MEMORANDUM

To: File

From: G Mark Grubb, Clinical Program Manager

Date: 25 October 2018

Subject: E7113, iNod Feasibility Statistical Analysis Plan

This Cover Memo is to document that for the attached study plan,

Statistical Analysis Plan
Feasibility Study of a Bronchoscopic Ultrasound-Guided Tissue Acquisition System with Real-time Visualization for Collection of Cytology Specimens of Peripheral Pulmonary Lesions

iNod Feasibility Study

Study Reference number E7113

The following is confirmed:

1) This plan is relevant to ClinicalTrial.gov identifier NCT02832284
2) This plan was finalized/released on 12 August 2016, within Boston Scientific's controlled document system, and was the only released version of this document though the course of this clinical study.

G Mark Grubb
Clinical Program Manager

Statistical Analysis Plan

Feasibility Study of a Bronchoscopic Ultrasound-Guided Tissue Acquisition System with Real-time Visualization for Collection of Cytology Specimens of Peripheral Pulmonary Lesions

iNod Feasibility Study

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PROTOCOL SUMMARY

Objective(s)	To demonstrate feasibility to access, visualize, and obtain specimens adequate for cytology of lung lesions in subjects with suspected lung cancer when using the iNod System.
Planned Indication(s) for Use	The iNod System is intended for use for diagnostic ultrasound imaging and ultrasound-guided fine needle aspiration (FNA) of extramural and submucosal lesions of the tracheobronchial tree.
Test Device	The iNod System, is comprised of the following components: • iNod Ultrasound Imaging System • iNod Ultrasound Catheter • iNod Biopsy Needle • iNod Motor Drive Unit • iNod Sled The iNod Biopsy Needle and the iNod Ultrasound Catheter are intended to be used, in combination, in the Olympus BF-P190 or Olympus BF-MP160 Bronchoscopes.
Control Device	None
Study Design	Multi-center, Prospective, Single-arm Feasibility Study with Salvage.
Number of Subjects and Centers	5 to 10 Subjects at 2-3 US study centers. 15 to 30 Subjects, across all study centers.
Primary Endpoint	Clinical success is defined as the iNod System's ability to acquire adequate specimens of cellular matter suitable for the cytologic evaluation of targeted lung lesions, under real-time visualization. Salvage Procedure: In case of primary endpoint failure with the iNod System, Radial EBUS-guided diagnostic sampling maneuvers (current standard-of-care) will be performed in an attempt to access, visualize, and sample targeted lung lesions.
Secondary Endpoints	1. Occurrence and severity of Adverse Events related to the iNod System biopsy procedures, as well as Adverse Events related to any subsequent Radial EBUS-guided salvage procedures. 2. Proportion of lesions visualized during iNod Maneuvers 3. Proportion of lesions accessed where iNod Biopsy Needles were deployed

	in the target lesion during study maneuvers 4. Proportion of iNod maneuvers that acquire specimens of cellular matter for cytology
Follow-up Schedule	Baseline Visit: Informed Consent, Medical History, including collection of a Chest CT image within 6 weeks of study procedure, which confirms the presence of peripheral pulmonary lesion(s). Bronchoscopy Procedure: iNod sampling of lesion followed by additional standard of care (salvage) procedures, should collected specimens be determined as inadequate for cytologic evaluation. Intra-procedural specimens collected for cytology will be documented. Completion / End of Study: • Following the bronchoscopic procedure, and per standard clinical practice, the subject will have a post-procedure chest x-ray. • The subject will have a Day 7 Post-Procedure Safety Call to check for any delayed-onset Device/Procedure/Anesthesia-related safety events.
Study Duration	The study will close after enrollment is completed. The enrollment period is estimated to be open for approximately 1 year from First Patient In (FPI) through Last Patient Out (LPO). Follow-up of unforeseen procedure-related safety events could extend LPO beyond the date of the last study procedure.

1 INTRODUCTION

This statistical plan addresses the planned analyses for the iNod Feasibility Study based on protocol # 91122035. Specified analyses may be used for scientific presentations and/or manuscripts and may not all be provided to Regulatory Authorities.

2 ENDPOINT ANALYSIS

2.1 Primary Endpoint

The primary endpoint is clinical success defined as the iNod System's ability to acquire adequate specimens of cellular matter suitable for the cytologic evaluation of targeted lung lesions, under real-time visualization.

In case of primary endpoint failure with the iNod System, a salvage procedure will be performed using Radial EBUS-guided diagnostic sampling maneuvers (current standard-of-care) in an attempt to access, visualize, and sample targeted lung lesions.

2.1.1 Analysis

The primary analysis for clinical success will be descriptive for patients in the per-protocol (PP) analysis set.

2.1.2 Sample Size

Since no formal hypothesis will be tested, there is no statistical justification of sample size.

Peripheral pulmonary lesions vary in their location in the tracheobronchial tree, their size, and their characteristics (e.g., concentric vs. eccentric). A sample size of 5-10 subjects per site allows greater potential to evaluate the usability and performance of the system for visualization and sampling this range of lesions.

Performance feedback for this traditional feasibility study is sought from more than 1 physician. While staying within the sample size confines of a traditional feasibility study, Boston Scientific has elected to seek the expertise of 2 to 3 interventional bronchoscopists.

2.1.3 Statistical Methods

For the primary endpoint of clinical success, the analysis will be performed as described below.

For all PP patients, the primary endpoint of clinical success occurs when there is at least one adequate specimen of cellular matter suitable for the cytologic evaluation of targeted lung lesions is acquired under real-time visualization by the iNod System. If there is no adequate specimen of cellular matter suitable for the cytologic evaluation of targeted lung lesions, under real-time visualization by the iNod System, then the patient will be considered a clinical failure. The primary endpoint will be evaluated as the number of clinical successes out of all PP patients; a 95% exact confidence interval will also be calculated for the primary endpoint.

For patients who do not have clinical success and a salvage procedure is done, the proportion of patients with a salvage procedure for which at least one adequate specimen of cellular matter suitable for the cytologic evaluation of targeted lung lesions will be calculated; a 95% exact

confidence interval will also be calculated for the proportion of patients with a successful salvage procedure.

3 GENERAL STATISTICAL METHODS

3.1 Description of Statistical Methods

Descriptive statistics will be presented for all intent-to-treat (ITT) and per-protocol (PP) patients. The mean (± standard deviation) will be used to describe continuous variables with a normal distribution and the median (and interquartile range) will be used to describe continuous variables with a skewed distribution. Frequency tables will be used to summarize discrete variables. Proportions of patients with adverse events and SAEs will be reported. No hypothesis testing will be performed.

3.2 Analysis Sets

3.2.1 Intent-to-Treat Cohort

The intent-to-treat (ITT) cohort consists of subjects enrolled in the study regardless of whether a specimen was obtained from the iNod System. The point of enrollment is the time at which, following recruitment, a subject signs and dates the informed consent form.

3.2.2 Per Protocol Cohort

The per-protocol (PP) cohort is a subset of the ITT subjects for whom a specimen was obtained using the iNod System.

3.2.3 Restricted Per Protocol Cohort

The restricted per-protocol (rPP) cohort is a subset of the PP subjects for whom the ICF was executed properly and all eligibility criteria were met.

3.3 Control of Systematic Error/Bias

All subjects who have met the inclusion/exclusion criteria and have signed the ICF will be eligible for enrollment in the study. Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

3.4 Number of Subjects per Investigative Site

Each investigative site is expected to enroll 5 to 10 patients.

4 ADDITIONAL DATA ANALYSES

4.1 Secondary Endpoints

1. Occurrence and severity of Adverse Events related to the iNod System biopsy procedures, as well as Adverse Events related to any subsequent Radial EBUS-guided salvage procedures.
2. Proportion of lesions visualized during iNod Maneuvers

3. Proportion of lesions accessed where iNod Biopsy Needles were deployed in the target lesion during study maneuvers
4. Proportion of iNod maneuvers that acquire specimens of cellular matter for cytology

4.2 Interim Analyses

No formal interim analyses are planned for the iNod Feasibility Study for the purpose of stopping the study early for declaring effectiveness or for futility. Informal interim analysis may be conducted for the purpose of submissions of abstracts to major professional meetings.

4.3 Subgroup Analyses

No subgroup analysis is planned.

4.4 Justification of Pooling

The analyses will be presented using data pooled across centers as well as by center for the primary endpoint. If deemed appropriate, stratified and multivariate analysis techniques, including Chi-square test or logistic regression, will be used to assess differences between study centers to justify pooling data across centers.

4.5 Multivariable Analyses

No multivariable analyses are planned for this study.

4.6 Other Analyses

4.6.1 Baseline Characteristics

Baseline data will be summarized to assess subject demographics, clinical history, risk factors, and pre-procedure characteristics. Data will be summarized as described in Section 3.1.

4.6.2 Post-Procedure Endpoints

Post-procedure information will be collected at regularly scheduled follow-up examinations as detailed in the clinical trial schedule in the protocol. Data will be summarized as described in Section 3.1.

4.6.3 Subject Disposition

Subject disposition (e.g., number completing the study, number lost-to-follow-up) will be summarized with frequency tables for each visit.

4.7 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended statistical analysis plan approved before performing the analyses. Changes to the planned statistical methods not documented in an updated statistical plan will be documented in the clinical study report along with a reason for the deviation.

5 VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation.

6 PROGRAMMING CONSIDERATIONS

6.1 Statistical Software

Statistical data review will be performed by the sponsor. Statistical analyses will be performed using SAS System software, version 9.2 or later (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

6.2 Format of Output

Results of analysis will be output programmatically to Word documents from SAS with no manual intervention. All output for the final statistical report will be in the form of a Word document containing tables, figures, graphs, and listings, as appropriate.

6.3 Rules and Definitions for Calculated Variables

The following sections describe the identification of the ITT and PP patients and the calculation of the primary endpoint of clinical success.

6.3.1 Intent-to-treat patients

A subject is in the ITT cohort if the subjects has signed and dates the ICF.

Valid Data Sources

- Screening Form

Valid Data Points from the Baseline Form:

- "Informed Consent Signature Date"

Analysis approach:

- **Include** a subject in the ITT cohort if the "Informed Consent Signature Date" is complete for all of day, month, and year
- **Exclude** a subject from the ITT cohort if the "Informed Consent Signature Date" if any or all of day, month, or year are missing.

6.3.2 Per-protocol patients

A subject is in the PP cohort if the subject is in the ITT cohort and at least one specimen was obtained using the iNod System.

Valid Data Sources

- ITT cohort subjects
- iNod Diagnostic Procedure Form

Valid Data Points:

- ITT cohort subjects
- iNod Diagnostic Procedure Form:

- "Was a sample obtained?"

Analysis approach:

- **Include** a subject in the PP cohort if **all the following conditions are met**:
  - Subject is in the ITT cohort
  - "Was a sample obtained?" is "Yes"
- **Exclude** a subject from the PP cohort if **one of the following conditions are met**:
  - Subject is not in the ITT cohort
  - "Was a sample obtained?" is "No" or missing

6.3.3 Restricted Per-protocol patients

A subject is in the rPP cohort if the subject is in the PP cohort, the ICF was executed properly, and all eligibility criteria were met.

Valid Data Sources

- PP cohort subjects
- Screening Form
- Protocol Deviation Form

Valid Data Points:

- PP cohort subjects
- Screening Form:
  - "Was all protocol specific entrance criteria met for this subject?"
- Protocol Deviation Form:
  - Protocol Deviation Category

Analysis approach:

- **Include** a subject in the rPP cohort if **all the following conditions are met**:
  - Subject is in the PP cohort
  - "Was all protocol specific entrance criteria met for this subject?" is "Yes"
  - The subject does not have a Protocol Deviation form where "Protocol Deviation Category" has response "Informed Consent"
- **Exclude** a subject from the rPP cohort if **one of the following conditions are met**:
  - Subject is not in the PP cohort
  - "Was all protocol specific entrance criteria met for this subject?" is "No" or missing
  - The subject has a Protocol Deviation form where "Protocol Deviation Category" has response "Informed Consent"

6.3.4 Primary endpoint

The primary endpoint is clinical success defined as the iNod System's ability to acquire adequate specimens of cellular matter suitable for the cytologic evaluation of targeted lung lesions, under real-time visualization.

Valid Data Sources

- PP cohort subjects
- iNod Diagnostic Procedure Form

Valid Data Points

- PP cohort subjects
- iNod Diagnostic Procedure Resection form: "If yes, was it adequate for Rapid On-Site Evaluation (ROSE) Diagnosis/Cytology?" following the question "Was a sample obtained?" on the same form

Analysis approach:

- Include subject in the **denominator** if **both of the following conditions are met**:
  - Subject is in the PP cohort
  - "If yes, was it adequate for Rapid On-Site Evaluation (ROSE) Diagnosis/Cytology?" is answered "Yes" or "No"
- Include subject in the **numerator** if **both of the following conditions are met**:
  - Subject is in the PP cohort
  - "If yes, was it adequate for Rapid On-Site Evaluation (ROSE) Diagnosis/Cytology?" is answered "Yes"

REVISION HISTORY

Document Revision Number	Template Number and Version	Section	Change	Reason for Change
AA	90702621, AC	All	Original version of the SAP	