Statistical Analysis Plan

Prospective, Multi-center, Randomized Controlled Study Comparing Endoscopic Clearance of Non-Complex Biliary Stones Using Fluoroscopy/Radiation-Free Direct Solitary Cholangioscopy (DSC) to Standard of Care Endoscopic Retrograde Cholangiography (ERC)

Non-Complex Biliary Stones DSC vs ERC RCT

E7131

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APPROVALS (Check/Complete one below):

☒ Approvals are captured electronically

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Lead Biostatistician – [Insert Name and Title]	Date (dd-mon-yyyy)
Clinical Project/Trial Manager – [Insert Name and Title]	Date (dd-mon-yyyy)
Medical Director – [Insert Name and Title]	Date (dd-mon-yyyy)

Revision History

Document Revision Number	Template Number and Version	Section	Change	Reason for Change

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1 PROTOCOL SUMMARY

E7131 – Non-Complex Biliary Stones DSC vs ERC RCT	
Study Objective	To prospectively compare non-complex biliary stone clearance using fluoroscopy/radiation-free direct solitary cholangioscopy (DSC) utilizing the SpyGlass™ system with non-complex biliary stone clearance using standard endoscopic retrograde cholangiography (ERC).
Indication(s) for Use	• ***SpyGlass™ DS Digital Controller*** is intended to provide illumination and receive, process, and output images from the SpyScope™ DS Access and Delivery Catheter for diagnostic and therapeutic applications during endoscopic procedures in the pancreatico-biliary system including the hepatic ducts. • ***SpyScope™ DS Access and Delivery Catheter*** is intended to provide direct visualization and to guide both optical and accessory devices for diagnostic and therapeutic applications during endoscopic procedures in the pancreatico-biliary system including the hepatic ducts. • *The following devices will be available upon commercialization:* o ***SpyScope™ DS II Access and Delivery Catheter*** is intended to provide direct visualization and to guide both optical and accessory devices for diagnostic and therapeutic applications during endoscopic procedures in the pancreatico-biliary system including the hepatic ducts. o ***SpyGlass™ Retrieval Basket*** is indicated for the endoscopic removal of stones, stone fragments, or foreign bodies in the pancreaticobiliary system. o ***SpyGlass™ Retrieval Snare*** is indicated for the endoscopic retrieval of foreign bodies in the pancreaticobiliary system
Device	SpyGlass™ Digital System
Study Design	• Prospective • Consecutive cases • Multi-center • Randomized 1:1 ratio: o Group A (ERC arm): Clearance of bile duct stones using standard-of-practice ERCP techniques

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E7131 – Non-Complex Biliary Stones DSC vs ERC RCT	
	○ Group B (DSC arm): Clearance of bile duct stones using DSC techniques ○ Block-randomization by site • Non-inferiority hypothesis • Validation of stone clearance by ERC in DSC arm and by DSC in ERC arm.
Number of Subjects	• 250 subjects • An additional 5 Roll-in cases. Each participating endoscopist at each of the participating centers must perform up to 5 Roll-in cases. These roll-in cases will not count towards enrollment ceiling of 250 cases. • Procedures to be conducted only by the Principal Investigator. Sub-Investigators will be authorized to do study procedures only on an exception basis. Such exception may be granted by the Sponsor in consultation with the Principal Investigator of the site and Lead Principal Investigator to the study.
Number of Sites	Up to 15 global sites
Primary Endpoint	Complete stone clearance by extraction of bile duct stones from the common bile duct (CBD) into duodenum as determined by fluoroscopy free cholangioscopy in the DSC arm and by cholangiography in the ERC arm.
Secondary Endpoints	1. Evaluation of all serious adverse events (SAEs) including all deaths (related and unrelated), severity, onset, time to resolution related to the DSC devices and/or procedure and/or the ERC procedure through 30 days post procedure. 2. Radiation exposure to the patient (total fluoroscopy time, total radiation dose, Dose Area Product (DAP), effective dose), from duodenoscope in to completion of stone clearance, not including the validation DSC procedure in ERC arm and ERC procedure in DSC arm. 3. Duration of procedure defined as time from duodenoscope in to completion of stone clearance, not including the validation DSC procedure in ERC arm and ERC procedure in DSC arm.
Follow-up Schedule	Telephone follow-up during the following post-procedure intervals: • 24 hours • 7 days

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	• 30 days
Study duration	Approximately 2 years
Inclusion Criteria	1. 18 years or older 2. Abdominal pain consistent with choledocholithiasis (procedure possible within 72 hours of onset of symptoms and imaging suggesting choledocholithiasis, contingent on persistent abdominal pain) 3. Abnormal LFTs 4. Non-complex biliary stone disease, defined as 5 or fewer stones in the common bile or common hepatic duct with largest stone no larger than 10 mm in size. If stones not seen on imaging (US, CT) the bile duct diameter should be ≤12 mm* * Given the poor sensitivity (approximately 20%) for biliary stones of CT and US, the diameter of the dilated CBD is used as a surrogate for largest stone diameter 5. Availability of non-invasive imaging to determine the diameter of the bile duct and number and size of bile duct stones if visible on imaging a. If probability of stones is high per investigator assessment based on ASGE criteria, any standard of practice imaging modality (eg. abdominal US) is acceptable. b. If the probability of stones is either intermediate or low per investigator assessment based on ASGE criteria, MRCP or EUS imaging is required to confirm presence of stones. 6. Willing and able to comply with the study procedures and provide written informed consent to participate in the study
Exclusion Criteria	1. Potentially vulnerable subjects, including but not limited to pregnant women and subjects in whom an endoscopic procedure is contraindicated 2. Location of the stones in intrahepatic ducts, cystic duct or proximal to strictures 3. Bile duct stricture noted distal to stone on MRCP, which would make extraction without lithotripsy impossible

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	4. Ongoing cholangitis at time of randomization, manifested by fever with tachycardia and hypotension or evidence of pus at the ampulla 5. Patients with prior biliary sphincterotomy 6. Patients with Primary Sclerosing Cholangitis (PSC) 7. Acute pancreatitis, defined as abdominal pain and serum concentration of pancreatic enzymes [lipase (required), amylase (optional)] three or more times the upper limit of normal 8. Surgically altered gastro-duodenal luminal anatomy other than prior Billroth I reconstruction, as these would be anticipated to lead to more complicated procedures 9. Coagulopathy or ongoing need for anti-coagulation
Statistics	• Preliminary DSC-guided stone clearance rate was established in a Pilot study[1] and found to be comparable to that of ERC-guided stone clearance. • Eight relevant peer-reviewed publications[2-9] reporting on ERC-guided biliary stone clearance rates, representing 2721 patients were analyzed. A meta-analysis was conducted of the biliary stone clearance rates, yielding a point estimate of 90% with a 95% CI of [85%, 94%] (see Forest plot below). • Based on the two observations provided above, we hypothesize that the DSC-guided stone clearance rate is non-inferior to that of the ERC-guided stone clearance rate. We assume a DSC-guided and ERC-guided stone clearance rate of 90% and use a 10% non-inferiority margin for the sample size calculation provided below. The 10% non-inferiority margin is based on the fact that in the references used for the meta-analysis[2-9] stone clearance rates above 80% eliminate the lowest performing publications. **Test Method:** An exact test will be used to test the one-sided hypothesis of non-inferiority of the DSC-guided vs ERC-guided stone clearance rates. **Sample Size:** To detect non-inferiority of the clearance rate in DSC arm compared to the ERC arm with 80% power and one-sided alpha=0.05, a sample of 250 total is needed.

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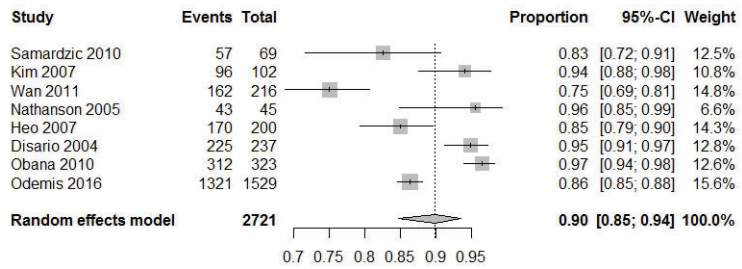

2 INTRODUCTION

This statistical plan addresses the planned analyses for the study on Non-Complex Biliary Stones DSC vs ERC based on the protocol dated February 16th 2018, Version D2. Specified analyses may be used for scientific presentation and/or manuscripts and may not all be provided to Competent Authorities.

3 ENDPOINT ANALYSIS

3.1 Primary/Secondary Safety/Efficacy/Effectiveness Endpoint

The primary endpoint is complete stone clearance by extraction of bile duct stones from the common bile duct (CBD) into duodenum as determined by fluoroscopy free cholangioscopy in the DSC arm and by cholangiography in the ERC arm.

Preliminary DSC-guided stone clearance rate was established in a pilot study[1] and found to be comparable to that of ERC-guided stone clearance. Eight relevant peer reviewed publications[2-9] reporting on ERC-guided biliary stone clearance rates representing 2721 patients were analyzed. A meta-analysis was conducted of the biliary stone clearance rates, yielding a point estimate of 90% with a 95% CI of [85%, 94%].

3.1.1 Hypotheses

We hypothesize that the DSC-guided stone clearance rate is non-inferior to that of the ERC-guided stone clearance rate. We assume a DSC-guided and ERC-guided stone clearance rate of 90% with a 10% non-inferiority margin. The following hypothesis will be tested:

$$H_0: P_{DSC} \text{ minus } P_{ERC} \leq -\Delta \text{ (Inferior)}$$
$$H_1: P_{DSC} \text{ minus } P_{ERC} > -\Delta \text{ (Non-inferior)}$$

where P_{DSC} and P_{ERC} are the stone clearance rates for the DSC arm (test) and the ERC arm (control), respectively, and (Δdelta) is the non-inferiority absolute margin.

3.1.2 Sample Size

The sample size was estimated based on the following assumptions:

- Expected stone clearance rate of 90% in DSC-guided and ERC-guided group
- Non-inferiority margin: 10%
- Alpha (1-sided): 0.05
- Power: 80%

With the above assumptions, a sample of 250 patients (125 in each arm) is needed to detect the non-inferiority of the clearance rate in the DSC arm compared to the ERC arm. This sample size was calculated using StatXact 9®.

3.1.3 Statistical Methods

An exact test will be used to test the non-inferiority hypothesis of the DSC-guided vs. ERC-guided stone clearance rates.

4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

4.1.1 Enrolled Cohort

A subject is considered enrolled after signing the study-specific Informed Consent Form (ICF). Patients who sign the ICF but subsequently do not meet one or more of the selection criteria will be considered screen failures and will be excluded from the study.

4.1.2 Intent-to-Treat Cohort (ITT)

This cohort consists of those enrolled patients who meet all inclusion/exclusion criteria and are subsequently randomized.

4.1.3 Per-Protocol Cohort (PP)

The per-protocol cohort is a subset of the ITT subjects who are treated per protocol post randomization with no major protocol deviations (ICH E9 definitions).

5 ADDITIONAL DATA ANALYSES

5.1 Secondary Endpoints

The following will be recorded as secondary outcomes during baseline and follow-up procedures:

- Evaluation of all serious adverse events (SAEs) including all deaths (related and unrelated), severity, onset, time to resolution related to the DSC devices and/or procedure and/or the ERC procedure through 30 days post procedure.
- Radiation exposure to the patient (total fluoroscopy time, total radiation dose, Dose Area Product (DAP), effective dose), from duodenoscope in to completion of stone clearance, not including the validation DSC procedure in ERC arm and ERC procedure in DSC arm.

- Duration of procedure defined as time from duodenoscope in to completion of stone clearance, not including the validation DSC procedure in ERC arm and ERC procedure in DSC arm.

5.2 Baseline Data

Baseline data will be summarized using but not limited to the following variables: subject demographics, medical history, and history of prior ERCP or sphincterotomy. Descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) will be reported for continuous variables and frequency tables for discrete variables.

5.3 Procedure Data

Procedure data, such as cannulation success, biliary sphincterotomy and stone removal will be collected and reported using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables for discrete variables.

5.4 Post-Procedure Data

Post-procedure data will be collected at 24 hours, 7 days, and 30 days, and will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables for discrete variables.

5.5 Interim Analyses

No formal interim analyses are planned for this study.

5.6 Subgroup Analyses

Stratified analyses will include tabulating the primary and select secondary endpoints by gender.

5.7 Justification of Pooling

The analyses will be performed using data pooled across institutions. An assessment of the poolability of patients across sites will be made by fitting generalized linear models with site as the factor of interest and the primary endpoint as the outcome variable.

5.8 Multivariable Analyses

Multivariable analyses may be performed to identify potential predictors and assess their effect on the primary endpoint.

5.9 Learning Curve Analyses

A generalized linear model will be fit to investigate the effect of time since first enrollment and sites/physicians (and potential interaction between time and sites/physicians) on the primary and select secondary endpoints.

5.10 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 prior to performing the analyses.

6 VALIDATION

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

7 PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

All statistical analyses will be done using The SAS System software, version 8 or higher (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved). StatXact9® software may be used for the primary endpoint analysis, as SAS does not provide exact non-inferiority test at the time of writing this SAP.

7.2 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.

7.3 Rules and Definitions

- Binary event rates (proportions) will be reported on a per-patient basis.
- The last follow-up date will be the latest of the following dates for each patient: date of an adverse event, procedure date, follow-up visit date, and device event date.
- Serious Adverse Event will be defined as an adverse event that:
    - Led to death
    - Led 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 hospitalization or prolonged hospitalization (of an existing hospitalization), or
        - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
    - Led to fetal distress, fetal death, or a congenital abnormality or birth defect.
- When calculating rates of adverse events, missing and partial dates will be handled as follows:

Partial Date Description	Action Taken
Entire onset date is missing	The procedure date will be used for the onset date.

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Partial Date Description	Action Taken
The month and the day of the month are missing but the year is available	January 1 will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

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