UK).

Principal Investigator: Joseph B. Shrager, MD

Study Enrollment and Duration:	**Type of Study:**
Study enrollment will be approximately 12 months, or until the last patient is enrolled. Study duration will be 15 months (from first patient in to last patient out). Individual subject participation will be a total of 90 days: after catheter insertion, subjects will be evaluated at 14-day, 30-day, 60-day, and 90-day follow-up visits plus telephone assessments at 7 days, 45 days and 75 days.	Pre-market device study

Study objectives:

The **primary objective** is to demonstrate that the Silver Nitrate-Coated Indwelling Pleural Catheter (SNCIPC) shows superiority compared with the PleurX Pleural Catheter in the proportion of subjects achieving pleurodesis without recurrence at 30 days. Recurrence is defined as symptomatic pleural effusion confirmed by chest X-ray (CXR) and computed tomography (CT) scan with an estimated >300 mL of fluid in the treated hemithorax.

The **secondary objectives** of this study are to summarize measures of time to confirmed pleurodesis and time to recurrence.

For the secondary objectives, when non-inferiority is achieved, superiority will subsequently be tested to show SNCIPC superiority over the PleurX Catheter.

Methodology:

This is a prospective, multicenter, randomized, controlled, single-blinded pivotal study of the SNCIPC as compared to the PleurX Pleural Catheter when used as intended to palliate dyspnea in subjects with recurrent pleural effusions. Subjects will be recruited during consult for their procedure and will return to the study center to be randomized to receive either the SNCIPC (treatment group) or the PleurX Pleural Catheter (control group) in a 2:1 ratio on the day of the procedure. The subjects will be considered enrolled at the time

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of randomization. A trained study staff member will insert the catheter in a dedicated procedure room or operating suite, using the same technique as for insertion of the PleurX catheter. The day of indwelling pleural catheter (IPC) insertion is defined as Day 0. Subjects or their caregiver (friend, family member or paid healthcare professional) must be able to perform at-home pleural effusion drainage for up to 90 days post-catheter insertion. After IPC insertion, subjects will be evaluated at 14-day (±2), 30-day (±2), 60-day, (±3), and 90-day (±3) follow-up visits plus a telephone assessment by study center personnel at 7 (±2) days, 45 (±3) days and 75 (±3) days. In addition, subjects must call the study center to make an appointment for an unscheduled visit to assess for pleurodesis and potential IPC removal once they measure an output of ≤50 mL of pleural fluid on 3 consecutive drainages over a minimum of 5 days. Once pleurodesis is confirmed by CXR, the IPC will be removed as soon as feasible. At removal, the SNCIPC will be shipped to the designated analytical laboratory to be analyzed for residual silver content. Recurrence is defined as symptomatic pleural effusion confirmed by CXR and CT scan with an estimated >300 mL of fluid in the treated hemithorax following initially confirmed pleurodesis.

Follow-up activities:

Face-to-face follow-up visit assessments to include, as appropriate:

- Maximal catheter drainage (fluid sample retained for subjects who received SNCIPC) and CXR
- Determination of pleurodesis
- Determination of previously unidentified trapped lung (as defined in Exclusion Criterion #1)
- Record of AE(s) since last visit
- Record of further pleural interventions needed
- Assessment of recurrence post-pleurodesis
- Record of current oncological treatment
- Review of subject diary (temperature, drainage volumes, over-the-counter [OTC] and prescription medications, oxygen use, chest pain and dyspnea scores, and unplanned hospital or emergency department visits)
- Assessment of analgesia requirements
- Examination of drain insertion site (with removal of stitches if necessary)
- Physical examination (including vital signs, oxygen saturations and respiratory rate)
- EQ-5D-5L health status questionnaire
- Collection of blood samples (for subjects with SNCIPC, this includes samples for serum silver analysis)
- Serum and/or urine pregnancy test
- Record of MRU.

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Telephone assessments to include, as appropriate:

- Record of AEs since last visit
- Record of further pleural interventions needed
- Record of current oncological treatment
- Record of MRU
- Assessment of analgesia requirements
- Review of subject diary (temperature, drainage volumes, OTC and prescription medications, oxygen use, chest pain and dyspnea scores and unplanned hospital or emergency department visits)
- Assessment of pleurodesis
- EQ-5D-5L health status questionnaire.

Subject population:

Eligible subjects will be ≥ 18 years old, experiencing dyspnea secondary to recurrent malignant pleural effusions (MPE) and meet all other inclusion and exclusion criteria. Additionally, subjects or their caregiver (friend, family member or paid healthcare professional) must be capable of managing at-home pleural effusion drainage.

Diagnosis and Inclusion Criteria:

Subjects must meet all of the following inclusion criteria:

1. Male or female, at least 18 years of age, inclusive.
2. Subject has a symptomatic MPE requiring intervention. For an effusion to be defined as malignant, at least one of the following must be true:
    a. There is histocytological confirmation of pleural malignancy
    b. The effusion is an exudate (per Light's criteria) in the context of histocytologically proven malignancy elsewhere, with no other clear cause for fluid identified.
3. Subject has a history of at least 1 ipsilateral pleural effusion causing dyspnea that responded to thoracentesis where the lung expanded and the dyspnea was improved.
4. Subject is willing and able to provide written informed consent.
5. Subject is willing and able to meet all study requirements, including follow-up visits and receiving study-related telephone calls.
6. Subject has sufficient pleural fluid to allow safe insertion of an IPC.
7. Subject has negative pregnancy test if appropriate.

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8. Subject or caregiver is able to perform home drainage of the pleural effusion (a caregiver can be a friend, family member or paid healthcare professional).

Exclusion Criteria:

Potential study subjects will be excluded if 1 or more of the following exclusion criteria is present:

1. Subject has significant trapped lung, or a proximal bronchial obstruction which is likely to lead to trapped lung. For a subject to be eligible for this study, two separate study center clinicians must agree that there is no significant trapped lung on the same CXR using visual estimation (reference guide). The CXR used to make this decision must have been performed ≤30 days preceding the consent form being signed, and must have been performed preferably on the same day, but no more than 7 calendar days after a pleural drainage.

   Significant trapped lung is deemed present if any 1 of the following criteria is met:

   a) A CXR shows hydropneumothorax.
   b) A CXR shows ≥20% of the affected hemithorax to be free of the expected lung parenchymal markings and there is no suggestion of pleural fluid.
   c) A CXR shows ≥20% of the affected hemithorax to be occupied with pleural fluid AFTER a pleural aspiration which resulted in symptoms suggestive of trapped lung (e.g., chest pain or cough).

2. Subject has a Karnofsky score <50, or a World Health Organization (WHO)/ Eastern Cooperative Oncology Group (ECOG) performance status ≥3. Subjects who have a performance status of 3 may be considered for the study if the removal of their fluid would likely improve their performance score by 1 or more.
3. Subject is pregnant, planning to become pregnant, or is lactating.
4. Subject has a history of empyema.
5. Subject has a history of chylothorax.
6. Subject has an uncorrected coagulopathy.
7. Subject has a hypersensitivity to silver, silver nitrate, or silicone. For subjects with a self-reported silver hypersensitivity who wish to be considered for enrollment in the study, a confirmation test for hypersensitivity to silver nitrate will be performed.
8. Subject has evidence, in the opinion of the Investigator, of either on-going systemic or pleural infection.
9. Subject has had a lobectomy or pneumonectomy on the side of the effusion.
10. Subject has undergone a previous attempt at ipsilateral pleurodesis which has failed.
11. Subject has previously been diagnosed with a serious immunodeficiency disorder.

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12. Subject has bilateral pleural effusions, with both being at least moderate in size (greater than one-third of the hemithorax on CXR).
13. Subject has evidence of fluid loculation such that attempts at pleurodesis are likely to be futile.
14. Subject has a mediastinal shift of ≥2 cm toward the side of the effusion.
15. Subject is receiving concurrent intrapleural chemotherapy or radiation therapy to the ipsilateral chest.
16. Subject has any clinical condition, diagnosis, or social circumstance that, in the opinion of the Investigator, would mean participation in the study would be contraindicated.
17. Subject has no access to a telephone.
18. Subject has no documented blood values (complete blood count [CBC], coagulation tests, urea and electrolytes, and liver function tests [LFTs]) within the last 10 days.
19. Subject has previously participated in any clinical trial with the investigational SNCIPC device.
20. Subject currently enrolled in any other clinical investigation or who has participated in any clinical investigation in the 30 days prior to starting this study.

Number of Subjects (Planned/total for each treatment arm with an estimated/approximate statement): Approximately 119 subjects will be enrolled in the study, with subjects randomized 2:1 to receive SNCIPC and PleurX catheters (79 subjects and 40 subjects, respectively).

Test Device: SNCIPC (manufactured by CareFusion 2200, Inc.)

The SNCIPC is a pleural catheter which is indicated for palliation of dyspnea due to pleural effusions and for providing pleurodesis (resolution of the effusion). It can provide intermittent, long-term drainage of symptomatic, recurrent pleural effusion. It consists of a fenestrated silicone catheter with a proximal valve mechanism, a polyester cuff, and a barium sulphate stripe to aid visualization under fluoroscopy, identical to the PleurX catheter on which it is based. The fenestrated portion of the SNCIPC is coated with 100 mg (+/- 15 mg) of the pleurodesis agent silver nitrate ($AgNO_3$) and inert materials which control drug release.

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Control/Reference Device:
PleurX Pleural Catheter (manufactured by CareFusion 2200, Inc.)

The PleurX Pleural Catheter is a currently marketed device that provides intermittent, long-term drainage of symptomatic, recurrent pleural effusion. It consists of a fenestrated silicone catheter with a proximal valve mechanism, a polyester cuff, and a barium sulphate stripe to aid visualization under fluoroscopy.

Criteria for Evaluation:

Primary Endpoint

Primary Efficacy Endpoint

The primary efficacy endpoint will be the proportion (%) of subjects achieving pleurodesis without recurrence by 30 days after IPC placement, where pleurodesis is defined as:

- The collection of a minimum of 3 consecutive drainages of ≤ 50 mL of pleural fluid over a minimum of 5 days (which begin with the first drainage of ≤ 50 mL)

AND

- CXR, which shows opacification due to pleural fluid occupying less than one quarter of the hemithorax (as judged by the investigative study center and the blinded third party central radiology service.)

The date of pleurodesis is defined as the day on which the first of 3 consecutive drainages of ≤50 mL was recorded. Recurrence is defined as symptomatic pleural effusion confirmed by CXR and CT scan with an estimated >300 mL of fluid in the treated hemithorax. All 3 drainages and the radiological findings to confirm pleurodesis must occur within the 90-day follow-up period.

Secondary Endpoints

Secondary Efficacy Endpoints

- Time to confirmed pleurodesis
  Time to pleurodesis is defined as the duration between the study device insertion and the date a subject achieves pleurodesis.

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- Time to recurrence
  Time to recurrence is calculated for subjects who achieved confirmed pleurodesis. It is defined as the duration between successful pleurodesis (the first of a minimum of 3 consecutive drainages of ≤50 mL of pleural fluid over a minimum of 5 days) and the date subject presents with symptoms of recurrence that is later confirmed by CXR and CT scan.

Exploratory Efficacy Analysis

The following exploratory analysis will be performed comparing the two treatment groups:

- Proportion of surviving subjects without a trapped lung diagnosis following IPC placement who have confirmed pleurodesis without recurrence at 14, 30, 60 and 90 days.
- Proportion of subjects with confirmed pleurodesis and without recurrence 30 days after IPC placement by cancer type (lung, breast and others).

Safety Evaluations

The following safety evaluations will be compared between the two treatment groups:

- Device related safety and adverse events (AEs)
- Incidence of IPC occlusion
- Incidence of empyema and cellulitis

Descriptive statistics for serum and pleural fluid silver levels by time point will be provided for subjects who receive SNCIPC.

Stopping rules for safety will be defined by the Data Safety Monitoring Board (DSMB) and outlined in the DSMB charter. The stopping rules are based on safety criteria andthere will be no stopping based on efficacy criteria. The DSMB will receive notification of any expedited unanticipated adverse device effects (UADEs).

QoL and MRU Analysis

- Pain using 100 mm visual analog scale (VAS)
- Dyspnea relief (breathlessness) using Modified Borg dyspnea scale
- Health status as measured by the EQ-5D-5L health status questionnaire
- MRU data (length of procedure; hospital stay [hours]; unplanned in-hospital medical procedures as a result of IPC placement; emergency department visits related to IPC placement; length of time IPC in place; drainage schedule and frequency; frequency, dose and type [brand name/generic] of prescription and OTC

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medications; frequency and use of oxygen; services required to diagnose, treat, and follow up AEs).

Statistical Methods:

Analysis of Primary Efficacy Parameter

The primary analysis will be performed on the Intent-to-Treat (ITT) population.

The proportion of subjects achieving pleurodesis without recurrence 30 days after IPC placement and its 95% confidence interval (CI) by exact binomial method will be summarized for each treatment group. Exact unconditional CI for risk difference will be used to calculate rate difference and 95% CI. Superiority will be demonstrated when the one-sided p-value is less than 0.025.

A supportive analysis will be done using the Per-protocol (PP) population.

Analysis of Secondary Efficacy Parameters

Time to confirmed pleurodesis analysis will be performed using proportional hazards model and Kaplan-Meier time-to-event analysis. The analysis will be performed on all subjects in the ITT population, and on all subjects in the PP population as a supportive analysis. A proportional hazards model will be used to estimate the hazard ratio (HR). Non-inferiority will be established when HR > 0.7. Time to confirmed pleurodesis will be summarized by 25th percentile, median, and 75th percentile, when estimable from the Kaplan-Meier estimates for each treatment group. Kaplan-Meier curves for each treatment group will be provided. Time to confirmed pleurodesis is defined as the duration between the study device insertion and the date of confirmed pleurodesis. For subjects who do not have confirmed pleurodesis, censoring rules will be described in the SAP. Incidence density for time to confirmed pleurodesis will be evaluated between the two groups by summarizing the number of subjects in the ITT population, number of confirmed pluerodeses, number of subjects censored in the time to pleurodesis, and patient-days in each treatment group. Patient-days within the treatment group will be calculated as the total number of days from study device insertion to confirmed pleurodesis or termination of study participation summed for all subjects within the treatment group.

Time to recurrence analysis will be performed using proportional hazards model and Kaplan-Meier time-to-event analysis. The analysis will be performed on all subjects in the ITT population who had confirmed pleurodesis, and on all subjects in the PP population who had confirmed pleurodesis as a supportive analysis. A proportional hazards model will be used to estimate the hazard ratio. Non-inferiority will be established when HR < 1.3. Time to recurrence will be summarized by 25th percentile, median, and 75th percentile,

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when estimable from the Kaplan-Meier estimates for each treatment group. Kaplan-Meier curves for each treatment group will be provided. Time to recurrence is defined as the duration between confirmed pleurodesis and the date of recurrence. For subjects who do not have a recurrence after confirmed pleurodesis, censoring rules and incidence density analysis will be described in the SAP. Incidence density for time to recurrence will be evaluated between the two groups by summarizing the number of subjects with confirmed pleurodesis, number of recurrences, number of subjects censored in the time to recurrence, and patient-days in each treatment group. Patient-days within the treatment group will be calculated as the total number of days from confirmed pleurodesis to recurrence or termination of study participation summed for all subjects within the treatment group.

Following the non-inferiority test, superiority will be demonstrated when the one-sided p-value is less than 0.025 using a proportional hazards model.

Analysis of Exploratory Efficacy Parameters

The exploratory efficacy endpoints involving a proportion will be analyzed in the same fashion as the primary endpoint. These analyses involve the following endpoints:

- Proportion of surviving subjects without a trapped lung diagnosis following IPC placement and who have confirmed pleurodesis without recurrence at 14, 30, 60 and 90 days.
- Proportion of subjects achieving pleurodesis without recurrence 30 days after IPC placement by cancer type.

The proportion (%) of patients achieving pleurodesis without recurrence at 30 days will be summarized for each treatment group by cancer type (lung, breast and others). The proportions will be compared using a Cochran-Mantel-Haenszel test using the cancer type as a stratification factor. The primary analysis will be performed using the ITT population and on the PP population as a supportive analysis.

Analysis of Safety Parameters

All comparisons between treatment groups for the safety parameters will be descriptive in nature. Analyses will include duration of subject exposure to study treatment, incidence of IPC occlusion and incidence rate of empyema and cellulitis. For subjects who received SNCIPC, serum and pleural fluid silver levels will be measured at regular intervals (inductively coupled plasma mass spectrometry [ICP-MS] analysis).

AEs will be mapped to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary and will include AEs, SAEs, adverse

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device effects (ADEs), serious adverse device effects (SADEs), unanticipated adverse device effects (UADEs), and unanticipated serious adverse device effects (USADEs).

Results for clinical laboratory tests, vital signs, and physical examination findings and their change from baseline will be summarized.

Analysis of QoL and MRU Parameters

Pain and dyspnea (breathlessness) will be evaluated using the 100 mm VAS and the Modified Borg dyspnea scale, respectively. Patient-reported health status will be evaluated using the EQ-5D-5L. Comparison between the two treatment groups involving continuous variables will be done using a two-sample t-test. Change from baseline between the two treatment groups will be analyzed using a two-sample t-test. Comparison between the two treatment groups involving categorical variables will be done using the chi-square test, or Fisher's exact test if more appropriate

Comparison between the two treatment groups involving continuous variables such as length of procedure, length of hospital stay and length of time IPC in place will be done using a t-test. All other resource utilization data will be summarized as frequencies and counts.

Subgroup Analysis

If at least 80% of the total number of US subjects participating in this study are Medicare beneficiaries, then no subgroup analysis will be conducted. However, if less than 80% of all US subjects enrolled are Medicare beneficiaries, then a subgroup analysis will be conducted to evaluate outcomes specifically for the Medicare beneficiaries enrolled in the study. All primary and secondary outcomes for the subgroup analyses will be the same as for the main analysis.

Glossary of Abbreviations

Abbreviation	Definition
AE(s)	Adverse event(s)
ADE(s)	Adverse device effect(s)
$AgNO_3$	Silver nitrate
ATC	Anatomical Therapeutic Chemical
C	Celsius degree
CBC	Complete blood count
CE	Conformite Europeenne mark
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CP	Conditional power
CRO	Contract research organization
CRP	C-reactive protein
CT	Computed tomography
CXR	Chest X-Ray
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOS	End of study
F	Fahrenheit degree
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HR	Hazard Ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IDE	Investigational Device Exemption
IEC	Institutional Ethics Committee
IFU	Instructions for Use
IPC	Indwelling pleural catheter
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-treat
kg	Kilogram
LDH	Lactate dehydrogenase
LFT	Liver function tests

Abbreviation	Definition
LSLV	Last subject last visit
m	Meter
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mg/d	Milligrams per day
min	Minimum
mL	Milliliter
mm	Millimeter
MPE	Malignant pleural effusion
MRU	Medical resource utilization
N	Number of subjects
NSAID(s)	Non-steroidal anti-inflammatory drug(s)
OTC	Over-the-counter
PIS	Patient information sheet
PP	Per protocol
QoL	Quality of Life
SADE	Serious adverse device effect
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SAS	Statistical analysis software
SD	Standard deviation
SNCIPC	Silver Nitrate-Coated Indwelling Pleural Catheter
SOP	Standard operating procedure
TEAE(s)	Treatment-emergent adverse event(s)
UADE(s)	Unanticipated adverse device effect(s)
UK	United Kingdom
US	United States
USADE(s)	Unanticipated serious adverse device effect(s)
VAS	Visual Analog Scale
WHO	World Health Organization

1 Study Administration

1.1 Investigators and Study Administrative Structure

The Investigator responsible for the conduct of this study, in compliance with this clinical investigation plan (CIP), is identified on the Signature page. The Investigator will also sign the Investigator Agreement and provide it to the Sponsor or Sponsor's representative prior to receipt of the investigational device and study initiation at that investigational center.

Sponsor:	CareFusion 2200, Inc.
Clinical Project Manager:	Lydia Blank
Contract Research Organization (CRO):	Chiltern International, Ltd
Project Lead (CRO):	Neely Bagwell
Biostatistician (CRO):	Qin Pan, PhD
Safety Officer (CRO):	Riyaz Visram
Principal Investigator	Joseph B Shrager, MD

Clinical laboratory tests will be performed locally. Testing for silver in pleural fluid, serum silver, and residual silver nitrate on the removed Silver Nitrate-Coated Indwelling Pleural Catheter (SNCIPC) will be performed at a central analytical laboratory. Independent review of chest X-ray (CXR) and computed tomography (CT) scans will be performed at a central laboratory.

1.2 Institutional Review Board/ Institutional Ethics Committee Approval

The Investigator agrees that the study will be conducted according to the CIP and the principles of Good Clinical Practice (GCP), International Organization for Standardization (ISO), and provided in the International Conference on Harmonisation (ICH) guidelines governing clinical study conduct.

The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the pertinent regulatory authorities.

The CIP, any CIP amendments, the informed consent form (ICF), and all other forms of subject information related to the study and any other necessary documents will be reviewed by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

It is required that a valid IRB/IEC approves, in writing, the conduct of this clinical study, together with the ICF to be used at the respective investigational study center, prior to study initiation.

The Investigator will submit the protocol and ICF for IRB/IEC review. This will be appropriately documented. The IRB/IEC should be asked to give its approval in writing. The names and qualifications of the members of the review committee will be recorded and submitted to the Sponsor, together with the written approval for the conduct of the study. The members of the

IRB/IEC must be independent of the Sponsor and the Investigator. The written approval should consist of a completed IRB/IEC approval form or written documentation from the IRB/IEC containing the same information.

Until written approval by the IRB/IEC at an investigational study center has been received by the Sponsor, no subject at that study center may undergo any procedures solely for the purpose of determining eligibility for this study.

CIP amendments must also be reviewed and approved by the IRB/IEC and written approval from the committee or at least the chairperson (or a designated committee member) must be received by the Sponsor before implementation. This written approval will consist of a completed IRB/IEC approval form or written documentation from the IRB/IEC containing the same information. Any additional requirements imposed by the IRB/IEC or regulatory authority shall be followed, if appropriate.

1.3 Ethical Conduct of the Study

The study will be conducted in compliance with the following:

- the protocol
- ethical principles of the Declaration of Helsinki and its amendments
- the principles of the GCP provided in the ICH Harmonised Tripartite Guidelines for GCP, 1996
- the latest revision of the ISO guidelines
- all applicable national laws and regulations including country-specific GCP.

1.4 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to each subject, and answer all questions regarding this study, prior to obtaining informed consent. Study consent must be taken by a medical member of the study team.

The Investigator will obtain informed consent from each subject prior to being enrolled in the study, in accordance with the current version of the GCP guidelines and the laws and regulations of the country in which the investigation is being conducted.

The IRB/IEC must approve the ICF to be used by the Investigator prior to its use. It is the responsibility of the Investigator to assure that the subject has signed the ICF before any activity or treatment is undertaken. This includes, but is not limited to, the performance of diagnostic or therapeutic procedures and the placement of the IPC. The document may be further updated if new important information becomes available that may affect subject’s willingness to participate or continue in the trial.

1.5 Subject Confidentiality

Adequate records must be maintained for the study, including patient medical records, electronic case report forms (eCRFs), laboratory reports, worksheets, nursing notes, signed ICFs, product forms, SAE forms, and information regarding subject discontinuation and reasons for discontinuation. The confidentiality of each record with subject identification is to be guaranteed by the clinical Investigator. Personal medical information may be reviewed by the study monitor, properly authorized persons on behalf of the sponsor, or regulatory authorities for the purpose of verifying data recorded on the eCRF. Personal medical information will always be treated as confidential.

Anonymous subject identifiers are established within eCRFs and other study documents, including image material, that do not disclose protected health information to the Sponsor, CRO or Imaging Core Lab. Study information stored electronically is only available to study personnel directly involved in the study. Study information stored in any database must be in a password-protected database. Information gathered will not be reused or disclosed to any other person or entity or for research other than as detailed within this document. Once the research has been completed, subject study information maintained at the study site will be retained for as long as is required by law or regulations and at that point will be destroyed.

This CIP and other study documents contain trade secrets and commercial information that is privileged and confidential. Such information is not to be disclosed unless required by laws or regulations. The Investigator agrees to use this information only in conducting this study and is not allowed to use it for other purposes without written consent from the Sponsor. Results obtained from this study as well as any blood, tissue sample, or fluid collected for this study in accordance with the protocol, are the property of the Sponsor.

1.6 Compensation, Insurance, and Indemnity

Information regarding compensation, insurance, and indemnity will be provided to the Investigator in the Clinical Trial Agreement. Country-specific insurance will be obtained in accordance with local regulations.

1.7 Study Monitoring

For protocol monitoring and compliance, an investigational center visit will be held prior to initiation of subject enrollment. The CIP, eCRFs, study supplies, and study procedures will be explained in detail.

The purpose of monitoring is to verify the rights and well-being of human subjects are protected; that study data are accurate, complete, and verifiable with source data; and that the study is conducted in compliance with the protocol, GCP, and the applicable regulatory requirements.

A monitor assigned by the CRO will conduct regular investigational center visits for the purpose of study monitoring per the monitoring plan.

The Investigator must agree to allow the study monitor and authorized representatives of Chiltern or the Sponsor to inspect all eCRFs and corresponding source documents (e.g., original medical records, patient records and laboratory raw data); to allow access to the clinical supplies, dispensing, and storage areas; and to agree to assist with their activities, if requested. The Investigator should provide adequate time, availability, and space for monitoring visits.

The monitor will query any missing or spurious data with the Investigator, which should be resolved in a timely manner. A monitoring log will be maintained to record each visit, the reason for the visit, the monitor's signature, and the Investigator's or designee's confirmation signature.

1.8 Case Report Forms and Study Records

The Investigator agrees to retain copies of the eCRFs with other study documents (e.g., the CIP and any amendments, the Summary of Product Characteristics, IRB/IEC approval, signed consent forms, and source documents for each subject in the study [e.g., all demographic and medical information, including laboratory data, electrocardiograms, medication disposal and subject diaries]) in a secure place for a minimum of 2 years after receiving written notification from Sponsor that investigational device has been cleared for marketing. These records must be made available for inspection upon reasonable request by a representative of the Sponsor or regulatory authorities.

Subject source documents are the physician's records maintained at the investigational center. The information collected on the eCRF must match the information found on the charts.

The eCRF data will be collected electronically. Instructions for entering data via internet will be provided in the eCRF Completion Guidelines and training will be provided to the investigational center staff prior to initiation of the center.

Periodically, where appropriate, the Monitor or other authorized Sponsor personnel will visit the investigational center for the purpose of comparing the data on the eCRF with the source documents. The Investigator agrees to make source documents available for this purpose. The eCRF should be completed as soon as possible after the data are available.

In the event the Investigator retires, relocates, or for any other reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records will be transferred to any other person who accepts responsibility for the records, e.g., the Sponsor, an IRB/IEC, or another Investigator. Notice of such transfer will be provided in writing to the Sponsor.

1.9 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be responsible for recommending whether changes to the study may be required and whether to continue or terminate the trial as established in its stopping rules. Stopping rules will be defined by the DSMB and outlined in the DSMB charter. The stopping rules are based on safety criteria and there will be no stopping based on efficacy criteria.

The DSMB will receive notification of any expedited unanticipated adverse device effects (UADEs). A consideration for holding a review meeting or stopping further enrollment to the trial may be made if there is:

- an unanticipated patient death definitely or probably related to the device, or
- there is a pattern of serious toxicity clearly related to the device as assessed by the DSMB members based on the severity of disease of the enrolled population. Such a toxicity pattern must be different from what might be expected from those events associated with progression of the patient's disease.

The DSMB may provide additional considerations as outlined in the DSMB charter. In order to ensure that the DSMB will be fully informed while reviewing UADEs, serious toxicity or any other safety concerns related to the device, the DSMB will be unblinded in its assessment of this safety data. The DSMB will develop a consensus on its list of recommendations, including that relating to whether the trial should continue.

In the absence of notifications of UADEs or serious safety related concerns, DSMB will schedule regular meetings at a frequency outlined in the DSMB charter.

The Sponsor will be responsible for deciding whether to amend the protocol, to continue or to stop the trial based on the DSMB recommendations.

1.10 Termination of the Study

The Sponsor reserves the right to terminate this study prematurely, either in its entirety or at a specific study center, for reasonable cause provided that written notice is submitted a reasonable time in advance of the intended termination. The Investigator may also terminate the study at their study center for reasonable cause, after providing written notice to the Sponsor a reasonable time in advance of the intended termination. Neither party requires advance notice if the study is stopped due to safety concerns. If the Sponsor chooses to terminate the study for safety reasons, it will immediately notify the Investigator and subsequently provide written instructions for study termination. Subjects who have not completed treatment in the study at the time of termination will be advised and offered alternative treatment, as medically appropriate.

1.11 Publication Policy

Study information is considered confidential and may not be published or otherwise disclosed without permission from the Sponsor. At a minimum, study results will be published on www.clinicaltrials.gov on all primary and secondary outcomes, no later than 1 year after completion of the trial (including completion of the trial if it has been terminated early).

1.12 Financial Disclosure

Consistent with Title 21 CFR Part 54, all Investigators will complete a Financial Disclosure Form that permits the Sponsor to demonstrate that an Investigator has no personal or professional

financial incentive regarding study outcome or the future approval or disapproval of an investigational device such that the Investigator's research might be biased by such incentive.

1.13 Personnel Responsibilities

1.13.1 Investigator(s)

The following are the responsibilities of the Investigator(s):

1. Permit Sponsor representatives to inspect facilities and records.
2. Submit CIP and ICF to the IRB/IEC and await approval.
3. Submit proposed amendments to the CIP and ICF to the IRB/IEC and await approval, unless the change reduces the risk to subjects.
4. Obtain signed ICF from each subject prior to subject enrollment.
5. Maintain subject blinding regarding the randomization arm to which they are assigned, throughout the study.
6. Enroll subjects, execute study, transcribe data from source documents to case report forms.
7. Address questions and/or inconsistencies reported on the eCRFs.
8. Submit annual progress reports, final reports and AE reports to IRB/IEC and to Sponsor.
9. Maintain device accountability throughout the study, including recording their receipt, use, disposition and return of all devices at the end of the study.
10. Conduct study in accordance with the CIP and in compliance with GCP.
11. Maintain medical histories of subjects.
12. Retain study records for a minimum of 2 years after receiving written notification from Sponsor that the investigational device has been cleared for marketing.

1.13.2 Institutional Review Board/Institutional Ethics Committee

The following are the responsibilities as defined by IRB/IEC policies:

1. Review and approve, modify or disapprove the study CIP.
2. Receive annual and final reports on study progress.
3. Review and approve, modify or disapprove the ICF.

1.13.3 Sponsor and/or Designee

1. Submit and obtain an approved Investigational Device Exemption (IDE) from Food and Drug Administration (FDA) prior to initiating this study.
2. Ensure study is conducted in accordance with the CIP and GCP.

3. Assure IRB/IEC approval of the CIP and ICF is obtained.
4. Select Investigators.
5. Review prospective Investigator curriculum vitae (CVs) and qualify Investigators for the study.
6. Obtain investigator agreement and financial disclosure for all study personnel for which it is required.
7. Provide the devices to the study centers as needed.
8. Conduct day-to-day administration of study.
9. Investigate unanticipated AEs.
10. Document CIP deviations.
11. Submit required reports to FDA and other regulatory agencies as applicable.

2 Introduction and Study Rationale

Pleural effusions, or excess fluid build-up between the pleural linings of the lung, affect over 1 million people in the United States annually.[1] While some effusions are asymptomatic, most result in significant breathlessness for patients. Of these, over 150,000 effusions are secondary to a malignancy,[1,2] and most of those are recurrent and unresponsive to traditional medical management. The prognosis for patients with malignant pleural effusion (MPE) is nearly always poor, with average life expectancy following diagnosis of 4-6 months.[1]

Treatment for MPE has traditionally focused on three approaches: repeat thoracentesis, chemical pleurodesis, or placement of an IPC. Although a single thoracentesis procedure is the least invasive and least expensive option, relief is usually short lived. Repeated thoracentesis is possible, but requires the subject to visit the clinic frequently in order to manage their symptoms. This approach does not lead to consistent symptom control, increases risks of infection, and is particularly time consuming for patients with a short life expectancy.

The most commonly used alternative, chemical pleurodesis, is intended to fully resolve the effusions but requires a typical in-patient hospital stay of 4 to 9 days[2,3] and may result in significant pain and fever following the introduction of the pleurodesis agent. The agent is usually introduced via a chest tube (inserted under local anesthetic) or insufflated during thoracoscopy (which may be performed under sedation or general anesthetic). The most commonly used agent for pleurodesis worldwide is talc.[1,2,4] Although talc is effective, it still fails to achieve pleurodesis in a significant proportion of patients. Additionally, even for those talc patients who initially achieve pleurodesis, up to 30% have recurrence after 30 days.[1,4] Silver nitrate has also been used and studied extensively for pleurodesis, both in animals and in humans. From 1932 to 1983, silver nitrate was one of the primary agents to initiate pleurodesis for pneumothorax and other conditions, including pleural effusions.[5-10]

More recently, a clinical study in 2005 showed silver nitrate to be effective in achieving pleurodesis with minimal side effects.[11]

In 2007, a clinical study of over 600 subjects showed silver nitrate to be effective in achieving pleurodesis.[12] By contrast, an IPC is typically placed on an out-patient basis using local anesthesia, and can be used to drain a recurrent pleural effusion at home by the patient or caregiver using vacuum bottles. The market-leading IPC is the PleurX Pleural Catheter, manufactured by CareFusion, Inc. It is currently indicated for both the palliation of dyspnea due to pleural effusion and for providing pleurodesis.

The ideal approach to managing MPE, therefore would be to reliably and permanently resolve effusions (i.e., achieve pleurodesis), in a short period of time and in an out-patient setting, with lower levels of pain and lower costs. This is particularly true if the outpatient management of MPE can provide equivalent or even favorable quality of life (QoL) results compared to other (inpatient) treatment options without negatively impacting mortality.[13]

In addition to the cost-savings, outpatient treatment, when possible, is important because patients with MPE are older, on average (between 60 to 67 years old)[13-16] with a relatively a short life expectancy. Although the PleurX catheter is currently indicated for pleurodesis, its rate of achieving pleurodesis is typically lower than that of talc (46% in a median of 26.5 days and mean of 56 days[14] for PleurX vs 78% talc insufflation pleurodesis success at 30 days).[4] Furthermore, the average time required to achieve pleurodesis using PleurX (around 2 months)[14] is less than optimal for clinicians and patients who desire both a timely and definitive resolution of the pleural effusion symptoms. The SNCIPC has been designed with the aim of enhancing the PleurX pleural catheter's pleurodesis performance by the addition of an established pleurodesis agent, silver nitrate. A secondary benefit to this approach for the relatively small proportion of patients who potentially may not achieve pleurodesis even with the addition of silver nitrate is the ability for those patients to still drain the pleural effusions through the same catheter, without the need for an additional invasive procedure.

2.1 PleurX Indwelling Pleural Catheter System

The PleurX pleural catheter first received FDA clearance and Conformite Europeenne (CE) marking in 1997 through 510(k) K971753 and TUV certificate G1 11 06 70837 016, respectively. The safety and effectiveness of the PleurX product line was originally established following a clinical study (IDE G930085) performed by Putnam et al. from 1994 to 1997 and since this time, physicians around the world have gained considerable experience using pleural catheters in both in-patient and out-patient settings.[14] The Putnam study was also able to support the literature which suggested that pleurodesis could be achieved more readily if the pleural space was well drained, keeping the pleura in close apposition. In that study, 42 of 91 (46%) subjects treated with an IPC achieved pleurodesis within 8 to 223 days (median = 26.5, mean = 56 days). Four subsequent studies of the PleurX pleural catheter yielded pleurodesis rates of 41 to 59% within median times of 39 to 90 days[17-20], leading to the conclusion that although an uncoated PleurX pleural catheter can achieve pleurodesis, it is likely to do so in a timeframe and at rate of occurrence that is variable and less than optimal for some subjects.

The primary PleurX pleural catheter material is silicone, which includes a stripe of barium sulphate to aid visualization under fluoroscopy. The indwelling portion of the catheter includes multiple fenestrations to help collect the excess pleural fluid to be drained, as well as a polyester cuff that allows tissue in-growth near the skin to help reduce infection. The external portion of the catheter includes a valve at the proximal end, which is used to seal the catheter when not in use and allow controlled access during drainage (Figure 2-1; for the purposes of this document, distal is defined as furthest away from the clinician and proximal is defined as closest to the clinician).

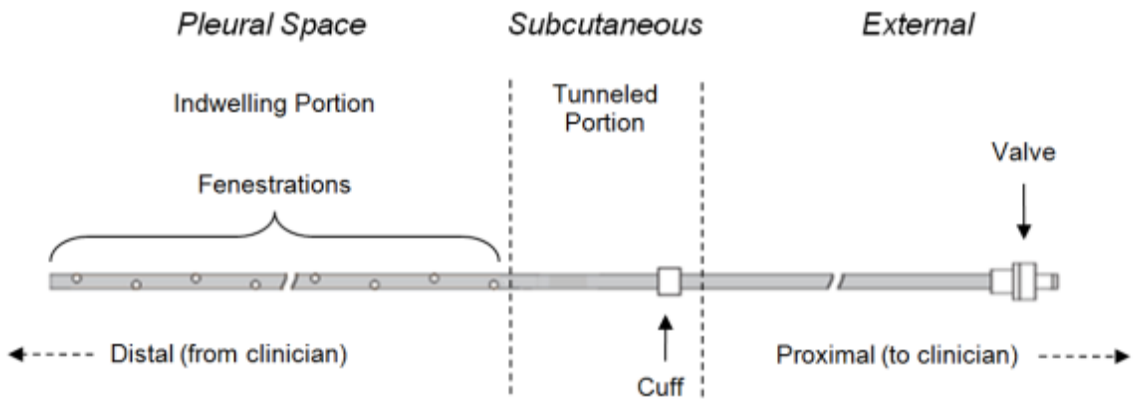


Figure 2-1. The PleurX indwelling pleural catheter

As noted above, the PleurX pleural catheter is FDA cleared and CE marked for both palliation of dyspnea associated with pleural effusions and for pleurodesis. In clinical practice, the current PleurX product is most commonly used to palliate symptoms associated with recurrent pleural effusions in terminal cancer patients.

2.2 Silver Nitrate-Coated Indwelling Catheter System

Silver nitrate has been used and studied extensively for pleurodesis, both in animals and in humans.[5-12, 21-33] The addition of a silver nitrate coating to the PleurX pleural catheter is expected to create a more consistent pleural layer inflammatory response, and thereby reduce the variability and overall timeframe in which the PleurX pleural catheter achieves pleurodesis. From 1932 to 1983, silver nitrate was one of the primary agents to initiate pleurodesis for pneumothorax and other conditions, including pleural effusions.[5-10]

More recently, a clinical study in 2005 showed silver nitrate to be effective in achieving pleurodesis with minimal side effects, utilizing half the dose typically used in earlier studies (i.e. 100 mg vs. 200 mg).[11]

A clinical study of over 600 subjects in 2007 showed silver nitrate to be effective in achieving pleurodesis, utilizing a relatively high dose of 1000 to 1500 mg.[12] Beginning in the early 1990s, new research was conducted to see if lower concentrations (doses) of silver nitrate could still be effective, with the intention of reducing past side-effects associated with the agent which often included pain. The research showed that lower doses could indeed still produce pleurodesis, while reducing the side effects.[24, 27, 28] Several animal studies since 1995 have also confirmed the safety and efficacy of lower-dose silver nitrate for pleurodesis when compared with other pleurodesis agents that are more commonly used today.[24-32]

Silver nitrate has also been used as an antimicrobial, a cautery agent, and to treat warts.[34]

A pilot clinical trial was also conducted to evaluate the investigational SNCIPC device. The SEAL-MPE Trial was a Pilot Study Evaluating the Initial Safety and Efficacy of the Silver Nitrate-Coated

Indwelling Pleural Catheter for the Medical Management of Symptomatic, Recurrent, Malignant Pleural Effusions. This single study center, single-arm investigation was the first use of this device with enrollment of 10 patients and was conducted at Southmead Hospital, in Bristol, UK.

The purpose of the pilot study was primarily to provide data regarding the safety of the SNCIPC in patients suffering with recurrent, symptomatic MPE. However, clinical effectiveness and performance characteristics of the SNCIPC were also assessed. The primary endpoint was to evaluate device-related safety and AEs. Secondary endpoints included breathlessness and chest pain (as measured by visual analog scale [VAS]); pleurodesis success at 14, 28 and 60 days; time to pleurodesis; QoL as measured by the EQ-5D-5L health status questionnaire; serum and pleural fluid silver levels; and to assess the need for further pleural intervention post-IPC removal. Overall, the results indicated that there were no safety concerns that would prevent the device from moving onto the larger, multi-center, pivotal clinical trial being proposed. There were no unanticipated serious adverse device effects (USADEs) reported during the 60-day follow-up period. The pilot study findings and observations were used to inform the design of the proposed pivotal trial. Further details on results of this study are discussed in the Report of Prior Investigations.

In summary, published data and preliminary results of the unpublished pilot study suggest that silver nitrate is effective in achieving pleurodesis and that lower doses than those used historically are likely to improve its safety profile for this indication. This clinical investigation will evaluate the safety and performance of SNCIPC, a modified PleurX catheter which contains a silver nitrate coating on the indwelling portion of the catheter to enhance pleurodesis.

An overall image and detailed description of the device is provided in Section 6.

3 Study Purpose/Objectives

The primary objective is to demonstrate that the SNCIPC Pleural Catheter shows superiority compared with the PleurX Pleural Catheter in the proportion of subjects achieving pleurodesis without recurrence at 30 days. Recurrence is defined as symptomatic pleural effusion confirmed by CXR and computed tomography (CT) scan with an estimated >300 mL of fluid in the treated hemithorax.

The secondary objectives of this study are to summarize measures of time to confirmed pleurodesis and time to recurrence.

For the secondary objectives, when non-inferiority is achieved, superiority will subsequently be tested to show SNCIPC superiority over the PleurX Catheter.

The following exploratory objectives will be evaluated including device safety, device performance, quality of life (QoL) and medical resource utilization (MRU).

4 Investigational Plan

4.1 Overall Design and Plan of the Study

This is a prospective, multicenter, randomized, controlled, single-blinded pivotal study of the SNCIPC as compared to the PleurX Pleural Catheter when used as intended to palliate dyspnea in subjects with recurrent pleural effusions. The study is designed to provide powered evidence that the SNCIPC shows superiority compared to PleurX Pleural Catheter in the proportion of subjects achieving pleurodesis without recurrence at 30 days.

The SNCIPC is equivalent to the predicate device (PleurX Pleural Catheter) in design, materials, manufacturing, intended use, and preclinical test results, with the exception of the added silver nitrate coating. The silver nitrate coating is intended to enhance the pleurodesis-inducing properties of the IPC.

Eligible subjects will have undergone at least 1 successful lung expansion after thoracentesis and are experiencing a reoccurrence of pleural effusions that are causing dyspnea. Subjects or their caregiver (friend, family member or paid healthcare professional) must be able to perform at-home pleural effusion drainage for up to 90 days post-IPC insertion. Clinicians, caregivers and patients will be adequately trained to ensure that the drainage procedure and measurement of drainage volumes will be consistent.

Subjects will be recruited during consult for their procedure and will return to the study center to be randomized to receive either the SNCIPC (treatment group) or the PleurX Pleural Catheter (control group) in a 2:1 ratio on the day of the procedure. Subjects will be considered enrolled at the time of randomization. A trained study staff member will insert the IPC in a dedicated procedure room or operating suite using the same technique as for insertion of the PleurX catheter. At the time of insertion, the pleural cavity should be maximally drained (as limited by subject signs or symptoms). The day of IPC insertion is defined as Day 0. Subjects should have a post-insertion CXR (posterior-anterior and lateral) within 6 hours of the procedure concluding, but after they have been maximally drained. Assessments for trapped lung should be done at Day 14 and Day 30 post insertion.

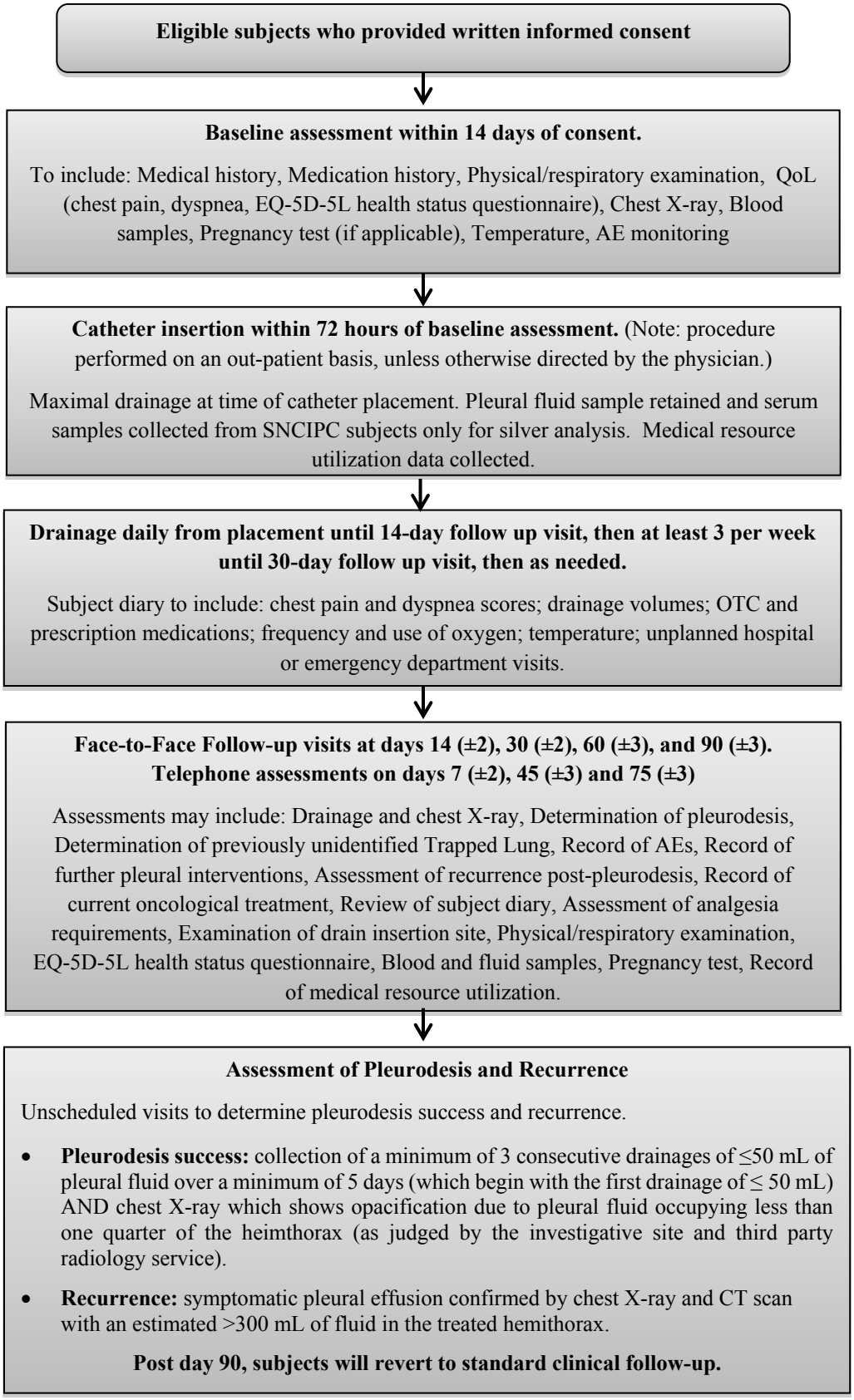
After IPC insertion, subjects will be evaluated at 14-day (± 2), 30-day (±2), 60-day (±3), and 90-day (±3) follow-up visits plus telephone assessments by study center personnel at 7 (±2) days, 45 (±3) days and 75 (±3) days.

In addition, subjects must call the study center to make an appointment for an unscheduled visit to assess for pleurodesis and potential IPC removal once they measure an output of ≤50 mL of pleural fluid on 3 consecutive drainages over a minimum of 5 days. Once pleurodesis is confirmed every effort should be made to schedule IPC removal as soon as feasible. At the time of SNCIPC removal, the SNCIPC should be shipped to the designated central analytical laboratory for residual silver testing.

Safety and efficacy assessments will be performed as noted in the Schedule of Procedures and Assessments (Section 7.1).

End of study (EOS) is defined as the date the last subject completes the last visit of the study (LSLV).

Figure 4-1. Study Flow Diagram



4.2 Risk/Benefit and Ethical Assessment

4.2.1 Description of Patient Population

The patients likely to be considered for eligibility in this study typically have end-stage cancer, are on average between 60 to 67 years old, and may have additional significant health issues that could be secondary to the malignancy. Eligible subjects will be ≥ 18 years old (male or female), experiencing dyspnea secondary to recurrent MPE, who are capable of managing at-home pleural infusion drainage and meet all other inclusion and exclusion criteria as defined in the study protocol (Section 5). A targeted total of 119 subjects will be enrolled in the investigation. Information regarding sample size justification is described in Section 10.6.

4.2.2 Justification for Investigation

The proposed clinical investigation presented in this IDE application involves the use of the SNCIPC investigational medical device. The SNCIPC investigational device is a modification to the PleurX catheter (a previously FDA cleared IPC).

The use of IPCs to manage MPE is well established in clinical practice. They have two purposes: to provide a means of draining large volumes of pleural effusion in the patient's home or outpatient setting, thereby reducing dyspnea, and to induce pleurodesis in some patients. This pleurodesis is thought to be induced by the presence of the catheter through mechanical irritation of the pleural surfaces and keeping the pleural space dry through repeated drainages. It results in a closure of the pleural space which eliminates the effusion and related symptoms. There are a number of IPCs available in the US market as FDA cleared devices for this use. The proposed investigation is designed to provide evidence of safety and efficacy of a modified FDA cleared IPC (510 [k] K121849), the PleurX catheter (CareFusion 2200, Inc.).

The modification associated with the SNCIPC investigational device involves the application of the silver nitrate coating that enhances the pleurodesis-inducing properties of the catheter. The device description (Section 6.1) provides further details on the silver nitrate coating.

The intention is that the SNCIPC investigational device will increase clinical utility by providing clinically significant improvements in time to pleurodesis, as well as the likelihood of pleurodesis in the patient.

4.2.3 Scientific Soundness and Ethical Considerations

This study is designed to provide scientifically sound data to support conclusions about the safety and effectiveness of the SNCIPC in subjects with symptomatic, recurrent MPE. Measures taken to ensure that the study provides scientifically valid data and to minimize potential bias are as follows:

1. Subject selection, study procedures and endpoints are prospectively defined in a detailed clinical investigational plan.

2. To address issues of potential bias, subjects are randomly assigned to treatment with either the SNCIPC or PleurX control device and subjects remain blinded to the treatment assignment throughout the study duration.
3. Standardization of the primary outcome measure. The primary study effectiveness endpoint, pleurodesis, is an objective measurement obtained independently by trained research personnel using drainage volumes and CXR.
4. Non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and other anti-inflammatory agents are tracked during the study, as well as other medications and supplements.
5. Subject blinding will be maintained through the study duration.
6. Standardized eCRFs will be used for all subjects to ensure uniform data collection.

4.2.4 Anticipated Benefits to Study Subjects

The use of the SNCIPC device is expected to both increase the proportion of patients who achieve pleurodesis and to reduce the time in which pleurodesis occurs, when compared to a standard IPC. The clinical benefits anticipated from the SNCIPC and its potential early removal once pleurodesis is attained are as follows:

- Improved patient QoL
- Reduced risk of pleural infection
- Reduced risk of procedure site infection
- Reduced risk of IPC-related pain.

4.2.5 Anticipated Risks to Study Subjects

4.2.5.1 Treatment Related Anticipated Adverse Events

Anticipated AEs are those AEs which are anticipated to occur during this clinical trial and are believed to be consistent with those associated with the study population, the IPC insertion procedure or pleural effusion drainage, or those which have been identified by CareFusion as part of their risk assessment. These risks are well understood for any IPC placement, and are not necessarily unique to the SNCIPC.

The following are anticipated AEs and should be recorded. This list is not exhaustive; any other AE which is considered by the Investigator to be relevant should also be recorded. If an expected AE meets the criteria for a serious AE (SAE) then it should also be recorded and reported to the designated CRO and to the ethics committee as described in Section 8.3.

Associated with IPC insertion procedure (including initial drainage), and removal procedure:

- Catheter site bleeding after skin closure following placement, requiring treatment beyond redressing or application of pressure
- Chest pain/ discomfort related to the insertion (and initial drainage) procedure, requiring treatment beyond oral analgesia
- Hypersensitivity reaction to either local anesthetic, conscious sedation (if used), or general anesthetic
- Accidental or non-accidental damage to catheter due to placement technique
- Catheter dislodgement after insertion which results in cuff migration through the skin incision
- Damage to underlying lung or other viscera during placement
- Surgical emphysema which either causes patient symptoms or requires treatment
- Pleural fluid leakage or ooze from insertion site requiring intervention
- Wound dehiscence requiring intervention
- Persistent hemodynamic compromise unresolved after basic measures
- Pneumothorax/ hydropneumothorax on post-insertion CXR, requiring intervention
- Need to remain in hospital after insertion for reasons related to trial participation
- Re-expansion pulmonary edema requiring treatment
- Hemothorax, as defined by a pleural fluid hematocrit ≥50% of the blood hematocrit
- Catheter site bleeding after skin closure following removal, requiring treatment beyond redressing or application of pressure
- Catheter removal site infection (as defined by the presence of either erythema or discharge in association with the removal site) requiring treatment
- Chest pain/ discomfort related to the catheter removal procedure, requiring treatment beyond oral analgesia
- Inability to remove catheter without causing undue distress.

Associated with the on-going placement and drainage of the IPC:

- Catheter site bleeding after skin closure, requiring treatment beyond redressing or application of pressure
- Catheter site infection (as defined by the presence of either erythema or discharge in association with the insertion site) requiring treatment

- Pleural infection (as defined by the presence of any of the following: positive pleural fluid culture; purulent pleural fluid; clinical signs and test results consistent with pleural infection)
- Chest pain/ discomfort related to the insertion procedure, requiring treatment beyond oral analgesia
- Other pain associated with position or repeated drainage of the catheter, requiring treatment beyond simple analgesia (paracetamol, NSAIDs, weak opiates)
- Accidental or non-accidental damage to catheter during use
- Catheter dislodgement which results in cuff migration through the skin incision
- Hypersensitivity reaction to associated dressings, requiring treatment
- Surgical emphysema which either causes patient symptoms or requires treatment
- Pleural fluid leakage or ooze from insertion site requiring intervention
- Wound dehiscence requiring intervention
- Persistent hemodynamic compromise unresolved after basic measures
- Pneumothorax/ hydropneumothorax on post-insertion CXR, requiring intervention
- Procedure tract metastasis, as defined as a new subcutaneous nodule >1 cm in diameter (that is not considered to be granulation tissue) within 5 cm of a relevant incision site
- Hemithorax, as defined by a pleural fluid hematocrit ≥50% of the blood hematocrit
- Re-expansion pulmonary edema requiring treatment
- Pleural fluid loculation, as seen on thoracic ultrasound or CXR, resulting in either:

  a) an increase in symptoms or

  b) a reduction in drainage output not considered to be due to pleurodesis or drain blockage to such an extent such that the Investigator would consider device removal or the administration of intrapleural fibrinolytics.

Associated with trial participants' underlying malignancy:

- Death or hospital admission due to disease progression or complication(s) of said disease
- Symptoms attributable to side effects of medications used for control of underlying malignancy, or symptoms caused by it, leading to hospital admission or death.

4.2.5.2 Anticipated Adverse Device Effects

- Allergic reaction
- Transient pain
- Increased production of pleural fluids shortly after catheter placement leading to increased dyspnea and/ or pain

- Coated portion of catheter placed in the tunnel resulting in pain/ irritation
- Catheter/ valve malfunction resulting in fluid leakage or pneumothorax and leading to catheter removal
- Coating damage during placement resulting in difficulty feeding through peel-away sheath, change in the drug elution profile, or some top-coat being left in the body after catheter removal
- Catheter cut by physician during catheter placement resulting in a lower dose of silver nitrate, a change in elution profile, or cause the coating to be left in the body when the catheter is removed
- Occlusions of the drainage system (drainage bottle or drainage line) resulting in the need for another drainage bottle or line to be used
- Catheter occlusion resulting in the physician needing to perform a flushing procedure or removing the catheter
- Silver nitrate left in tunnel from placement procedure resulting in limited tissue ingrowth to the cuff
- Encasement of catheter/ loculation of pleural space resulting in the inability to fully drain the space and requiring another intervention
- Failures related to drug content and elution
    - Wrong dosage (outside specified range) resulting in pain if too high or lower pleurodesis effect if too small
    - Non-homogenous silver nitrate coating resulting in highly concentrated silver nitrate causing tissue damage or bleeding in the pleural space
    - Wrong elution curve resulting in pain if too fast or lower pleurodesis effect if too slow
    - Effects of silver nitrate on the pleural space including increased pleural effusion leading to increased dyspnea and pain associated with the therapeutic effect of the device
- Effects of the coating on catheter mechanical properties including a reduction in catheter strength causing tears or rips during removal, a reduction in valve sealing properties causing fluid leakage or pneumothorax
- Premature catheter removal when pleurodesis is incorrectly assumed leading to dyspnea and need for further intervention
- Effect of unblocking the catheter on pleurodesis when a fibrinolytic agent used to unblock the catheter decreases the pleurodesis effect
- Silver nitrate coating affected by light exposure causing degradation that reduces the pleurodesis effect
- Biocompatibility including leachables/ extractables leading to a patient reaction to the device.

4.2.6 Mitigation Efforts

The following features of the design and manufacturing/ quality control are intended to minimize the occurrence and/or impact of the anticipated adverse device effects (ADEs) noted above should they occur.

Coated portion of catheter placed in the tunnel: The coated portion of the device has been limited in length to just beyond the most proximal fenestration in order to reduce the likelihood of leaving the coated portion of the catheter in the tunnel tract.

Catheter/ valve malfunction: The catheter and valve have undergone stringent design testing, and are manufactured under Good Manufacturing Practice (GMP) to ensure the highest quality standards.

Coating damage during placement: The choice of the top-coat polymer material is intended to simultaneously control the release of the silver nitrate and ensure durability for the typical forces and stresses applied during the placement procedure. The coated catheter has undergone design testing to ensure the coating is not damaged during placement.

Catheter cut by physician: Physicians are trained and instructed (per instructions for use [IFU]) not to cut the tip of the catheter during tunneling. In addition, this protocol specifically calls out the placement procedure (which does not include cutting of the catheter tip).

Occlusions of the drainage system (drainage bottle or drainage line): Occlusions of the drainage system, including the bottle or drainage line are easily managed by use of additional bottles or replacement of the drainage line. This can be performed at home without the need to return to the hospital. Patient follow-up occurs at regular intervals, and will assist in mitigation of this risk. Proper instruction is given to all patients when an IPC is placed to ensure they are capable of managing the effusion at home.

Catheter occlusion: Catheter occlusion may occur due to patient physiology. The Catheter Access Kit is intended to assist in clearing blockages or obstructions within the catheter without the need to remove the catheter.

Silver nitrate in tunnel: The choice of the top-coat polymer material is intended to simultaneously control the release of the silver nitrate and ensure durability for the typical forces and stresses applied during the placement procedure. The coated catheter has undergone design testing to ensure the coating is not damaged during placement resulting in being left in the tunnel.

Encasement of catheter/ loculation of pleural space: Loculation may occur due to patient physiology and clinical state. However, frequent follow-ups reviewing the drainage output, symptoms and CXR will determine if this has occurred and adjust treatment accordingly.

Failures related to drug content and elution: The catheter is designed to contain 100 mg of silver nitrate which will elute over time. The manufacturing process applies a spray coat of the silver nitrate. This process limits the amount of total silver on the catheter based on tightly controlled parameters and multiple tests to confirm the amount of silver nitrate applied.

The spray technology also creates a homogeneous coating of silver nitrate along the coated length. This is confirmed through design testing.

The design of the coating is intended to limit the silver nitrate from releasing as a bolus. The coating is applied in a dip process. Dip parameters are tightly controlled and tested to confirm the elution rate of the catheter.

Effects of the coating on catheter mechanical properties: The choice of the top-coat polymer material is intended to simultaneously control the release of the silver nitrate and ensure durability for the typical forces and stresses applied during the placement procedure. The coated catheter has undergone design testing to ensure the coating is not damaged during placement.

Premature catheter removal: Premature catheter removal is not anticipated based on the design of the protocol and mandatory checks in place to confirm pleurodesis. Catheter removal due to patient health concerns will be documented per AE reporting requirements.

Effect of unblocking the catheter on pleurodesis: Unblocking the catheter using a declotting agent is not anticipated to effect pleurodesis. The Catheter Access Kit IFU provides information on the internal volume of the catheter so that the declotting agent will be limited to the catheter and not significantly enter the pleural space.

Silver nitrate coating affected by light exposure: The SNCIPC is protected from ultra-violet light during manufacturing by the addition of UV filters in the coating area. In addition, the catheters are protected from light by the packaging, including a foil pouch. Light should not affect the catheter during the length of a typical catheter placement procedure.

Biocompatibility including leachables/ extractables: The catheter is considered biocompatible per applicable ISO 10993 testing. Leachables/ Extractables testing has been performed and has shown no increased toxicological risk over the PleurX catheter.

4.2.6.1 Changes to the IFU, As Identified In The Risk Analysis Report

The following risk items are to be included in the SNCIPC IFU due to the residual risks associated with the silver nitrate coating. They were not, therefore, previously included in the standard PleurX Catheter IFU.

- A new contraindication was added: “Use of the Coated Pleural Catheter is contraindicated when there is a known silver hypersensitivity.”
- Two new cautions were added: “To preserve coating integrity, avoid excessive handling of the coated portion of the catheter.” and “Potential complications of a silver nitrate coated catheter may include loculations or catheter occlusions.”
- The following note is given when attaching the fenestrated end of the catheter to the tunneler: “Note: Hold the catheter by the distal tip when assembling to the tunneler.”

- The following note is given when detaching the catheter from the tunneler: "Disconnect the tunneler from the catheter by pulling it. Note: Do not cut the catheter."
- An incise patch will be used to cover the fenestration in the sterile drape, to protect the patient's skin from exposure to silver nitrate during the procedure.

4.2.7 Possible Interactions with Concomitant Medical Treatments

There are not expected to be any reactions with subject's concomitant medications.

4.2.8 Benefit-Risk Analysis Conclusion

The potential benefits for patients in the trial are centered on the potential for a more rapid achievement of pleurodesis. These clinical benefits are a reduction in dyspnea and reduction in effusion volume. The risks associated with the trial are largely in relation to administration of silver nitrate in conjunction with the well-established PleurX IPC. The toxicity of silver is well documented, and the use of silver nitrate in pleurodesis has been extensively reported in numerous publications as recently as 2013. Silver nitrate is an appropriate pleurodesing agent with established efficacy, and the risks (pain, increased effusion) are documented as being mitigated by a lower dose of silver nitrate administered over time rather than as a bolus. Care has been taken in the design and manufacture of the silver nitrate coating. The coating has been designed and manufactured to minimize risks as far as possible, while maintaining the incremental benefits over the current standards of care for MPE. The majority of the potential AEs that could be anticipated in the study (Section 4.2.5) are related to the procedures involved in management of MPE with a standard IPC and are well known and easily managed by the treating physician. Potential events related to the silver nitrate (hypersensitivity, transient pain, increased effusion volume) are mitigated by the patient follow-up schedules, clinician training, and the protocol design. These risks are clinically comparatively insignificant when set against the potential benefits afforded to a patient population of the type to be included in this investigation.

5 Selection of Study Population

Eligible subjects will be ≥18 years old, experiencing dyspnea secondary to recurrent MPE and meet all other inclusion and exclusion criteria. Additionally, subjects or their caregiver (friend, family member or paid healthcare professional) must be capable of managing at-home pleural effusion drainage.

Investigators must keep a record of subjects who were considered for enrollment but were never enrolled (e.g., subject screening log so as to address concerns over selection bias).

5.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

1. Male or female, at least 18 years of age, inclusive.
2. Subject has a symptomatic MPE requiring intervention. For an effusion to be defined as malignant, at least one of the following must be true:
    a. There is histocytological confirmation of pleural malignancy.
    b. The effusion is an exudate (per Light's criteria) in the context of histocytologically proven malignancy elsewhere, with no other clear cause for fluid identified.
3. Subject has a history of at least 1 ipsilateral pleural effusion causing dyspnea that responded to thoracentesis where the lung expanded and the dyspnea was improved.
4. Subject is willing and able to provide written informed consent.
5. Subject is willing and able to meet all study requirements, including follow-up visits and receiving study-related telephone calls.
6. Subject has sufficient pleural fluid to allow safe insertion of an IPC.
7. Subject has negative pregnancy test if appropriate.
8. Subject or caregiver is able to perform home drainage of the pleural effusion (a caregiver can be a friend, family member or paid healthcare professional).

5.2 Exclusion Criteria

Potential study subjects will be excluded if 1 or more of the following exclusion criteria is present:

1. Subject has significant trapped lung, or a proximal bronchial obstruction which is likely to lead to trapped lung. For a subject to be eligible for this study, two separate study center clinicians must agree that there is no significant trapped lung on the same CXR using visual estimation (reference guide). The CXR used to make this decision must have been performed ≤30 days preceding the consent form being signed, and must have been performed preferably on the same day, but no more than 7 calendar days after a pleural drainage.

    Significant trapped lung is deemed present if any 1 of the following criteria is met:

    a) A CXR shows hydropneumothorax.

b) A CXR shows ≥20% of the affected hemithorax to be free of the expected lung parenchymal markings and there is no suggestion of pleural fluid.

c) A CXR shows ≥20% of the affected hemithorax to be occupied with pleural fluid AFTER a pleural aspiration which resulted in symptoms suggestive of trapped lung (e.g., chest pain or cough).

2. Subject has a Karnofsky score <50, or a World Health Organization (WHO)/ Eastern Cooperative Oncology Group (ECOG) performance status ≥3. Subjects who have a performance status of 3 may be considered for the study if the removal of their fluid would likely improve their performance score by 1 or more.
3. Subject is pregnant, planning to become pregnant, or is lactating.
4. Subject has a history of empyema.
5. Subject has a history of chylothorax.
6. Subject has an uncorrected coagulopathy.
7. Subject has a hypersensitivity to silver, silver nitrate, or silicone. For subjects with a self-reported silver hypersensitivity who wish to be considered for enrollment in the study, a confirmation test for hypersensitivity to silver nitrate will be performed.
8. Subject has evidence, in the opinion of the Investigator, of either on-going systemic or pleural infection.
9. Subject has had a lobectomy or pneumonectomy on the side of the effusion.
10. Subject has undergone a previous attempt at ipsilateral pleurodesis which has failed.
11. Subject has previously been diagnosed with a serious immunodeficiency disorder.
12. Subject has bilateral pleural effusions, with both being at least moderate in size (greater than one-third of the hemithorax on CXR).
13. Subject has evidence of fluid loculation such that attempts at pleurodesis are likely to be futile.
14. Subject has a mediastinal shift of ≥ 2 cm toward the side of the effusion.
15. Subject is receiving concurrent intrapleural chemotherapy or radiation therapy to the ipsilateral chest.
16. Subject has any clinical condition, diagnosis, or social circumstance that, in the opinion of the Investigator, would mean participation in the study would be contraindicated.
17. Subject has no access to a telephone.
18. Subject has no documented blood values (complete blood count [CBC], coagulation tests, urea and electrolytes, and liver function tests [LFTs]) within the last 10 days.
19. Subject has previously participated in any clinical trial with the investigational SNCIPC device.
20. Subject currently enrolled in any other clinical investigation or who has participated in any clinical investigation in the 30 days prior to starting this study.

5.3 Withdrawal of Subjects

Subjects may be discontinued from study treatment and assessments at any time. Subjects are also free to discontinue their participation in the study at any time, without prejudice to further treatment.

Wherever possible, subjects should be seen and assessed by the Investigator(s) at withdrawal.

In the eCRF, study completion or discontinuation will be documented with the reason for any discontinuation. Possible reasons for a subject discontinuing participation in the study are:

- AE(s) that endanger the health of subjects, making it ethically unacceptable to continue
- deterioration of the subject's clinical condition(s) that requires appropriate therapy/treatment during the study period
- withdrawal of consent
- lost to follow up
- death.

In case of an AE, the subject is to be followed up until resolution of the AE.

6 Device Description

6.1 Investigational Device –SNCIPC

The investigational device is manufactured by the Sponsor, CareFusion 2200, Inc., and is termed the Silver Nitrate-Coated Indwelling Pleural Catheter, or SNCIPC.

The SNCIPC consists of a fenestrated silicone catheter with a proximal valve mechanism and a polyester cuff, identical to the PleurX catheter on which it is based. The fenestrated portion of the catheter is coated with 100 mg (+/- 15 mg) of the pleurodesis agent silver nitrate ($AgNO_3$) and inert materials which control the drug release. The inert coating materials cover the entire fenestrated portion of the catheter, while the silver nitrate begins approximately 3 cm from the distal tip. The coating ends before the subcutaneously tunneled portion of the catheter. The entire coated region is visually detectable (Figure 6-1).

A barium sulphate stripe runs the entire length of the catheter to aid visualization under fluoroscopy. The valve is designed to prevent the passage of air or fluid in either direction unless it is accessed with the specifically matched drainage line or vacuum bottles, also manufactured and provided by CareFusion (Section 6.2).

Manufacturing will be carried out in accordance with the requirements of Annex 13 of the GMP guidelines, ICH GCP requirements, Sponsor approved SOPs and all applicable US/EU laws as well as the local and applicable regulatory requirements.

Mode of Action

Like the uncoated IPC on which it is based, the primary mode of action of the SNCIPC is to provide intermittent drainage of fluid accumulation from around the lungs, which in turn provides palliative care and pleurodesis for recurrent symptomatic pleural effusions that do not respond to treatment of the underlying disease. Secondary to its primary mode of action, the catheter is coated with silver nitrate that elutes into the pleural space over time to increase the rate and proportion of pleurodesis events. Pleurodesis provides for catheter removal with long-lasting reduction in effusion volume and dyspnea without ongoing pleural drainage, catheter management, and catheter-associated complications.

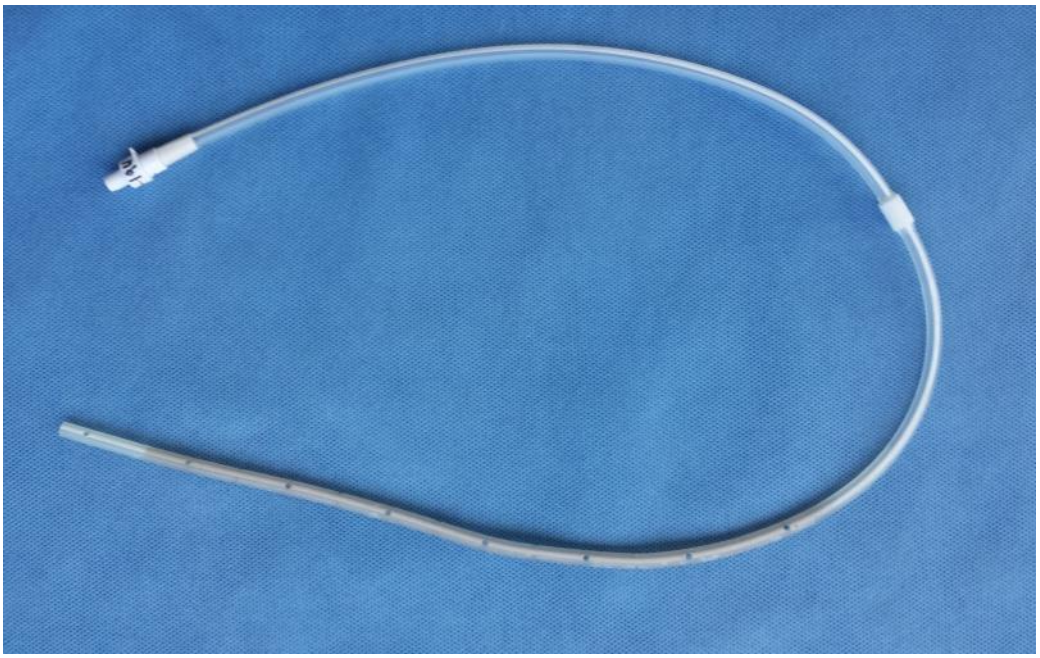


Figure 6-1. Silver Nitrate-Coated Indwelling Pleural Catheter

6.2 Control Device – PleurX® Pleural Catheter

The control device in this study is the currently marketed, FDA-approved PleurX Pleural Catheter system which is provided in a kit as described in Section 6.3.

The PleurX pleural catheter consists of a fenestrated silicone catheter with a proximal valve mechanism, a polyester cuff, and a barium sulphate stripe to aid visualization under fluoroscopy. When the catheter has been placed in the pleural space, the fenestrations allow the excess pleural fluid to be removed by drainage through the outer end of the catheter. The valve is designed to prevent the passage of air or fluid in either direction unless it is accessed with the specifically matched drainage line or vacuum bottles, also manufactured and provided by CareFusion.

6.3 Devices to be Used

The SNCIPC will be provided in two different kits (catalog codes) for the clinical investigation: catalog code 50-4999 will be used for the US Clinical Trial study centers and catalog code 50-2999 will be used for the UK Clinical Trial study centers. The SNCIPC will be exactly the same in both kits. The only difference between the two kits are the placement components that accompany the device.

The control device will also be provided in two different kits (catalog codes). Catalog code 50-7000B will be used for the US control device and code 50-7050 will be used for the UK control device. The kits contain preparation, placement, closing, drainage and dressing components as described in the manufacturer's IFU.

During the clinical investigation, the SNCIPC will be used with certain non-investigational devices for placement, drainage and management of occlusions (if needed) as described below. The non-investigational devices are FDA cleared and CE marked and will be used in the clinical investigation in accordance with the manufacturer's intended uses.

6.3.1 Drainage Bottle

The SNCIPC will be intended for use with the existing FDA cleared PleurX Drainage Kit (50-7500B). This comprises a 500 mL vacuum bottle with drainage line. The intended uses of the PleurX drainage kit components are consistent with their 510K and CE-marked intended purpose and they are not, therefore, regarded as investigational devices.

The SNCIPC or control device can be attached to the PleurX Vacuum Bottle (500 mL; Figure **6-2**) for suction and drainage collection. The PleurX Vacuum Bottle is a pre-evacuated single use plastic vacuum bottle. The bottle is fitted with a pre-attached drainage line with an access tip that is unique to the PleurX pleural catheter and SNCIPC. The pinch clamp on the drainage line is closed before the access tip is connected to the catheter valve. Once the access tip is securely mated to the catheter valve, the support clip is removed from the bottle and discarded. Without the support clip, the flexible bottle cap and white T-plunger can be depressed, driving the spike into the foil covering, piercing the seal and releasing the vacuum. The pinch clamp is released and drainage begins.

The materials intended for the drainage of the PleurX and SNCIPC catheters are designed to be used by anyone who has undergone a short training session (e.g., patients, caregivers, nurses, or other health professionals).

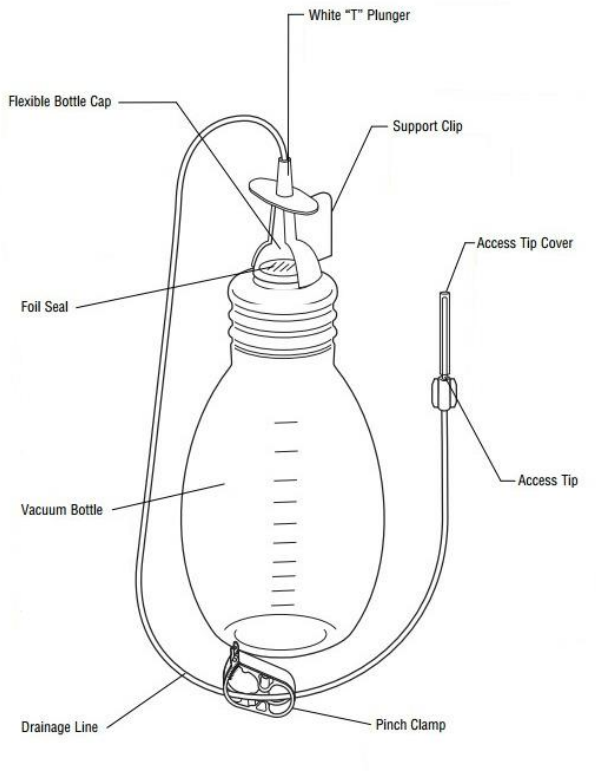


Figure 6-2. PleurX Vacuum Drainage Bottle (500 mL)

6.3.2 Catheter Access Kit

The PleurX Catheter Access Kit (50-7280; Figure 6-3) will be used to provide access to the PleurX Catheter for any necessary flushing to unblock the catheter. To access the SNCIPC or control device, the access tip is connected to the valve and a syringe with flushing agent is connected to the Needleless Access Valve. The intended uses of the PleurX Catheter Access Kit components are consistent with their 510(k) cleared and CE-marked intended purpose and they are not, therefore, regarded as investigational devices.

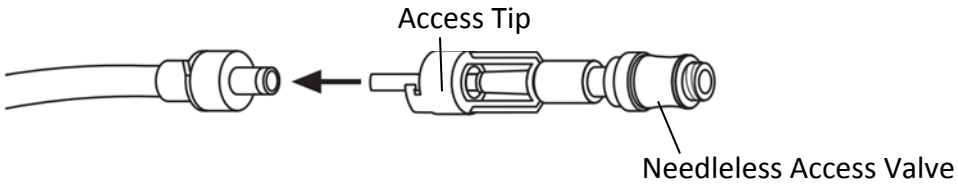


Figure 6-3. Catheter Access Kit

6.3.3 Catheter Insertion Stylet (Component of Supplemental Insertion Kit)

The PleurX Supplemental Insertion Kit (50-7262) contains a Catheter Insertion Stylet (Figure **6-4**) which can be used to aid in insertion of the SNCIPC or control device by stiffening the catheter during insertion through the peel-away sheath. The US kit 50-4999 *Coated Indwelling Pleural Catheter System* contains the Catheter Insertion Stylet, but the UK kit 50-2999 *Catheter Placement Mini-Kit* does not. It is an optional component which the physician may choose to use if desired. UK physicians may pull a Catheter Insertion Stylet from the Supplemental Insertion Kit. The intended uses of the Catheter Insertion Stylet components are consistent with their 510(k) cleared and CE-marked intended purpose and they are not, therefore, regarded as investigational devices. The Kit also contains a valved peel-away sheath which should not be used as a part of this trial.

Figure 6-4. Catheter Insertion Stylet

6.4 Packaging and Labeling

Packaging and labeling will be carried out in accordance with the requirements of Annex 13 of the GMP guidelines, ICH GCP requirements, Sponsor approved SOPs and all applicable US/EU laws as well as the local and applicable regulations.

Final labeling and packaging of the products will be performed by CareFusion 2200, Inc. in accordance with their SOPs, FDA and international regulation. Product labels comply with US and EU regulatory requirements including the statements “USA: CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use” and/or “EU: CAUTION: Investigational device exclusively for use in a clinical investigation”.

6.5 Device Storage and Accountability

All investigational devices supplied to the study center will be fully catalogued and traceable from manufacture to subject insertion, and, if removed or returned, from subject to disposal, back to the Sponsor, or to the central analytical lab for the SNCIPC residual silver testing.

All devices will be stored in a Sponsor-approved environment at the study center prior to insertion (Table 6-1); 50-7050 (UK Control Device), 50-7500B (Drainage Bottles), 50-7280 (Catheter Access Kit), and 50-7262 (Supplemental Insertion Kit) do not have specific storage requirements.

Batches of the SNCIPC will be identified by unique batch number. The Principal Investigator, or an authorized designee, will maintain adequate records of the receipt and, when appropriate return or disposal of all investigational devices.

The Principal Investigator will return to the study Sponsor any unused devices and a copy of the completed device inventory.

Table 6-1. Device Storage Conditions

US Control Device	US Test Device	UK Test Device
50-7000B	50-4999	50-2999
Store at controlled room temperature (68°F to 77°F/20°C to 25°C). Avoid freezing and excessive heat above 104°F (40°C). Caution: Contains Alcohol and gives off flammable vapors. Keep away from heat, sparks, and open flame.	Store at controlled room temperature (68°F to 77°F/20°C to 25°C). Avoid freezing and excessive heat above 104°F (40°C). Caution: Contains Alcohol and gives off flammable vapors. Keep away from heat, sparks, and open flame.	Store at controlled room temperature (59°F to 77°F/15°C to 25°C). Avoid freezing and excessive heat above 104°F (40°C). *Note: UK test device does not include Lidocaine or Chloroprep,therefore the approved temperature range is wider than the US devices.*
Note: 50-7050 (UK Control Device), 50-7500B (Drainage Bottles), 50-7280 (Catheter Access Kit), and 50-7262 (Supplemental Insertion Kit) do not have specific storage requirements.		

6.6 Investigational Device Proposed Intended Use

The proposed investigational device, SNCIPC, is anticipated to have the identical indications for use as the originally cleared PleurX pleural catheter:

Indicated for intermittent, long term drainage of symptomatic, recurrent, malignant pleural effusion. The device is indicated for 1) the palliation of dyspnea due to pleural effusion and 2) providing pleurodesis (resolution of the pleural effusion).

The current PleurX device has been primarily used in patients diagnosed with terminal malignancies.

The PleurX pleural catheter allows a patient to periodically drain excess pleural fluid into a vacuum bottle in the comfort of their own home and it also leads to pleurodesis. The investigational SNCIPC product will be used in the same manner, but with added irritation coming from a sclerosing agent (silver nitrate) within the catheter coating. Since it is well established that silver nitrate can be used as a pleurodesis agent, it is believed that adding a silver nitrate coating to the currently cleared IPC will create a more consistent pleural layer inflammatory response, and will therefore reduce the overall timeframe in which the PleurX pleural catheter achieves pleurodesis and increase the frequency of pleurodesis occurrence.

6.7 Investigational Device Insertion and Removal

The SNCIPC investigational device is inserted in a procedure virtually identical to that of the PleurX catheter on which it is based; the only difference in procedure is that the SNCIPC insertion will utilize an incise patch over the fenestration of the sterile drape to protect the patient's skin

against potential exposure to silver nitrate. Full details of this procedure can be found in the SNCIPC IFU. One IPC will be placed per patient. Briefly, a subject is positioned so as to allow easy access to their fluid collection and to ensure comfort during insertion. The IPC may be inserted under general anesthetic or small amounts of conscious sedation, although it is typically performed using only local anesthetic which is infiltrated after an appropriate sterile field has been created. Two small skin incisions are made, between which the catheter is tunneled using a tunneler attached to the distal end. The fenestrated portion of the tube is then inserted into the pleural space using a break-away introducer and a standard Seldinger technique. The skin incisions are sutured closed and the catheter dressed. A typical insertion procedure may take 15 to 30 minutes.

If removal of an SNCIPC is required, the procedure is once again identical to that of the PleurX catheter removal. The method is undertaken using aseptic technique and local anesthesia. A small incision is made adjacent to the area where the tube enters the subcutaneous tissues, before the cuff is freed using blunt forceps dissection. Once loose, the catheter is withdrawn in a single smooth motion. A typical removal procedure may take 5 to 15 minutes, although this may be extended if more fibrous adhesion than normal has developed.

For the purposes of this study, all investigational device removals and insertions will be performed by a medical professionals trained and experienced in the use of the PleurX device.

6.8 Method of Assigning Subjects to Treatment Groups

Subjects will be randomly allocated to treatment groups on the day of IPC placement. The randomization will be stratified by site. The randomization codes will be generated within the Biometrics Department of the designated contract research organization (CRO) by a statistician not involved in the study. The randomization algorithm will be based on the PROC PLAN procedure of SAS®, Version 9.2 or higher.

The Investigators will randomize the subjects in ascending order of the site-specific randomization lists.

The randomization codes and the complete generation procedure will be filed in a secure location by the designated CRO until the study database is opened. A copy of the list will be sent to CareFusion 2200, Inc., for the purpose of assigning the kits to the subjects.

6.9 Blinding

Study subjects will be blinded since the external components for either study device are the same; however, the Principal Investigators will remain unblinded since the two study devices can be readily distinguished by outward appearance prior to placement. The independent radiologist(s) who will evaluate the scans will be blinded to the identity of the investigational product given to the subject.

The blind will be broken at the end of the study, after every subject has completed the study, been entered in the database, and the database is locked.

The DSMB or other regulatory bodies (i.e., FDA, IRB/IEC) will have access to the unblinded data when necessary for reviewing, evaluating and/or reporting on subject safety issues or concerns during the conduct of the clinical research trial. Details of this process will be explained in the DSMB Charter.

This is a single-blinded study; a dummy randomization scheme will be followed when programming summary outputs so as not to program with bias on safety and efficacy outputs prepared for the DSMB. However, actual treatment codes will be used to validate programs for production of the displays. Details of the process are explained in the SAP.

6.10 Concomitant Medication and Therapy

Medication required for treatment of symptoms/diseases is permitted during the study and has to be documented in the eCRF as described in Section 10.1.8 (including name of the medication, date of administration and its duration, dose, and indication for use). Concomitant pleurodesis procedures (i.e. talc pleurodesis) will not be allowed.

7 Study Procedures

7.1 Schedule of Events

The schedule of events is provided in Table 7-1 and detailed in the sections below.

Table 7-1. Schedule of Events

Study Visit / Procedure	Pre-Screening[a]	Screening (Day -14 to Day -1)	Baseline Assessment[b] (Day -3 to Day 0)	Insertion (Day 0)	Follow-Up Visits Study Day (+/- Days)							Follow-Up to Confirm Pleurodesis[d]	Pleural Catheter Removal	Confirm Recurrence[e]	Between Follow-Up Visits
					7[c] (+/- 2)	14 (+/- 2)	30 (+/- 2)	45[c] (+/- 3)	60 (+/- 3)	75[c] (+/- 3)	90 (+/- 3)				
I/E criteria and PIS	X	X	X												
Sign consent form(s)		X													
Medical history			X												
Prior and concomitant medications[f]			X		X	X	X	X	X	X	X				
Physical examination[g]			X	X		X	X		X		X				
Assessment of analgesia requirements					X	X	X	X	X	X	X				
Serum (S) or urine (U) pregnancy test[h]		S	(U)								S				
Silver nitrate hypersensitivity test[i]		(X)													
Chest X-ray[j]		(X)	X	X		X	X		X		X	X	X	X	
CT Scan														X	
Randomization (within 24 hours prior to IPC insertion)				X											
Collect blood samples for clinical safety tests[k]		X	X			X	X		X		X				
Collect blood samples for serum silver testing (SNCIPC only)[l]				X		X	X		X		X		X		
Maximal pleural drainage[m]				X		X	X		X		X				X
Pleural fluid samples for silver testing (SNCIPC only)[n]				X		X	X		X		X				
Medical resource utilization[o]				X	X	X	X	X	X	X	X	X	X		X
Diary completion[p]					X	X	X	X	X	X	X	X	X		X
QoL measurements (pain and dyspnea)[p,q]			X	X	X	X	X	X	X	X	X				X
QoL measurements (EQ-5D-5L health status questionnaire)[q]			X	X	X	X	X	X	X	X	X				
AE monitoring			X	X	X	X	X	X	X	X	X	X	X		X
Previously unidentified trapped lung[r]						X	X								
Residual silver testing (SNCIPC only)[s]													X		

Abbreviations: CBC = complete blood count; eCRF = electronic case report form; CRP = C-reactive protein; CXR = chest X-ray; EQ-5D-5L = European Quality of Life-5 Dimensions; I/E = inclusion/exclusion; IPC = indwelling pleural catheter; LFT = liver function tests; OTC = over-the-counter; PIS = patient information sheet; SNCIPC = Silver Nitrate-Coated Indwelling Pleural Catheter; PA = poster-anterior; VAS = visual analog scale

[a.] Review of existing CXR and laboratory data will be performed during pre-screening I/E criteria review.

[b.] The Baseline Assessment must take place by the end of the 14th day after consent is obtained, and ≤72 hours prior to placement of IPC.

[c.] Follow-up on Days 7, 45, and 75 will be by telephone.

[d.] Subjects must call the site to make an appointment for an unscheduled visit to assess for pleurodesis and potential IPC removal once they measure an output of ≤50 mL of pleural fluid on 3 consecutive drainages over a minimum of 5 days. IPC removal may or may not occur on the same day as the follow-up visit to confirm pleurodesis.

[e.] An unscheduled CXR and CT scan may be performed on subjects who present with signs and symptoms consistent with potential recurrence as described in the protocol.

[f.] Including current oncological treatment and analgesia requirements.

[g.] A complete physical examination including vital signs (blood pressure, temperature and heart rate), blood oxygen saturations and respiratory rate.

[h.] For subjects who have a screening and baseline visit on the same day, only the serum (S) pregnancy test will be required. For subjects who have screening and baseline visits on different days, both pregnancy tests will need to be conducted as indicated.

[i.] For subjects with a self-reported silver hypersensitivity and who wish to be considered for enrollment in this study, a patch test will be performed to confirm silver nitrate hypersensitivity.

[j.] Subjects require a baseline CXR only if they have not had one in the previous 5 days. CXR to include 3 views (single decubitus, PA and lateral) for insertion day (post-placement) and pleurodesis assessment and two views (PA and lateral) for baseline and all other follow-up visits.

[k.] Clinical blood tests to include CBC, CRP, coagulation tests, urea and electrolytes and LFTs.

[l.] For patients who receive SNCIPC, clinical blood tests will include serum silver testing.

[m.] Pleural drainage is to take place daily until the day 14 follow up visit, and no less than 3 times per week between the day 14 follow up visit and the day 30 follow up visit. The frequency of drainage from the day 30 visit onwards is according to clinical need. All drainages are to occur in the subject's home or in a suitable clinical area.

[n.] For subjects with SNCIPC, pleural fluid samples will be collected for silver testing until the point of catheter removal.

[o.] Information regarding but not limited to length of procedure for IPC insertion; hospital stay (hours); length of time IPC in place; drainage schedule/ frequency; frequency/dose/type of prescription/OTC medications; frequency/use of oxygen should be recorded in the notes and appropriate eCRF.

[p.] The following should be documented in the appropriate page of the diary: all drainages, chest pain measurements (VAS), dyspnea scores (Modified Borg dyspnea scale), self-measured temperature as well as the frequency and use of oxygen, OTC and prescription medications, and unplanned hospital or emergency department visits. Chest pain, dyspnea and temperature measurements should take place after day's drainage, if appropriate.

[q.] QoL measurements include chest pain and dyspnea scores (baseline assessment and insertion day [post placement and drainage] will be on the appropriate eCRF; all other time points will be captured in the subject diary) and EQ-5D-5L health status questionnaire (on the appropriate eCRF).

[r.] Significant trapped lung is deemed present if any 1 of the following criteria is met: (1) CXR shows hydropneumothorax, (2) CXR shows ≥20% of the affected hemithorax to be free of the expected lung parenchymal markings and there is no suggestion of pleural fluid, or (3) CXR shows ≥20% of the affected hemithorax to be occupied with pleural fluid AFTER a pleural aspiration which resulted in symptoms suggestive of trapped lung.

[s.] Upon removal, SNCIPC should shipped to the designated central analytical lab for residual silver testing.

7.2 Written Informed Consent and Screening

All subjects who present with a recurrent, symptomatic MPE will be considered for study entry. Subjects will be selected based upon the study inclusion and exclusion criteria (Section 5). Potential participants who are amenable to study entry will be provided with a patient information sheet (PIS). Following this, subjects will be allowed sufficient time, in their own opinion, to consider study entry, and will be offered the opportunity to ask any further questions and complete an ICF and consent for placement of the IPC.

The subject is to be informed verbally and in writing about the nature, risks, benefits, and expectations of participating in the clinical study and a copy of the subject ICF is to be given to the subject in the appropriate language (Section 1.4).

The ICF is to be signed by the subject and countersigned by the attending Investigator prior to proceeding with the visit. All subjects who were provided a PIS and who signed the ICF will be defined as having been screened. At this point, a subject screening number will be assigned and all screened subjects will be recorded on a dedicated screening log. A subject will be defined as having been enrolled from the date of their randomization. Subjects who are unable to provide written informed consent will not be enrolled and no study-related procedures will be performed.

The following observations/procedures are to be performed and checked at the screening visit:

- Check of inclusion/exclusion criteria
- CXR if they have not had one in the previous 5 days
- Patch testing if the subject has a self-identified silver hypersensitivity and consents to silver nitrate hypersensitivity testing in order to determine eligibility.
- Blood samples will be collected for clinical tests including: CBC, coagulation tests, urea and electrolytes, LFTs, C-reactive protein (CRP), and serum pregnancy test (if applicable).

7.3 Baseline Assessment (Day -3 to Day 0)

The study baseline assessment must take place by the end of the 14th day after study consent is obtained, and within 72 hours prior to placement of the IPC. The assessment may be performed by any appropriately trained member of the study team, and should include:

- Review of inclusion/exclusion criteria
- Complete physical examination including vital signs (blood pressure and heart rate), blood oxygen saturations and respiratory rate
- Complete medical history with a specific focus on dyspnea symptoms, previous procedures and cancer treatments
- Review of the use of previous/concomitant treatments or medications or any other clinical condition(s)

- Gender, age, race, body weight and body height
- QoL by subjective VAS score for chest pain, Modified Borg dyspnea scale, and EQ-5D-5L health status questionnaire (see Appendices, Section 12)
- CXR (posterior-anterior view and lateral view), unless performed within the previous 5 days
- Urine pregnancy test (for subjects who have a screening and baseline visit on the same day, only the serum pregnancy test will be required.)
- Collection of blood samples, as detailed in Section 7.10 below.

Subjects should have their IPC inserted within 72 hours of the baseline assessment taking place. If insertion is not possible within 72 hours, the subject should be withdrawn from the study. In this circumstance, should the subject become eligible for study entry at a later date they may be re-consented using a new unique identifier.

7.4 Pleural Catheter Insertion (Day 0)

A description of the insertion technique for the SNCIPC is summarized in Section 6.7 and detailed in the IFU. Catheters must be placed by a member of the study team who is trained and adequately experienced in the insertion of the standard PleurX catheter. The procedure should take place in a dedicated procedure room or operating suite, and should be performed under local anesthetic with or without conscious sedation or under general anesthesia. The IPC should be inserted and fixed in place using the same positioning and technique as for a PleurX catheter. At the time of insertion the pleural cavity should be maximally drained (as limited by subject signs or symptoms). For SNCIPC subjects, a sample of this fluid should be reserved and processed for silver analysis.

Drainage volume, details of procedural complications and drug doses should be recorded in the notes as well as on the appropriate eCRF. The day of IPC insertion is defined as study Day 0.

7.5 Post Catheter Insertion (Day 0)

Subjects should have a post-insertion CXR (single decubitus, PA and lateral views) within 6 hours of the procedure concluding, but after they have been maximally drained.

After insertion, subjects should be admitted to an appropriate clinical area or ward and should have physiological observations (pulse, blood pressure, temperature, blood oxygen saturations and respiratory rate) checked and recorded at least every 30 minutes for 2 hours, beginning with the end of the procedure. Subjects may be discharged home after 2 hours, as long as they are stable and meet local post-procedure discharge criteria. Appropriate analgesia should be available to subjects post-procedure.

Before discharge, subjects should be provided with the necessary study documentation, including:

- A participant diary (Section 7.7)
- Emergency contact card
- Pre-paid envelopes addressed to the study team
- Instructions for draining and the drainage schedule
- Instructions for properly measuring drainage volumes
- Instructions on obtaining drainage bottles
- Instruction to call clinical site once the subject has drained ≤50 mL on 3 consecutive drainages over a minimum of 5 days (i.e., meet pleurodesis requirement).

IPC insertion in this study should be completed as an outpatient procedure (or per hospital standard of practice) unless the Principal Investigator determines there is a clinical need for the subject to remain in-patient, in which case the reason for the delay should be documented in the notes and on the appropriate eCRF. Subjects requiring hospital admission post-procedure may need to have this event recorded as an SAE (Section 8.3). Subjects who remain in hospital for more than 24 hours should have drainage volumes, observations and symptoms recorded in their diary in the same manner as those who are discharged.

MRU information including but not limited to procedure start and end times (length of procedure), hospital stay [hours], and unplanned in-hospital medical procedures as a result of IPC placement should be recorded in the notes as well as on the appropriate eCRF. Further details regarding MRU information to be collected is provided in Section 7.14.

7.6 Regular Fluid Drainage

Drainage may take place either in the subject's home or in a suitable clinical area. All drainages after discharge should be performed using standard aseptic technique and, unless taking place in a hospital setting, should be done using PleurX vacuum drainage bottles. All drainage volumes must be recorded in the subject's diary. Subject must contact the clinical site once he/she has drained ≤50 mL on 3 consecutive drainages over a minimum of 5 days (i.e., met pleurodesis requirement).

Drainage schedule

- Study Day 1 to Day 14 follow up visit (Day 14 ±2 days): subjects should be drained at least once daily.
- Study Day 15 (or after 14-day follow up visit, whichever comes later) to Day 30 follow up visit (Day 30 ±2 days): subjects should be drained ≥ 3 times per week, with the actual frequency determined by the clinician according to clinical need.
- Study Day 31 (or after 30 day follow up visit, whichever comes later) to EOS/Day 90: subjects may be drained as often as is necessary, with the actual frequency determined by the clinician according to clinical need.

Subjects will continue to drain according to the schedule above until the time that pleurodesis is confirmed by CXR. Following pleurodesis confirmation, the patient does not need to drain from that time until IPC removal, unless there is a clinical need.

7.7 Subject Diary and Home Measurements

Prior to discharge, subjects should be issued with a calibrated in-ear or oral thermometer and a study-specific diary record. The diary will allow for the charting of fluid drainage volumes; frequency, dose and type (generic or brand name) of over-the-counter (OTC) and prescription medications; frequency and use of oxygen; QoL measures for chest pain and dyspnea (Section 7.13); and the daily recording of the subject's self-measured temperature. The diary will also include the question(s) if any unplanned hospital visits or emergency department visits occurred due to IPC placement.

The diary and thermometer should be brought to each face-to-face follow-up visit (study Days 14, 30, 60, 90/EOS) where they will be reviewed by the study team; during telephone consults, diary entries will be reviewed over the phone (Section 7.8).

All measurements should take place on the same days as drainage (i.e. daily for study Days 1 to 14 days, then ≥3 times per week until Day 30; then as often as necessary according to clinical need). Chest pain, dyspnea and temperature measurements should take place after the day's drainage, if appropriate.

If a subject is no longer able to complete follow-up visits, the diary should be returned to the study team in the prepaid envelope provided by the study site.

7.8 Follow-Up Period

The per-subject follow-up period for this study is 90 days post IPC insertion. Follow-up will be face-to-face (Days 14, 30, 60, and 90) and by telephone (Days 7, 45, and 75).

7.8.1 Face-to-Face Follow-Up Visits

Subjects should attend the study site for face-to-face study follow-up visits on study Days 14 and 30. If possible, subjects should attend the site for face-to-face visits on study Days 60 and 90 as well. If an appointment cannot be arranged for the designated day, the follow-up visit may take place within the designated allowable range. If the subject is unable to attend the study site due to illness or incapacity the follow-up visit may be performed either over the telephone (with necessary documentation sent by post); alternatively, a member of the study team may visit the subject at home. If a follow-up visit is still not possible, or takes place outside of the allotted window (±2 days for Study Days 14 and 30; ±3 days for Study Days 60 and 90), then a protocol deviation should be recorded. In the event of a subject's death during the follow-up period, any information which can be obtained by examination of standard health records may be used to complete the appropriate eCRF, and any study-related data collected by the subject prior to their death should be mailed to the study team.

Face-to-face follow-up visits may be performed by any appropriately trained member of the study team, and should be preceded by both a maximal catheter drainage (with fluid sample storage for patients who received SNCIPC) and CXR (PA and lateral views).

Each face-to-face visit should include the following:

- Determination of pleurodesis
- Determination of previously unidentified Trapped Lung (as defined in Exclusion Criterion #1; Day 14 and Day 30)
- Record of AE(s) since last visit
- Record of further pleural interventions needed
- Assessment of recurrence post-pleurodesis (as defined in Section 7.9)
- Record of current oncological treatment
- Review of subject diary (temperature, drainage volumes, OTC and prescription medications, oxygen use, chest pain and dyspnea scores, and unplanned hospital or emergency department visits)
- Assessment of analgesia requirements
- Examination of drain insertion site (with removal of stitches if necessary)
- Physical examination (including vital signs, oxygen saturations and respiratory rate)
- EQ-5D-5L health status questionnaire
- Collection of blood samples (for subjects with SNCIPC, this includes samples for serum silver analysis)
- Serum pregnancy test (Day 90)
- Record of MRU.

Data obtained at the follow-up visit should be entered onto the appropriate eCRF. Subjects should be given an appointment for their next visit or telephone follow-up before the end of the consultation.

7.8.2 Telephone Follow-Up Visits

On study Days 7, 45 and 75, subjects should be contacted by a member of the study team to undergo a telephone follow-up consultation. If subjects are unavailable on the allocated day then the call may take place either 2 days before or 2 days after. If a face-to-face or home visit is clinically indicated, then the follow-up may take place as a face-to-face visit instead. If neither a face-to-face nor a telephone follow-up can be completed, or if either takes place outside of the allocated window, then a protocol deviation should be recorded.

Subjects should be contacted at home, ideally after that day's drainage has taken place (if scheduled). They should be reminded to complete their VAS and Modified Borg measurements

for chest pain and dyspnea for that day and the EQ-5D-5L health status questionnaire, which can be conducted via phone or on paper. These should be either mailed to the study team or brought to the next face-to-face appointment. The telephone consultation should involve:

- Record of AE(s) since last visit
- Record of further pleural interventions needed
- Record of current oncological treatment
- Assessment of pleurodesis
- Assessment of analgesia requirements
- Review of subject diary (temperature, drainage volumes, OTC and prescription medications, oxygen use, chest pain and dyspnea scores, and unplanned hospital or emergency department visits)
- Assessment of pleurodesis
- EQ-5D-5L health status questionnaire
- Record of MRU.

Data obtained during the telephone follow-up should be entered onto the appropriate eCRF. Subjects should be given an appointment for their next visit or telephone follow-up before the end of the consultation.

7.9 Pleurodesis

Pleurodesis will be defined as:

- the collection of at least 3 consecutive drainages of ≤50 mL of pleural fluid over a minimum of 5 days (which begin with the first drainage of ≤50 mL)
- CXR (minimally PA, lateral, and single decubitus views), which shows opacification due to pleural fluid occupying less than one quarter of the hemithorax (as judged by the investigative site and the blinded third party central radiology service).

Determination of response for clinical management of subjects will be assessed at the clinical sites per criteria outlined in the protocol. Scans (CXR and CT) will be submitted to the imaging core laboratory for assessment. Details of how assessments will be performed will be included within the Imaging Charter which is specific and only used for the independent review.

Detailed information regarding the acquisition and submission of images to the imaging core laboratory is found in the Imaging Manual, which is specific to the clinical sites.

Subjects must call the site to make an appointment for an unscheduled visit to assess for pleurodesis and potential IPC removal once they measure an output of ≤50 mL of pleural fluid on 3 consecutive drainages over a minimum of 5 days.

The date of pleurodesis is defined as the day on which the first of 3 consecutive drainages of ≤50 mL was recorded. All 3 drainages and the radiological findings to confirm pleurodesis must occur within the 90 day follow-up period.

Subjects should be assessed for pleurodesis at each face-to-face and telephone follow-up assessment by the review of their participant diary. Those in whom pleurodesis is confirmed to have occurred should be scheduled for IPC removal as soon as feasible.

If more than one drainage of >50 mL occurs during the period between pleurodesis being confirmed and the planned IPC removal date, then the removal should be cancelled until the conditions for pleurodesis are met once more. If this occurs then new dates for pleurodesis and IPC removal should be recorded and planned based on the second set of 3 consecutive drainages.

Recurrence is defined as symptomatic pleural effusion confirmed by CXR and CT scan with an estimated >300 mL of fluid in the treated hemithorax. Post-pleurodesis recurrence is evaluated by the physician using the following criteria:

1. Is the subject experiencing increasing dyspnea compared with the time of pleurodesis? *If yes order a CXR. If no, there is no recurrence.*
2. Does the CXR show evidence of increasing opacification compared with the CXR at the time of pleurodesis (confirmed by two clinicians)? *If yes, order a CT scan. If no, there is no recurrence.*
3. Does the CT scan show an effusion estimated at least 300 mL (either unloculated, loculated or multi-loculated)? *If yes, there is a recurrence. If no, there is no recurrence.*

Note: If it is possible to do a thoracentesis and drain the fluid, then the volume removed should be recorded, as well as whether the subject experienced symptom relief. However, this information does not affect the determination of recurrence.

7.10 Collection of Blood Samples

To be eligible for study participation, subjects must have had blood taken for CBC, coagulation tests, urea and electrolytes and LFTs within 10 days of study consent.

Methods for blood sample collection, processing, and shipment are described in instructional materials provided to investigational sites. Samples for clinical blood tests will be processed in the local laboratory for analysis; samples for serum silver analysis will be processed at the specified central laboratory.

During their baseline assessment, at each face-to-face follow-up visit and on the first post-insertion in-patient day, subjects should have blood taken for the assessment of CBC, coagulation tests, urea and electrolytes, LFTs, and CRP, with the results entered into the eCRF as soon as available. For patients who received SNCIPC, a blood sample will also be taken for serum silver analysis (Section 7.11).

7.11 Silver Testing

For subjects who received the SNCIPC, the following samples will be collected for silver testing:

- Blood samples will be collected at SNCIPC insertion day and at each face-to-face follow-up visit for serum silver testing.
- On the day of SNCIPC insertion and at each face-to-face follow-up visit, a sample of pleural fluid is to be collected from the applicable drainage container after the fluid volume has been measured and recorded. Samples will be sent to the central laboratory for silver level analysis.
- At the time of SNCIPC removal (at Pleurodesis, end of study (EOS) or Early Termination as applicable), the SNCIPC should be inspected for structural integrity then the SNCIPC should be shipped to the designated analytical laboratory for residual silver testing.

Methods for blood and pleural fluid sample collection, processing, and shipment are described in instructional materials provided to investigational sites. Samples for clinical blood tests will be processed in the local laboratory for analysis. Pleural fluid and blood samples for silver analysis will be processed at the specified central laboratory.

7.12 Catheter Blockage

Catheters should be suspected of being blocked if pleural fluid is not consistently being drained in the context of radiological findings suggestive of an increasing effusion, or if a piece of debris is visible within the exterior portion of the drainage tube.

In the first instance, an attempt should be made to unblock the catheter using simple methods such as flushing or agitating with a small amount of sterile 0.9% saline solution. The Catheter Access Kit (50-7280) is provided for this purpose. Should these attempts fail, the Investigator may consider the use of a fibrinolytic agent in line with local policy. Such an agent, if used for the purposes of catheter unblocking, should only be instilled into the catheter itself, with as little as possible being injected into the pleural space.

7.13 Quality of Life Measurements

QoL measurements include VAS score for chest pain, Modified Borg scale for dyspnea, and EQ-5D-5L health status questionnaire (see Appendix, Section 12).

Chest pain and dyspnea scores will be collected for each subject, beginning at their baseline assessment and ending when their follow-up is completed or is terminated due to death or withdrawal.

All subjects will provide a score for thoracic pain and dyspnea during their baseline assessment. Beginning on study Day 1 (the day after IPC insertion), subjects should repeat these measurements using the participant diary provided. Scores for pain and dyspnea should be recorded on a daily basis for the first 14 days after insertion, with subsequent recordings on each day that drainage takes place. The score should be noted after that day's drainage takes place.

All subjects will complete the EQ-5D-5L health status questionnaire during their baseline assessment and at each follow-up visit through EOS.

If a subject dies before their diary can be collected, this should be sent via mail to the study site.

7.14 Medical Resource Utilization

Select face-to-face and telephone visits also will include collection of MRU information. To evaluate MRU, information will be collected within the following categories: hospitalizations, emergency department visits, provider visits, medications, other treatments, procedures. Within these categories, information will include planned and unplanned treatments procedures and provider visits, duration/frequency of treatment, medication name(s) dose, frequency, and overall duration, use of medical equipment, treatment of AEs as well as OTC and prescription treatments. In addition, insurance information, including both primary and secondary, if applicable, will be collected. Specific information will include, but may not be limited to: length of procedure; hospital stay (hours); unplanned in-hospital medical procedures as a result of IPC placement; emergency department visits related to IPC placement; length of time IPC in place; drainage schedule and frequency; frequency, dose and type of prescription and OTC medications; frequency and use of oxygen; and services required to diagnose, treat, and follow up AEs.

7.15 End of Study

The study will cease recruitment once the last subject has been randomized and treated (ITT) after any sample size readjustments have been taken into consideration. However, as subjects may be followed up to day 90 post IPC insertion, the provisional EOS date will be 90 days after the insertion of the last study subject's IPC. At the end of each subject's follow-up period they will be stratified as 'alive or 'dead,' and survival data collated.

7.16 SNCIPC Management Following Study Completion

For all subjects who continue to have an SNCIPC in situ at EOS/ Day 90, the subject's physician will be responsible for administering patient care. If clinically appropriate in the opinion of the Principal Investigator, subjects will be offered the choice of having their catheter removed or, if regular drainage with symptomatic benefit continues, having the catheter left in place. Subjects who choose to have their catheter removed will be made aware that they may require insertion of a standard PleurX catheter, or an alternative procedure (or procedures) for the purposes of pleural fluid management.

8 Efficacy and Safety Assessments

8.1 Methods of Assessment/Evaluations

8.1.1 Primary Efficacy Endpoint

The primary objective is to demonstrate that the SNCIPC Pleural Catheter shows superiority compared to the PleurX Pleural Catheter in the proportion of subjects achieving pleurodesis without recurrence at 30 days.

$Ho: pT - pC \leq 0$ *versus* $Ha: pT - pC > 0$

where pT is the rate of pleurodesis without recurrence at 30 days for the study device, pC is the rate for the control device. Rejecting the null hypothesis will establish superiority of the study device over the control device.

Exact unconditional CI for risk difference will be used to calculate rate difference and 95% CI.[35]

The primary efficacy endpoint is the proportion (%) of subjects achieving pleurodesis without recurrence by 30 days, where pleurodesis is defined as:

- The collection of a minimum of 3 consecutive drainages of ≤ 50 mL of pleural fluid over a minimum of 5 days (which begin with the first drainage of ≤ 50 mL)

AND

- CXR, which shows opacification due to pleural fluid occupying less than one-quarter of the hemithorax (as judged by the investigative site and the blinded third party central radiology service).

The date of pleurodesis is defined as the day on which the first of 3 consecutive drainages of ≤50 mL was recorded.

Radiologic endpoint data will be based on scans (CXR and CT) submitted to the third party imaging core laboratory for assessment. Clinical endpoint data will be based on data collected from the clinical study centers. The primary efficacy endpoint will be based on a combination of radiologic and clinical data.

8.1.2 Secondary Efficacy Endpoints

- Time to confirmed pleurodesis

  Time to confirmed pleurodesis is defined as the duration between the study device insertion and the date a subject achieves pleurodesis.

- Time to recurrence

  Time to recurrence is calculated for subjects who achieved confirmed pleurodesis. It is defined as the duration between successful pleurodesis (the first of a minimum of 3 consecutive drainages of ≤50 mL of pleural fluid over a minimum of 5 days) and the date

the subject presents with symptoms of recurrence that is later confirmed by CXR and CT scan.

8.1.3 Exploratory Efficacy Analysis

The following exploratory analysis will be performed comparing the two treatment groups:

- Proportion of surviving subjects without a trapped lung diagnosis following IPC placement who have confirmed pleurodesis without recurrence at 14, 30, 60, and 90 days
- Proportion of subjects with confirmed pleurodesis and without recurrence by 30 days after IPC placement by cancer type (lung, breast and others).

8.1.4 Safety Evaluations

The following safety evaluations will be performed comparing the two treatment groups:

- Device related safety and AEs
- Incidence of IPC occlusion
- Incidence of empyema and cellulitis (as coded by Medical Dictionary for Regulatory Activities [MedDRA] and described in the data management plan).

Descriptive statistics for serum and pleural fluid silver levels by time point will be provided for subjects who receive SNCIPC.

8.1.5 Quality of Life and Medical Resource Utilization Analysis

- Pain using 100 mm VAS scale
- Dyspnea relief (breathlessness) using Modified Borg dyspnea scale
- Health status as measured by the EQ-5D-5L health status questionnaire
- MRU data (length of procedure; hospital stay [hours]; unplanned in-hospital medical procedures as a result of IPC placement; emergency department visits related to IPC placement; length of time IPC in place; drainage schedule and frequency; frequency, dose and type [brand name/generic] of prescription and OTC medications; frequency and use of oxygen; services required to diagnose, treat, and follow up AEs).

8.2 Protocol Deviations

A protocol deviation is defined as an instance of failure to follow, intentionally or unintentionally, the requirements of the protocol.

After signing the ICF, all care pertaining to a subject's involvement in the study or their SNCIPC should be completed as defined in this CIP, without deviation. However, at the medical discretion of the Investigator or other healthcare teams, or under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of study participants may proceed without prior approval of the Sponsor and the regulatory body/bodies. Such deviations should be documented and reported to the Sponsor and regulatory body/bodies (as necessary) as soon as

possible (ideally within 48 hours of knowledge of the deviation occurring), using the study deviation page of the eCRF.

All deviations from the CIP will be monitored by the Sponsor or appropriate designee. Protocol deviations will not be granted, but, if they occur, sites will be required to report them.

The Sponsor retains the right to suspend the study or disqualify the Principal Investigator if deemed necessary based upon the nature of reported protocol deviations. CIP deviations which may result in suspension include not complying with the signed tripartite agreement, the investigational plan, FDA regulations, or any conditions of approval imposed by the reviewing regulatory agency.

8.3 Safety Parameters

AEs that occur during the study after the subject has signed the ICF are to be collected and reported on the eCRF, regardless of whether they are reported by the subject, elicited by Investigator questioning, detected through physical examination, or by other means.

As far as possible, each AE is described by:

- duration (start and end dates)
- start/end of study medication
- severity grade (mild, moderate, severe)
- Investigator causality (relationship to the study product)
- action(s) taken (concomitant medication, change of study medication etc.) including start and end of respective action
- concomitant diseases and respective medication in general
- start, end and dosage of rescue medication
- outcome.

AE

An AE is any untoward medical occurrence (change in anatomical, physiological, or metabolic function) in a subject, which does not necessarily have any causal relationship with the product under investigation.

TEAE

Treatment-emergent AEs (TEAEs) are those AEs occurring from time point of device insertion until last visit.

Device Deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

ADE

An ADE is an AE related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate IFU, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. The definition also includes any event resulting from use error or from intentional misuse of the investigational medical device. Further details regarding anticipated ADEs are provided in Section 4.2.

UADE

A UADE is any serious AE on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

SAE

A serious adverse event (SAE) is defined in the ISO 14155 standard as an AE that led to death or to a serious deterioration in the health of the subject that either resulted in:

- a life threatening illness or injury, or,
- a permanent impairment of a body structure or a body function, or,
- in-patient or prolonged hospitalization, or,
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

An SADE is an ADE that has resulted in any of the consequences characteristic of an SAE.

A USADE is an SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE: ‘Anticipated’ means an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

Events that require intervention to prevent one or more of the outcomes listed in the definition above are also to be considered as serious. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias or convulsion that does not result in hospitalization, or development of drug dependency or drug abuse.

However, medical judgment will be exercised in deciding whether an event is serious in any other situations considered medically relevant.

The evaluation of the AE as serious or not-serious is made independently of any attribution of causality.

Events NOT considered to be SAEs are those that require:

- treatment, which is elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and does not worsen

- treatment on an emergency, out-patient basis for an event NOT fulfilling any of the definitions of serious given above and NOT resulting in hospital admission for the purpose of this study, a hospitalization is defined as a hospital stay of at least 8 hours and/or an overnight stay.

AE Intensity

AE intensity determined by the clinical Investigator on the basis of his/her direct observations or the subject's reporting:

- Mild: causes no limitation of usual activities; the subject may experience slight discomfort
- Moderate: causes some limitation of usual activities; the subject may experience annoying discomfort
- Severe: causes inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

AE Causality (relationship guide)

Any AE has to be judged for causality (relationship to study device and relationship to study procedure).

The relationship of an AE to the study product is to be graded on the basis of the following:

- Probable: a reaction that follows a reasonable temporal sequence from administration of the product; that follows a known response pattern to the suspected product; that is confirmed by an improvement on stopping the product; and that cannot be reasonably explained by the subject's clinical state
- Possible: a reaction that follows a reasonable temporal sequence from administration of the product; that follows a known response pattern to the suspected device; but that may have been produced by the subject's clinical state or other therapeutic interventions on him/her
- Unlikely: a reaction that occurs with an improbable temporal sequence from administration of the product; that can be explained by the clinical state of the subject/participant or by other therapeutic interventions or other drugs or underlying disease providing plausible explanations.
- Unrelated: a reaction that occurs without a reasonable temporal sequence from administration of the product; that can be explained by the clinical state of the subject or by other therapeutic interventions on him/her and that does not improve or disappear following interruption of the product.

Handling of AEs

If an AE occurs, appropriate diagnostic and therapeutic measures are to be taken and the study product has to be discontinued if appropriate. Follow-up evaluations of the subject are to be

performed until the subject recovers or until the clinical Investigator considers the situation to be no longer clinically significant.

If clinically significant laboratory abnormalities appear at the final visit, appropriate additional tests may to be performed to clarify the nature of any clinically significant laboratory abnormalities that occur.

AEs are monitored and registered on the AE form of the eCRF at each visit. In absence of a specific diagnosis, an individual AE form has to be filled in for each sign or symptom.

Persistent AEs will be entered once in the eCRF until they are resolved or if a new event has to be documented due to deterioration. These AEs will be carefully monitored; further details of monitoring of persistent AEs will be provided in the monitoring plan. If an AE is still not resolved at the end of the study, this will documented as ongoing.

For recurrent AEs, i.e., AEs of the same nature, but with a different date of onset, an individual AE form has to be completed for each of them.

AEs occurring after the termination of the study individually and/or of the study in total are to be reported to CareFusion even after the clinical study has been finished if, in the judgment of the Investigator, there is an association between the event and the previous use of the product under investigation.

If the AE is classified as serious, the clinical Investigator also must complete the SAE report form. It is the responsibility of the Investigator to send the SAE report form by fax or email to the Global Safety Department of Chiltern within 1 working day and to retain the original copy of the form (keeping a photocopy in the Investigator Site File). At the earliest possible date, the SAE report form must be followed by a detailed report and any documentation that may be available, e.g., hospital case records, autopsy reports, and/or other pertinent documents.

If the AE is classified as UADE, the clinical Investigator must report the UADE to Chiltern within 1 working day.

The Investigator will be responsible for reporting the SAE to ethics committees. Chiltern will be responsible for initial reporting of SAEs/ UADEs to Sponsor with narratives and follow-up reports. The safety team will also be responsible for reporting expedited safety reports to international sites and regulatory authorities and Central Ethics Committees, distributing periodic line listings to international sites and regulatory authorities and Central Ethics Committees as required per local regulations.

Contact information for Chiltern's Global Safety Department:

US Fax: (866) 869-1551
UK Fax: 00-800-6664-2277
Email: globalsafetyadvantage@chiltern.com

Pregnancy

While not considered an SAE unless a serious criterion is met, pregnancies occurring in subjects enrolled on the study or in their partners must be reported and followed to outcome. The Investigator should complete the pregnancy report form and submit within 1 business day of knowledge of the pregnancy. Following delivery or termination of pregnancy, the follow-up pregnancy report form should be completed and submitted via fax to the Global Safety Department of Chiltern. Spontaneous abortions should always be reported as SAEs.

The safety officer will forward pregnancy reports to CareFusion the next business day. Pregnancies occurring up to 30 days after the last follow-up should be reported. In the event the pregnancy outcome occurs following EOS, the Investigator will report the pregnancy outcome directly to CareFusion.

9 Data Quality Assurance

Detailed procedures will be separately provided in the data management, monitoring, and quality plans.

9.1 Data Collection

All subject data must be reported on the eCRFs in an anonymous fashion. Subjects are identified only by screening number.

The Investigator and staff will be responsible for the completeness, accuracy, and legibility of the information in the eCRF and other study documents. In line with Good Documentation Practices, the source data should be attributable, original, and contemporaneous. For documents other than eCRFs, only ballpoint pen is to be used and any change of data is to be done by striking out the incorrect data with a single line and dating and initialing the changes made.

The study monitors will check the eCRFs against the source documents for accuracy and validity as per the monitoring schedule, as applicable, which includes any data recorded directly on the eCRF (for example, no prior written or electronic record of data). Also, any step in creation of source data is to be identified such as a computerized system used to create, modify, maintain, archive, retrieve, or transmit source data. The subject diary will remain as source documentation at the investigational site and will only be source data verified by the monitors but not collected. Source data verification will include the diary data, eCRF data, and accountability of devices.

Upon completion of the eCRF, each site is to ensure quality of data and subject safety. Once eCRFs are completed, they will be available for review by the monitor and the designated CRO Clinical Data Management department. Completed eCRFs will be reviewed remotely for logical discrepancies. The monitor will ensure that all data queries and subsequent amendments in the eCRF documentation are made according to GCP guidelines.

A copy of the eCRF is to be archived by the Investigator together with the study documents, source data, and laboratory records for the time required by the national regulation.

Site Audits

The Sponsor or its designee may carry out an audit at any time. Investigators will be given adequate notice before the audit occurs. The purpose of an audit is to confirm that the study is conducted as per protocol, GCP/ISO and applicable regulatory requirements, that the rights and well-being of the subjects enrolled have been protected, and that the data relevant for the evaluation of the investigational product have been captured, processed and reported in compliance with the planned arrangements. The Investigator will permit direct access to all study documents, device accountability records, medical records, and source data.

Regulatory authorities may perform an inspection of the study, even up to several years after its completion. If an inspection is announced, the Investigator or the site must inform the Sponsor immediately.

9.2 Database Management and Quality Control

The CRO will be responsible for the activities associated with the data management of this study, including the production of an eCRF, setting up a relevant database, along with appropriate validation of data and resolution of queries. All data will be entered into an eCRF. Automated and manual checks will be made against the data entered into eCRF to ensure completeness and consistency. Resolution of queries will be implemented in the database.

AEs will be standardized for terminology and classification, using MedDRA. Concomitant medications will be classified by site of action and therapeutic and clinical characteristics using the World Health Organization (WHO) DRUG dictionary. Versions of the dictionaries to be used will be documented in the Data Management Plan and the Statistical Analysis Plan (SAP).

10 Statistical Methods

10.1 Statistical and Analytical Plans

Standard statistical methods will be employed to analyze all data. Assumptions of normality and homogeneity of variance will be tested and if distributional assumptions are violated, non-parametric techniques will be employed.

Data collected in this study will be reported using summary tables and patient data listings. Tables will display results for each group as well as all patients combined. For categorical variables, frequencies and percentages will be presented. For continuous variables, the number of subjects, mean, standard deviation, median, minimum, and maximum will be presented. Continuous data subject to censoring (i.e., time to event data) will be summarized by the 25th percentile, median, and 75th percentile, when estimable from the Kaplan-Meier estimates.

The SAP formally defines the analysis populations, describes any data handling conventions, and specifies all statistical methods to be used in analysis of the data.

A 30% non-inferiority margin was established for secondary objectives, based on clinical relevance. Justification of the non-inferiority margin for the secondary endpoints is included in the SAP.

10.1.1 Adjustments for Covariates

The primary efficacy analysis does not have any adjustment for covariates.

10.1.2 Stopping Rules and Data Monitoring

Stopping rules will be defined by the DSMB and outlined in the DSMB charter as described in Section 1.9. The stopping rules are based on safety criteria and there will be no stopping based on efficacy criteria.

10.1.3 Handling of Dropouts and Missing Data

In the primary efficacy endpoint, if a patient discontinues the study prior to 30 days, the subject will be counted as not achieving pleurodesis (considered a "failure"). Missing data will not be imputed. For time to event variables, subjects who discontinue the study will be censored at the time of discontinuation. Subjects who do not experience the event and did not discontinue the study will be censored at the subject's last visit.

10.1.4 Multi-center Studies and Pooling of Investigational Centers

No single site will enroll more than 40 subjects without prior approval from the Sponsor. In the event that there are small sample sizes at some sites, sites may be grouped using the following procedure to create "analysis-sites" for analysis purposes. These analysis sites will be created for US and UK independently to preserve the ability to differentiate between countries. Analysis-sites are based on a target size of at least 5 subjects per treatment group at each site. If investigative

sites have at least 5 ITT subjects per treatment group, they will retain their identities in the analyses. All investigative sites with fewer than 5 ITT subjects per treatment group will be rank ordered by size and sorted secondarily by site identification number to break ties. Starting with the smallest investigative site, subjects will be combined site by site by treatment group, until the first time the resulting analysis site has at least 5 ITT subjects in each treatment group. The process continues until all sites are accounted for. If the last analysis-site has fewer than 5 ITT subjects per treatment group, it will be combined with the most recently created analysis-site.

Although a site effect is not anticipated, the homogeneity of treatment effect across analysis-sites will be tested using a Breslow-Day test at a two-sided 15% alpha level. If the Breslow-Day test is significant at 15% level, a meta-analysis will be performed to investigate treatment differences across analysis-sites.

The proportion (and 95% CIs) of patients achieving pleurodesis without recurrence at 30 days will be presented for each treatment group by analysis-site for descriptive purposes.

10.1.5 Multiple Comparisons/ Multiplicity

Serial gatekeeping procedures will be used to preserve the overall alpha of the study at the one-sided 2.5% level.[36]

The endpoints will be tested sequentially in the following order with no adjustments for multiplicity:

1) Superiority test on the primary endpoint
2) Non-inferiority on the first secondary endpoint (time to pleurodesis)
3) Superiority on the first secondary endpoint (time to pleurodesis)
4) Non-inferiority test on the second secondary endpoint (time to recurrence)
5) Superiority on second secondary endpoint (time to recurrence).

Each of the above endpoints will be tested for superiority using a one-sided alpha of 2.5% for superiority.

Exploratory, safety, QOL and MRU analysis will not be considered for alpha spending since they will be evaluated for investigative purposes only. Any results obtained from these analyses will not be considered as a basis for any claims.

10.1.6 Analysis Populations

Analyses will be based on the Safety, All Randomized, Intent-to-Treat, and the Per-Protocol populations. The definitions of the analysis sets follow those given in the ICH E9 guideline.

- **All Randomized Population**: All subjects randomized to either the study device or the control device will be included in the All Randomized Population. The All Randomized Population will be analyzed according to the treatment group to which the subjects were randomized.

- **Safety Population**: Subjects in the All Randomized population who received either the study device or the control device will be included in the Safety population. The Safety Population will be analyzed according to the treatment subjects received.
- **Intent-to-Treat Population**: All subjects randomized to either the study device or the control device and received one of the treatments will be included in the ITT population. The ITT population will be analyzed according to the treatment group to which subjects were randomized.
- **Per-protocol Population**: Subjects in the ITT population who do not have major protocol deviations will be included in the Per-protocol (PP) population.

The major protocol deviations will be defined at the time of evaluability evaluation to occur in the blinded manner and finalized before database lock and unmasking.

10.1.7 Demographic and Other Baseline Characteristics

All baseline summaries will be based on the All Randomized and ITT populations.

Gender and race will be summarized using counts and percentages. Age, height (cm), and weight (kg) will be summarized with descriptive statistics (number of subjects [n], mean, standard deviation [SD], median, minimum [min], and maximum [max]). Age may be summarized by decades using n and %. Other baseline characteristics may be summarized as necessary.

Similar summary statistics for background and demographic characteristics for only the ITT population will also be done by center.

10.1.8 Prior and Concomitant Therapy

The World Health Organization (WHO) Drug Dictionary will be used to classify medications by preferred term and WHO Anatomical Therapeutic Chemical (ATC) classification of ingredients.

Medications will be summarized using counts and percentages by WHO ATC classification of ingredients and by preferred term. Anticoagulants will be summarized separately for the ITT population.

Medications with start date and stop date prior to insertion of study device will be included in the prior medication summary. Medications taken during the study, including those started prior to insertion of study device, will be included in the concomitant medication summary.

10.1.9 Analysis of Efficacy Parameters

10.1.9.1 Primary Efficacy Parameter

The primary analysis will be performed on the ITT Population.

The proportion of subjects achieving pleurodesis without recurrence 30 days after IPC placement and its 95% confidence interval (CI) by exact binomial method will be summarized for each

treatment group. Exact unconditional CI for risk difference will be used to calculate rate difference and 95% CI.[35]

Superiority will be demonstrated when the one-sided p-value is less than 0.025.

A supportive analysis will be performed in the exact same manner as described above but utilizing the PP Population.

10.1.9.2 Secondary Efficacy Parameter

Time to confirmed pleurodesis analysis will be performed using a proportional hazards model and Kaplan-Meier time-to-event analysis. The analysis will be performed on all subjects in the ITT population, and on all subjects in the PP population as a supportive analysis. A proportional hazards model will be used to estimate the hazard ratio. Non-inferiority will be established when HR >0.7.

Time to confirmed pleurodesis will be summarized by 25th percentile, median, and 75th percentile, when estimable from the Kaplan-Meier estimates for each treatment group. Kaplan-Meier curves for each treatment group will be provided. Time to confirmed pleurodesis is defined as the duration between the study device insertion and the date of confirmed pleurodesis. For subjects who do not have confirmed pleurodesis, censoring rules will be described in the SAP.

Incidence density for time to confirmed pleurodesis will be evaluated between the two groups by summarizing the number of subjects in the ITT population, number of confirmed pluerodeses, number of subjects censored in the time to pleurodesis, and patient-days in each treatment group. Patient-days within the treatment group will be calculated as the total number of days from study device insertion to confirmed pleurodesis or termination of study participation summed for all subjects within the treatment group.

Time to recurrence analysis will be performed using proportional hazards model and Kaplan-Meier time-to-event analysis. The analysis will be performed on all subjects in the ITT population who had confirmed pleurodesis, and on all subjects in the PP population who had confirmed pleurodesis as a supportive analysis. A proportional hazards model will be used to estimate the hazard ratio. Non-inferiority will be established when HR <1.3.

Time to recurrence will be summarized by 25th percentile, median, and 75th percentile, when estimable from the Kaplan-Meier estimates for each treatment group. Kaplan-Meier curves for each treatment group will be provided. Time to recurrence is defined as the duration between confirmed pleurodesis and the date of recurrence. For subjects who do not have a recurrence after confirmed pleurodesis, censoring rules and incidence density analysis will be described in the SAP.

Incidence density for time to recurrence will be evaluated between the two groups by summarizing the number of subjects with confirmed pleurodesis, number of recurrences, number of subjects censored in the time to recurrence, and patient-days in each treatment group. Patient-days within

the treatment group will be calculated as the total number of days from confirmed pleurodesis to recurrence or termination of study participation summed for all subjects within the treatment group.

Superiority will be demonstrated when the one-sided p-value is less than 0.025 using a proportional hazards model.

10.1.9.3 Exploratory Efficacy Parameter

The exploratory efficacy endpoints involving a proportion will be analyzed in the same fashion as the primary endpoint. These analyses involve the following endpoints:

- Proportion of surviving subjects without a trapped lung diagnosis following IPC placement and who have confirmed pleurodesis without recurrence at 14, 30, 60 and 90 days.
- Proportion of subjects achieving pleurodesis without recurrence by 30 days by cancer type.

The proportion (%) of subjects achieving pleurodesis without recurrence at 30 days will be summarized for each treatment group by cancer type (lung, breast and others). The proportions will be compared using a Cochran-Mantel-Haenszel test using the cancer type as a stratification factor. The primary analysis will be performed on the ITT population and a supportive analysis will use the PP population.

10.2 Analysis of Safety Parameters

All comparisons between treatment groups for the safety parameters will be descriptive in nature. Further details will be provided in the SAP.

10.2.1 Duration of Exposure

The duration of subject exposure to study treatment will be quantified as the number of days between IPC insertion and removal. It will be listed and summarized for all subjects in the Safety Population by treatment group.

10.2.2 Incidence of Catheter Occlusion

Incidence rate of IPC occlusion is defined as proportion of subjects who experienced IPC occlusion while on study. It will be summarized for all subjects in the Safety Population by treatment group. Fisher exact test will be used to compare between treatment groups.

10.2.3 Incidence of Infection

Incidence rate of empyema and cellulitis while on study, as coded by MedDRA and described in the data management plan, will be summarized for all subjects in the Safety population by treatment group. The Fisher exact test will be used to compare between treatment groups.

10.2.4 Serum and Pleural Fluid Silver Levels

Serum and pleural fluid silver levels will be measured at regular intervals for the SNCIPC subjects using the gold-standard inductively coupled plasma mass spectrometry (ICP-MS) analysis. It will be summarized for all subjects who received SNCIPC by summary statistics (N, mean, median, standard deviation, minimum and maximum values).

10.2.5 Adverse Events

The Investigator's verbatim term of each AE will be mapped to system organ class and preferred term using the MedDRA dictionary.

AEs will be summarized by system organ class and preferred term; a subject will only be counted once per system organ class and once per preferred term within a treatment. Subject counts and percentages and event counts will be presented for each treatment group and totaled for all treatment groups for the following:

- All AEs
- All AEs by severity
- All SAEs
- All ADEs
- All SADEs
- All UADEs and USADEs

Comparison between the two treatment groups for frequency of any AEs, and frequency of any ADEs will be done using a Fisher exact test.

Listings will be presented by subject for all AEs, SAEs, deaths, and AEs leading to discontinuation from the study.

10.2.6 Clinical Laboratory Evaluations

Clinical laboratory results at each time point and for change from baseline will be displayed using summary statistics (n, mean, median, standard deviation, minimum and maximum values).

All clinical laboratory data will be presented in listings. Within each listing, laboratory values outside the normal ranges will be flagged as either high (H) or low (L). In addition, shift tables will be presented to display the shift in the normal range categories (L, normal [N], H) from baseline to specified time point. Baseline is defined as the latest result obtained prior to the insertion of study device.

10.2.7 Other Observations Related to Safety

Vital Sign Measurements

Pre-implantation values, post-implantation values, and the change from baseline in vital sign measurements (blood pressure, heart rate, respiratory rate and temperature) will be summarized

with descriptive statistics (n, mean, SD, median, min and max) at each time point by treatment. The baseline value will be the latest value obtained prior to the insertion of the study device.

Physical Examination Findings

The number and percentage of subjects with abnormal findings on physical examination will be summarized by organ system.

10.3 Quality of Life and Medical Resource Utilization Parameters

10.3.1 Quality of Life

Pain and dyspnea (breathlessness) will be evaluated using the 100 mm VAS and the Modified Borg dyspnea scale, respectively. Patient-reported health status will be evaluated using the EQ-5D-5L health status questionnaire. Comparison between the two treatment groups involving continuous variables will be done using a two-sample t-test. Change from baseline between the two treatment groups will be analyzed using a two-sample t-test. Comparison between the two treatment groups involving categorical variables will be done using the chi-square test, or Fisher's exact test if more appropriate.

10.3.2 Medical Resource Utilization Parameters

Comparison between the two treatment groups involving continuous variables such as length of procedure, length of hospital stay and length of time IPC in place will be done using a t-test. All other resource utilization data will be summarized as frequencies and counts and compared using Fisher's Exact test as appropriate.

10.4 Interim Analysis

There will be an unblinded sample size evaluation to see if the assumption used for current sample size is reasonable. The sample size adjustment will be based on the promising zone approach as detailed in Mehta and Pocock (2011).[37]

The interim analysis will be conducted at 2/3 of the information rate, when 80 subjects are evaluable for the primary endpoint under the superiority hypothesis with the purpose of determining if the sample size needs to be increased to provide sufficient power for testing at the final analysis. Sample size will not be reduced under any circumstances. The study will not be stopped prematurely for efficacy prior to the 119 subjects being enrolled. Through simulation based on the methods outlined in Wang et al[38], it was determined that Type I error is controlled under 0.025 (details in SAP). The below rules will be followed, where conditional power (CP) is CP at interim.

- Unfavorable Zone: $CP < 0.395$ → Study size will remain the same at 119
- Promising Zone: $0.395 \leq CP < 0.8$ → Study size will be increased to 179
- Favorable Zone: $CP \geq 0.8$ → Study size will remain the same at 119

0.395 is the minimum CP derived from conservative extrapolation from Table 1 in Mehta and Pocock (2011)[37] to determine the unfavorable zone.

Interim analysis procedures and control of access to the unblinded interim data are described in the SAP.

10.5 Subgroup Analyses

If at least 80% of the total number of US subjects participating in this study are Medicare beneficiaries, then no subgroup analysis will be conducted. However, if less than 80% of all US subjects enrolled are Medicare beneficiaries, then a subgroup analysis will be conducted to evaluate outcomes specifically for the Medicare beneficiaries enrolled in the study. All primary and secondary outcomes for the subgroup analyses will be the same as for the main analysis.

For this analysis, the Medicare population will be defined as any subject recruited in the US, who is:

- is at least 65 years old (even if he/she did not indicate Medicare as primary insurance),
- or under 65 years old, and receives Medicare health insurance (due to a disability).

10.6 Determination of Sample Size

The sample size was calculated based on the primary efficacy endpoint: rate of pleurodesis at 30 days. A sample size of 79 subjects in the study device group and 40 subjects in the control study device group is planned for the study based on 80% power to demonstrate superiority of the study device group over the control group with a one-sided type I error 2.5%.

The unadjusted rates of pleurodesis are assumed to be 75% for the study device group, and 35% for the control device. Assuming 20% subjects will have trapped lung who cannot achieve pleurodesis, and 20% of the remaining subjects will drop out before reaching the 30 days follow up, and will be considered as failures for the primary endpoint, the adjusted pleurodesis rates [calculated as: expected rate *(1-drop-out rate)*(1-trapped lung rate)] are 48% for the study device group and 22% for the control device. Subjects who are discontinued/withdrawn after entering the randomized treatment phase will not be replaced. When 80 subjects reach the primary endpoint, an unblinded sample size reassessment will be performed as detailed in Section 10.4.

Details of sample size estimation are included in the SAP.

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12 Appendices

APPENDIX 1 | KARNOFSKY SCORING[39]

Level of function	Score	Symptoms
Able to carry on normal activity and to work; no special care needed.	**100**	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	**70**	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	**40**	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

APPENDIX 2 | WHO SCORING[40]

Grade	Explanation of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX 3 | LIGHT'S CRITERIA FOR DETERMINING EXUDATIVE EFFUSIONS[41]

An effusion is likely to be an exudate if at least one of the following is present:

- The ratio of pleural fluid protein to serum protein is greater than 0.5
- The ratio of pleural fluid lactate dehydrogenase (LDH) and serum LDH is greater than 0.6
- Pleural fluid LDH is greater than 0.6 (or ⅔) times the normal upper limit for serum.

APPENDIX 4 | MODIFIED BORG DYSPNEA SCALE[42]

Instructions for Borg Dyspnea Scale

- Use this scale to rate the difficulty of your breathing.
- It starts at number 0 where your breathing is causing you no difficulty at all and progresses through to number 10 where your breathing difficulty is maximal.
- How much difficulty is your breathing causing you right now?

0	**Nothing at all**
0.5	**Very, very slight (just noticeable**
1	**Very slight**
2	**Slight**
3	**Moderate**
4	**Somewhat severe**
5	**Severe**
6	
7	**Very severe**
8	
9	**Very, very severe (almost maximal)**
10	**Maximal**

APPENDIX 5 | SAMPLE EQ-5D-5L HEALTH STATUS QUESTIONNAIRE (UK VERSION)[43, 44]

A sample page of the EQ-5D-5L health status questionnaire is provided below. Currently there are 123 language versions of the EQ-5D-5L self-complete health status questionnaire, including UK and US English.

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

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APPENDIX 6 | VISUAL ANALOG SCALE[45]

The VAS is a horizontal line, 100 mm in length, anchored by word descriptors at each end for each symptom extreme, as illustrated below. The patient places a mark on the line the point which represents his/her current perception of his/her pain. The VAS score is determined by measuring in millimetres from the left hand end of the line to the point that the patient marks.

How severe is your pain today? Place a vertical mark on the line below to indicate how bad you feel your pain is today.

No pain |_____| Very severe pain