Final

STATISTICAL ANALYSIS PLAN

Study SAMISEN

Title: *(as per protocol/amendment)*	Safety and Performance of the Motorized Spiral Endoscope (PowerSpiral) in Subjects indicated for small-bowel enteroscopy: a PMCF Study.
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Date:	25-Feb-2021

Note:
This statistical analysis plan was prepared by SCO:SSiS using the SAP template Version 1 of SCO:SSiS

Abbreviations

Abbreviation	Description
AE	Adverse event
DT	Prototype table for descriptive statistics
FAS	Full analysis set
FT	Prototype of frequency table
GL	Prototype for general listings
ITT	Intent-to-treat
ND/UNK/NA	Not determined / unknown / not applicable
PP	Per-protocol
SAE	Serious adverse event
SOC	System organ class

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1 Relevant Documents and Standards

1.1 Protocol Version and Amendments

The statistical analysis plan is based on final version 02 of the study protocol of study SAMISEN dated April 23rd, 2019 (CIP#: 2018-GI(OEKG) – 01).

1.2 Applicable Standards

None.

1.3 Review Report

<text>

1.4 Other Documents

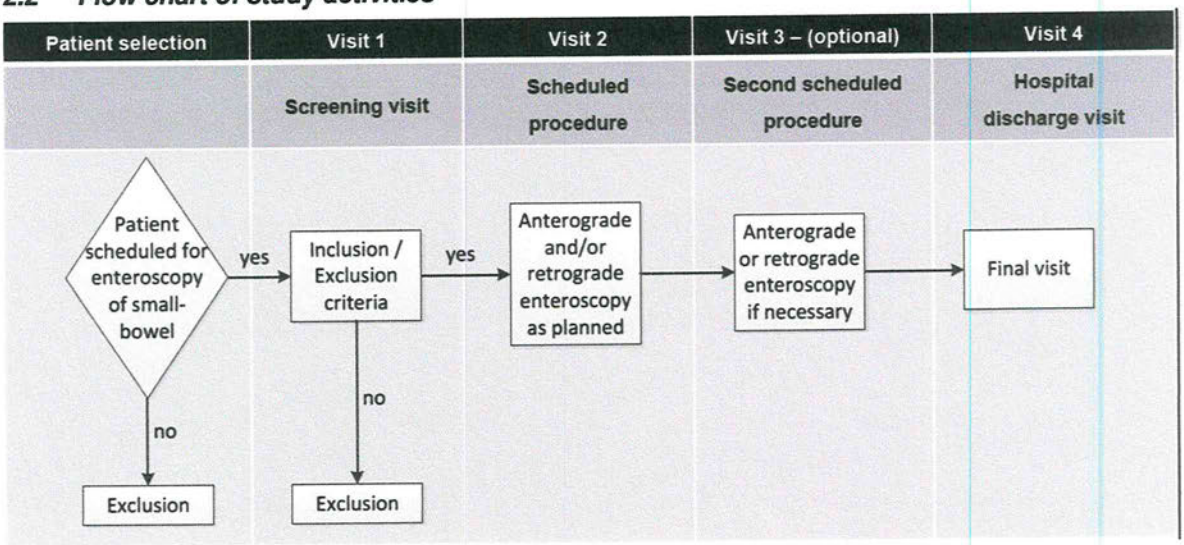
None.

2 Study Design and Objectives

2.1 Study Design

This is a international, multicenter, open label, non-randomized, prospective, observational study.

2.2 Flow chart of study activities



2.3 Study Objectives

The primary endpoint of this study is the assessment of the rate of serious adverse events to show a non-inferiority to preceding generations of balloon assisted enteroscopes. Thus, the observed rate of serious adverse events will be computed alongside it's 95% Clopper-Pearson confidence interval. If the upper confidence limit will be 8% or less, non-inferiority will be concluded.

Secondary objectives are the description of the following parameters:

- Reaching the anatomical region of interest
- Therapeutic yield
- Total procedure time
- Total small bowel enteroscopy rate
- User feedback
- Safety profile
- Effect of the learning curve

2.4 Primary and secondary variables

Primary efficacy variable:
The rate of serious adverse events during and after enteroscopy will constitute the primary endpoint for this study.

Secondary efficacy variables:

- Reaching the anatomical region of interest: The rate of successfully reaching the suspected anatomical target region (either by antegrade or by retrograde route) compared to all attempts represents the endpoint 'anatomical success rate'.
- Therapeutic yield: Defined as the percentage of patients with any endoscopic intervention / therapy with the exception of biopsies. (Sethi et al. 2014; Prachayakul et al. 2013; Sanaka et al. 2012)
- Total procedure time: Period in minutes needed to complete the procedure.
- Total therapeutic intervention time: Period in minutes dedicated to therapeutic intervention(s).
- Total small bowel enteroscopy rate: Defined as complete evaluation of the small bowel either with a single approach or combined anterograde and retrograde approach (if complete small bowel enteroscopy is intended anyway (Committee et al. 2015; Gerson et al. 2015).
- Diagnostic Yield (i.e. diagnosis, that explains findings from previous imaging or establishes a new diagnosis, that could explain clinical symptoms, thatindicated PSE)
- User feedback and judgment of handling characteristics and other aspects: User feedback and assessment of handling characteristics and other logistical aspects regarding:
    - Handling of PowerSpiral
    - Instrument insertion of PowerSpiral
    - Precision of positioning during therapy of PowerSpiral
    - Time needed for procedure of PowerSpiral
    - Staff and resource needed for procedure of PowerSpiral
- Serious adverse events (PS product related)
- Adverse events during enteroscopy procedure and adverse events (PS product related)

2.5 Coding dictionaries

- Adverse events: IMDRF current version
- Baseline findings: not applicable
- Medical history: not applicable
- Medication: not applicable

3 Statistical Evaluation

3.1 Populations for Analysis

All patients who did not undergo at least one enteroscopy will be considered as dropouts. Dropouts will be excluded from any statistical analyses.

Four different analysis populations will be defined:
The **core safety population (cSAF)** will consist of all patients who underwent at least one enteroscopy. Training patients will not be part of the cSAF.

The **general safety population (SAF)** will consist of all patients who underwent at least one enteroscopy including the training patients.

The **core intent-to-treat population (cITT)** will include all patients who underwent at least one enteroscopy and did not have any major protocol deviations. Training patients will not be part of the cITT.

The **general ITT population (ITT)** will comprise all patients who underwent at least on enteroscopy and did not have any major protocol deviation including the training patients.

Only patients of part A are covered by this SAP. For the analysis of data from patients of part B (ERCP patients), a separate SAP will be prepared.

The safety analysis will be performed on the safety population (SAF), which consists of all patients who underwent at least one enteroscopy.
Efficacy analyses will be based on the intent-to-treat (ITT) population, which includes all patients

- who underwent at least on enteroscopy and
- who had not major protocol deviations.

Note: Final decisions regarding validity will be made during the Review Meeting and documented in the Review Report (see Section 1.3).

3.2 Interim analyses

No interim analyses planned.

3.3 Subgroup analyses

The following subgroups will be additionally considered in the analysis of the primary endpoint:

- Previous abdominal surgery (yes/no)
- Bowel obstruction (yes/no)
- Crohn disease (yes/no)
- Treatment with Acetylsalicylic acid (80 – 100 mg) during procedure (yes/no)
- Treatment with Anticoagulant during procedure (yes/no)
- Procedure changed as compared to initally planned procedure (yes/no)
- Therapeutic intervention (yes/no)
- Concomitant diseases (Inflammation/Polyp/neoplasia/other)

3.4 Derived Data and Data Sets

3.4.1 Rules for incomplete data

Missing data will not be replaced.

3.4.2 Rules for efficacy

None.

3.4.3 Rules for adverse events

Seriousness: 0 ≈ 'no', 1 ≈ 'yes'.

Attribution of the AE to the PowerSpiral Device
A frequency table will be presented showing the the information on attribution of the AE to the PowerSpiral device using the categorization given on the CRFs:

1 ≈ 'not related', **2** ≈ 'unlikely', 3 ≈ 'possible', **4** ≈ 'probable', **5** ≈ 'causal relationship'.

Moreover, this categorization will be used in data listings.

3.4.4 Rules for laboratory data

Not applicable.

3.4.5 Rules for vital signs

Not applicable.

3.4.6 Rules for physical examination

Not applicable.

3.4.7 Other rules

None.

3.5 Demography, Medical History, Concomitant Medication, Study Procedures

Descriptive statistics (n, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum) will be calculated for quantitative variables; frequency counts by category will be given for qualitative variables. Confidence intervals will be given where appropriate. If not stated otherwise, these intervals will be two sided in each case and provide 95% confidence. Individual listings will be provided for each parameter examined in this study.

In addition, information on the intervention will be presented as follows:
- Number of patients in whom a complete intervention was planned.
- Number of patients by number of interventions
- Number of patients with complete and incomplete interventions

Intervention
- Were all interventions successfully completed?
- Type of intervention

Intervention time
- Descriptive statistics

Perception of investigator
- Handling of PowerSpiral vs. BAE (worse, similar, better)

Type of sedation
- number of patients with general anaesthesia and sedation

Concomitant medication and medical history will be listed only (if no codes are available).

3.6 Efficacy Analysis

The following efficacy analyses will be performed based on the cITT population and on the ITT population as sensitivity analysis:

- The anatomical success rate (number of cases in which the suspected anatomical region is reached compared to all attempts) will be computed alongside with its 95% Clopper-Pearson confidence interval.
- The therapeutic yield (percentage of patients with any endoscopic intervention/therapy with exception of biopsies) will be presented alongside its 95% Clopper-Pearson confidence interval.
- The total procedure time (period in minutes needed to complete the procedure) will be summarized descriptively.
- The total therapeutic intervention time will be summarized descriptively.
- The total small bowel enteroscopy rate (number of complete evaluations of the small bowel divided by all attempts to reach the small bowel) will be computed alongside its 95% Clopper- alongside their 95% Clopper-Pearson confidence intervals.
- The outcomes for the items in the user feedback for the judgement of handling characteristics and other aspects will be tabulated in frequency tables.
- Diagnostic Yield (i.e. diagnosis, that explains findings from previous imaging or establishes a new diagnosis, that could explain clinical symptoms, thatindicated PSE)
    - Diagnostic Yield is defined as the difference of proportion of patients for which a diagnosis was made and the proportion of patients with prior positive imaging (VKE, MRi, other)

3.7 Safety Analysis

3.7.1 Primary Safety Analysis

The primary safety analysis of the serious adverse events will be based on the cSAF. The rate of serious adverse events during and after enteroscopy procedure will be computed as the number of such serious adverse events divided by the number of patients in the cSAF. A 95% Clopper-Pearson confidence interval will be computed for the rate to assess the variability of the estimate. In case of an upper 95% confidence limit von 8% or below, non-inferiority to preceding generations of balloon assisted enteroscopes will be concluded.
The primary endpoint will be assessed in the core SAF as primary analysis. As secondary analyses, the primary endpoint will be assessed for the SAF, ITT and core ITT as well as for training patients only.

3.7.2 Adverse Events

The frequencies of adverse events, serious adverse events and device deficiencies will be reported in summary tables. These tables will show the number of subjects per group presenting a (serious) adverse event and the incidence of its occurrence.

Tabulations will be provided for system organ class and stratified by relation to the investigational product. Any withdrawals from the study due to adverse events will be reported. All measures taken due to adverse events will be reported.

AEs of special interest
- Number of patients with pancreatitis
- Number of patients with bleeding
- Number of patients with perforation
- Number of patients with complications associated with sedation/anesthesia
- Number of patients with other complications

For pre-treatment events summary tables and listings will be provided.

3.7.3 Laboratory Data

Not applicable.

3.7.4 Vital Signs

Vital signs will be analyzed descriptively by visit including changes from baseline.

3.7.5 ECG Data

Not applicable.

3.7.6 Other Safety Data

Physical examination at baseline will be analyzed descriptively by summary tables. Listings will be provided.

3.8 Other Analyses

None.

3.9 List of all tables / listings / figures with their location in Clinical Study Report

DT = Descriptive statistics table with n, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum

FT = Frequency table with absolute and relative frequencies, for the primary endpoint, 95% confidence intervals will be added

GL = General listing of parameters with patient ID, center, analysis population in each listing.

Description of table / figure / listing	Type
Tables	
11.1.1 Patient Disposition - All Enrolled Population Reference: annCRF page 5 Parameters: Patients with entries Analyses: absolute and relative frequencies	FT
11.1.2 Analysis Populations - All Enrolled Population Reference: None Parameters: Analyses populations (SAF, cSAF, ITT, cITT Analyses: absolute and relative frequencies	FT
11.1.3 In- and Exclusion criteria fulfilled? - SAF and cSAF Reference: annCRF page 5-6 Parameters: Categorical parameters Analyses: absolute and relative frequencies	FT
11.1.4 Visit Schedules - SAF and cSAF Reference: annCRF Page 3 Parameters: Median time from enrollmend to discharge Analyses: Descriptive analyses	DT
11.1.5.1 Demographics and Baseline Characteristics - Continuous Parameters - SAF and cSAF Reference: SAP chapter 3.5 Parameters: Age Analyses: Descriptive analyses	DT
11.1.5.2 Demographics and Baseline Characteristics - Categorical Parameters - SAF and cSAF Reference: SAP chapter 3.5 Parameters: Sex Analyses: absolute and relative frequencies	FT
11.1.6 Previous Abdominal Surgery - SAF and cSAF Reference: annCRF page 10-11 Parameters: Previous abdominal surgery, etc. Analyses: absolute and relative frequencies	FT
11.1.7.1 Information About Small-Bowel Enteroscopy - Listing of Indication - SAF and cSAF Reference: annCRF page 12 Parameters: Indication Analyses: Listing of freetext	GL
11.1.7.2 Information About Small-Bowel Enteroscopy - SAF and cSAF Reference: annCRF page 12 Parameters: Categorical parameters on information about planned small-bowel enteroscopy Analyses: absolute and relative frequencies	FT

Description of table / figure / listing	Type
11.1.7.3 Initially Planned Procedure with PowerSpiral - SAF and cSAF Reference: annCRF page 12-13 Parameters: Categorical parameters Analyses: absolute and relative frequencies	FT
11.1.7.4 Initially Planned Procedure with PowerSpiral - Listing of Freetext - SAF and cSAF Reference: annCRF page 12-13 Parameters: Freetext Analyses: Listing of freetext	GL
11.1.7.5 Procedure with PowerSpiral - Categorical Parameters - SAF and cSAF Reference: annCRF page 16-17 Parameters: Procedure with PowerSpiral, Procedural information Analyses: absolute and relative frequencies	FT
11.1.7.6 Procedure with PowerSpiral - Continuous Parameters - SAF and cSAF Reference: annCRF page 16-17 Parameters: Length of procedure, Time to reach deepest point of enteroscopy, Time score out Analyses: descriptive statistics	DT
11.1.7.7 Therapeutic Interventions - Listing of Comments - SAF and cSAF Reference: annCRF page 17 Parameters: Freetext, Start and Stop time of intervention by patient Analyses: Listing of freetext	GL
11.2.1 Assessment After Procedure - Categorical Parameters - ITT and cITT Reference: annCRF page 18 Parameters: Categorical parameters Analyses: absolute and relative frequencies	FT
11.2.2 Assessment After Procedure - Listing of Comments - ITT and cITT Reference: annCRF page 18 Parameters: Freetext Analyses: Listing of freetext	GL
11.2.3 Evaluation of Procedure - Categorical Parameters - ITT and cITT Reference: annCRF page 19-20 Parameters: Handling, instrument insertion, Precision, time needed, staff and recources needed Analyses: absolute and relative frequencies by category (worse, similar, better)	FT
11.2.4 Evaluation of Procedure - Diagnostic Yield - ITT and cITT Reference: SAP section 3.6 Parameters: positive imaging prior to precedure, information whether a diagnosis was made with PSE Analyses: absolute and relative frequencies	FT

Description of table / figure / listing	Type
11.3.1.1 Adverse Events during procedure - SAF and cSAF Reference: annCRF page 17 Parameters: Trigger question on AEs Analyses: absolute and relative frequencies	FT
11.3.1.2.1 Adverse Events by category - SAF and cSAF Reference: annCRF page 23 Parameters: Adverse event category Analyses: absolute and relative frequencies	FT
11.3.1.2.2 Serious Adverse Events by category - SAF and cSAF Reference: annCRF page 23 Parameters: Adverse event category Analyses: absolute and relative frequencies	FT
11.3.1.3 Adverse Events by category - Listing of other AEs - SAF and cSAF Reference: annCRF page 23 Parameters: Freetext Analyses: Listing of Freetext	GL
11.3.1.4.1 Adverse Events - Relatedness - SAF and cSAF Reference: annCRF page 23 Parameters: Relatedness Analyses: absolute and relative frequencies	FT
11.3.1.4.2 Serious Adverse Events - Relatedness - SAF and cSAF Reference: annCRF page 23 Parameters: Relatedness Analyses: absolute and relative frequencies	FT
11.3.1.5 Adverse Events - Seriousness - SAF and cSAF Reference: annCRF page 23-24 Parameters: Seriousness and seriousness components (e.g. death) Analyses: absolute and relative frequencies	FT
11.3.1.6.1 Adverse Events - Actions taken - SAF and cSAF Reference: annCRF page 24 Parameters: Actions Analyses: absolute and relative frequencies	FT
11.3.1.6.2 Adverse Events - Listing of Actions taken - SAF and cSAF Reference: annCRF page 24 Parameters: Freetext Analyses: Listing of Freetext	GL

Description of table / figure / listing	Type
11.3.1.7.1 Adverse Events - Causality to PowerSpiral Device - SAF and cSAF Reference: annCRF page 24 Parameters: Causality Analyses: absolute and relative frequencies	FT
11.3.1.7.2 Serious Adverse Events - Causality to PowerSpiral Device - SAF and cSAF Reference: annCRF page 24 Parameters: Causality Analyses: absolute and relative frequencies	FT
11.3.1.7.3 Adverse Events - Listing of Comments on Causality to PowerSpiral Device - SAF and cSAF Reference: annCRF page 25 Parameters: Freetext Analyses: Listing of freetext	GL
11.3.1.8.1 Adverse Events - AEs of special interest - SAF and cSAF Reference: SAP section 3.7.2 Parameters: Frequency Analyses: absolute and relative frequencies	FT
11.3.1.8.2 Serious Adverse Events - AEs of special interest - SAF and cSAF Reference: SAP section 3.7.2 Parameters: Frequency Analyses: absolute and relative frequencies	FT
11.3.1.9 Subgroup analyses for the primary endpoint SAEs - cSAF Reference: SAP chapter 3.3 Parameters: SAEs by Subgroup Analyses: absolute and relative frequencies	FT
11.3.2.1 Hospital Discharge - Categorical Parameters - SAF and cSAF Reference: annCRF page 22 Parameters: Categorical parameters Analyses: absolute and relative frequencies	FT
11.3.2.2 Hospital Discharge - Listing of Comments - SAF and cSAF Reference: annCRF page 22 Parameters: Freetext Analyses: Listing of freetext	GL
11.3.3.1 Physical Examination by visit - Continuous Parameters - SAF and cSAF Reference: annCRF page 7-8 Parameters: Height, Weight, Heart Rate, Blood Pressure (RR), Diagstolic blood Pressure Analyses: Measurement at each visit, change from baseline	DT