SAP EnteraSense

DETECT-1 Study

SIGNATURE PAGE

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DETECT-1 Study

Title: A Clinical Study to evaluate effectiveness and safety of the PillSense System in detecting blood in the stomach for the evaluation of upper gastrointestinal bleeding (UGIB)

Contents

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE(s)	Adverse Event(s)
CRF(s)	Case Report Form(s)
CP	Conditional Power
EGD	Esophagogastroduodenoscopy
GCP	Good Clinical Practice
GI	Gastro Intestine
ICH	International Conference on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
mITT	Modified Intent to Treat
NLR	Negative Likelihood Ratio
NPV	Negative Predictive Value
PPV	Positive Predictive Value
PT	Preferred Term
PLR	Positive Likelihood Ratio
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TPR	True Positive Rate
TNR	True Negative Rate
UGIB	Upper Gastrointestinal Bleeding

1. INTRODUCTION

This statistical analysis plan (SAP) provides a comprehensive and detailed description of the statistical methods and data presentations to be used in the summary and analysis of data from Protocol (CIP-019-03, DETECT-1 Study). Please refer to the study protocol and CRFs for details on study conduct, references, and data collection.

UGIB is defined as bleeding derived from a source proximal to the ligament of Treitz. UGIB is 4-5 times more common than the lower GI hemorrhage. Common signs and symptoms at presentation include hematemesis (73%), melena (21%), and coffee-ground emesis (6%); however, patients may also experience vague symptoms such as epigastric pain, abdominal tenderness, or dizziness.

The PillSense Capsule is a minimally invasive, single use device designed to detect blood in the stomach. Detection of blood in the stomach is used for evaluating the presence of upper gastrointestinal bleeding (UGIB). The battery powered PillSense Capsule features an optical sensor which detects blood and wirelessly transmits data to the PillSense Receiver. The optical sensor contained in the PillSense Capsule detects the presence of blood by measuring the absorption of multiple wavelengths of light. The data are then processed by an algorithm to determine if blood is present. The PillSense Capsule is designed to withstand the mechanical forces and chemical environment of the digestive system. The PillSense Capsule will make its way through the GI tract and is then passed naturally from the body. The PillSense Receiver collects and displays real-time information gathered by the PillSense Capsule. The PillSense Receiver interprets the data and displays a result message “Blood detected” or “No blood detected”.

The PillSense System includes an ingestible capsule which is designed to detect blood in the stomach and send real-time data to an external receiver. This minimally invasive device is intended to detect blood in the stomach providing direct evidence for UGIB.

In essence, PillSense System is intended to supplement but never replaces standard of care. In all cases, standard of care would continue to be utilized. The PillSense System will provide the gastroenterologist another important piece of information, which is the current presence of blood in the stomach. This information aids clinicians towards their diagnosis of UGIB vs. lower GI bleeding and helps to inform the subsequent care pathway.

The overall investigation from the PillSense Capsule activation and ingestion until the result message is displayed takes less than 10 minutes.

The PillSense System is a prescription only device.

2. PROTOCOL SYNOPSIS

Table below provides summary of the study purpose, study design, patient population, study objectives, endpoints, and inclusion/exclusion criteria.

Table 1. Study Summary

PillSense System	
Purpose and indication	The PillSense System is intended to be used for detection of blood in the stomach in adults with suspected UGIB.
Study design	This is a prospective, non-randomized, open-label clinical investigation to evaluate safety and effectiveness of the PillSense System when used for detection of blood in the stomach of patients suspected to have an Upper Gastrointestinal Bleed (UGIB). The study is also designed to confirm transit of the PillSense Capsule through the GI tract and patient tolerability of the PillSense Capsule. All Patients will undergo standard endoscopy following PillSense Capsule evaluation. The endoscopist will be blinded to the PillSense Capsule result, i.e., “Blood Detected” or “No Blood Detected
Sample size	86 Patients Minimum / 172 Patients Maximum
Study participation	All participants will receive the PillSense Capsule. All participants will receive EGD regardless of PillSense detection outcome within 4 hours of PillSense Capsule administration. Each Patient will spend up to 14±7 days in the investigation.
Study Objectives	The objective of the investigation is to demonstrate the PillSense System can detect blood in the stomach in clinically relevant scenarios and heterogenous environment of the upper GI tract. to assess the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the PillSense System in a clinical environment. to show that the PillSense Capsule will pass through the GI tract without incident in a timely manner.
Study Endpoints	Primary: 1. To assess the sensitivity of the PillSense System for detecting blood in the stomach. 2. To evaluate the specificity of the PillSense System for detecting blood in the stomach. Secondary: 1. To assess the positive predictive value (PPV) of the PillSense System, and 2. Negative predictive value (NPV) for the PillSense System 3. To evaluate the transit of the PillSense Capsule through the GI

PillSense System	
	tract
Inclusion criteria	1. Age 18 2. Ability to provide informed consent 3. Clinical suspicion of UGIB based on initial physical evaluation and intake history, e.g., prior episodes of UGI, presence of comorbid illnesses or medications associated with UGIB, laboratory data and symptom assessment such that patient is a candidate for endoscopy.
Exclusion criteria	1. Based on investigator's assessment there is a clear need for urgent endoscopy or surgery at the time of consent. 2. Known GI tract stricture 3. History of Zenker's diverticulum and fistulas 4. Using a pacemaker or other implantable electrical device 5. Dysphagia or difficulties in swallowing pills the size of the capsule 6. History of achalasia or known oesophageal dysmotility 7. History of gastroparesis 8. History of severe constipation (1 bowel movement per week or less) 9. Currently taking medications intended for stimulation of GI motility 10. Patients that have had Upper GI barium study within the previous 24 hours 11. Currently pregnant or breastfeeding, or intend to become pregnant during the investigation 12. Presence of psychological issues preventing participation 13. Presence of known gastric bezoar 14. History of Crohn's disease 15. History of small or large bowel obstruction 16. Suspected or previously diagnosed obstructing gastrointestinal tumour 17. Currently participating in another clinical trial that in the opinion of the investigator would interfere with the outcomes of this study or increase risk to the subject. 18. Planned MRI investigation (MRI needed before the capsule is excreted) 19. Presence of known hiatal hernia 5 cm or greater 20. Presence of known gastrointestinal abnormalities that could impact capsule performance

PillSense System	
	21. Presence of other concurrent conditions or known history that in the opinion of the Investigator would compromise patient safety or study objectives
Study Duration	The study is anticipated to be approximately 6 months in duration. The duration of each subject's participation will be approximately 1 day with a final follow up within a maximum of 3 weeks.

3. DEVICE DESCRIPTION

The PillSense System consists of the PillSense Capsule, an atraumatic, ingestible, and disposable capsule and PillSense Receiver, an external real-time monitor for results display.
The PillSense Capsule is a minimally invasive, single use device designed to detect blood in the stomach and wirelessly transmit the data to the external PillSense Receiver. The receiver is a handheld device which displays real-time information gathered from the capsule and clearly displays results, "Blood Detected" or "No Blood Detected".

3.1. Intended Use

The PillSense System is intended to be used for detection of blood in the stomach in adults with suspected UGIB. Detection of blood in the stomach is used for the evaluation of UGIB.

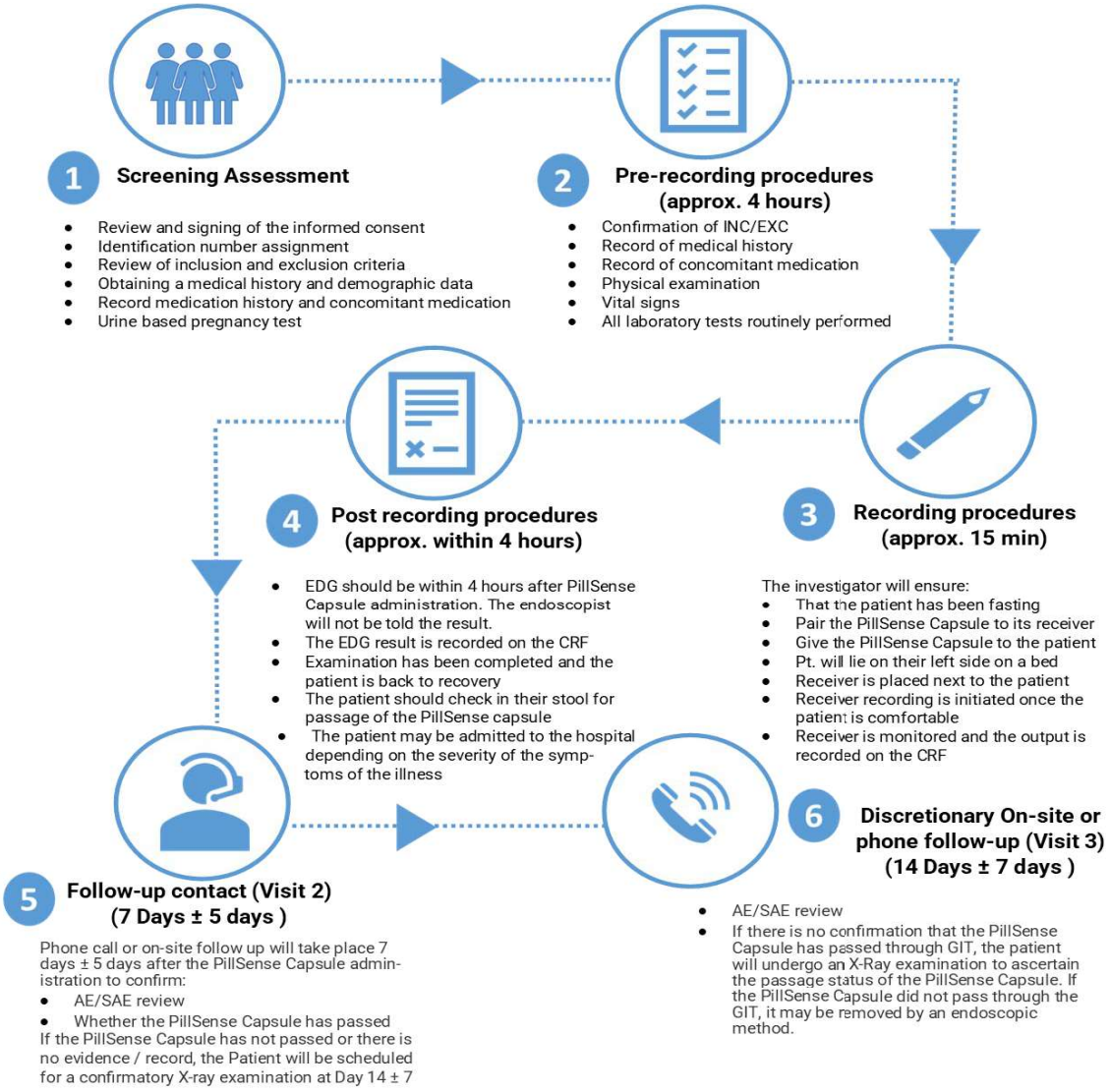
4. STUDY DESIGN

This is a prospective, non-randomized, open-label clinical investigation to evaluate feasibility, effectiveness and safety of the PillSense System, the transit of the PillSense Capsule through the GI tract, patient tolerability of the PillSense Capsule, and blood detection. Observation will take place for each Patient up to a maximum 21 days.
Subject Enrollment and Study Duration

The group of patients enrolled in the clinical investigation will be selected from a patient population with clinically suspected UGIB. Patients meeting the eligibility criteria as outlined in the protocol synopsis will be enrolled in the study.

The study is anticipated to be approximately 6 months in duration. The duration of each subject's participation will be approximately 1 day with a final follow up within a maximum of 3 weeks.

Study Flowchart



5. STUDY OBJECTIVES

5.1. Primary Endpoint

The co-primary endpoints are as follows:

- Sensitivity of the PillSense System for detecting upper GI bleeding.
- Specificity of the PillSense System for detecting upper GI bleeding.

These are defined as follows:

Sensitivity (True Positive Rate (TPR)): Probability that PillSense result will be “Blood Detected” when there is a bleeding.

$$\frac{\text{True positives}}{\text{True Positives + False Negatives}}$$

Specificity (True Negative Rate (TNR)): Probability that PillSense will be “No Blood detected” when there is no bleeding.

$$\frac{\text{True Negatives}}{\text{True Negatives + False Positives}}$$

- A True Positive is a subject with a bleed detected by the PillSense System that is confirmed by EGD.
- A False Negative is a subject with a bleed that is not detected by the PillSense Capsule but is detected by EGD.
- A True Negative is a subject with no bleed detected by the PillSense Capsule that is
- confirmed by EGD.
- A False Positive is a subject with a bleed detected by the PillSense Capsule that is not confirmed by EGD.

5.2. Secondary Endpoints

The secondary endpoints are as follows:

- Positive predictive value (PPV) of the PillSense System
- Negative predictive value (NPV) of the PillSense System
- Transit of the PillSense Capsule through the GI tract (yes/no)

PPV and NPV are defined as follows:

PPV: Probability of patients who have a “Blood detected” result having bleeding.

$$\frac{\text{True Positives}}{\text{True Positives + False Positives}}$$

NPV: Probability of patients who have a “No Blood detected” result and have no bleeding.

$$\frac{\text{True Negatives}}{\text{True Negatives + False Negatives}}$$

The above secondary endpoints are descriptive and will not be evaluated with a hypothesis test, and therefore no adjustment for multiplicity is required.

5.3. Exploratory Analysis

The exploratory analysis are as follows:

- Positive likelihood ratio (PLR) of the PillSense System
- Negative likelihood ratio(NLR) of the PillSense System
- Accuracy of PillSense capsule

These are defined as follows:

PLR: Probability (odds) of having “Blood detected” in a patient with bleeding.

$$\frac{\text{Sensitivity}}{\text{1-Specificity}}$$

NLR: Probability (odds) of having “Blood detected” in patients with no bleeding/

$$\frac{\text{1-Sensitivity}}{\text{Specificity}}$$

Accuracy: Correct classification rate is the proportion of observations for which the test result and actual response agree.

$$\frac{\text{True positive + True negative}}{\text{True positive + False negative + True negative + False positive}}$$

5.4. Safety Parameters

Safety will be assessed based on adverse events.
Summaries of adverse events (AEs) will be limited to treatment-emergent adverse events (TEAEs), which are those adverse events that begin or worsen after initiation of “treatment” with the investigational device (i.e., administration of the PillSense Capsule).
For AEs with a missing start date, the AE will be considered treatment-emergent unless there is additional information indicating that the AE started prior to study treatment.

The numbers and percentages of subjects with the below will be presented:

- at least one TEAE,
- at least one serious TEAE,
- at least one severe TEAE,
- at least one TEAE suspected to be related to the investigational device,
- at least one adverse device effect (ADE),
- at least one serious adverse device effect (SADE),
- at least one unanticipated serious adverse device effect (USADE), and any deaths.

AEs with a related, probable, or possible relationship, or for which the relationship is missing, will be considered related.

TEAEs and serious TEAEs will be summarized at the subject level by MedDRA system organ class (SOC) and preferred term (PT) using frequencies and percentages. TEAEs will also be summarized at the event level by SOC, PT, and severity and by SOC, PT, and relationship to the investigational device.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Descriptive Analysis

Data collected in this study will be documented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics, specifically the number of observations, mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized using frequencies and percentages.

6.2. Sample Size

Calculations were performed to estimate the minimum total sample size (TSS) required to achieve at least 80% probability of observing a successful outcome for both sensitivity and specificity to detection of Upper GI Bleed (UGIB), each relative to a performance goal. These calculations were performed assuming a prevalence of UGIB (PR) of 30%.

The probability of meeting the sensitivity endpoint is independent from the probability of meeting the specificity endpoint because they are based on different groups of patients. Therefore, the probability of meeting both endpoints (P) was calculated by multiplying the probabilities of meeting the sensitivity and specificity endpoints individually (i.e., by multiplying the statistical powers for the two endpoints).

The power for sensitivity was calculated based on the following specifications:

1. Single-arm study of PillSense
2. Primary endpoint: sensitivity to detection of Upper GI Bleed (UGIB)
3. Comparison to Performance Goal
4. True sensitivity: 0.975
5. Performance Goal: 0.75
6. Z-test with continuity correction
7. One-sided alpha = 0.025
8. Prevalence of UGIB = 30%

The power for specificity was calculated based on the following specifications:

1. Single-arm study of PillSense
2. Primary endpoint: specificity to detection of Upper GI Bleed (UGIB)
3. Comparison to Performance Goal
4. True specificity: 0.80
5. Performance Goal: 0.60
6. Z-test with continuity correction
7. One-sided alpha = 0.025
8. Prevalence of UGIB = 30%

Based on the above specifications, it was determined that 86 subjects (26 with UGIB for sensitivity and 60 without UGIB for specificity) are the minimum TSS that achieves ~80% probability of meeting both the sensitivity and specificity endpoints. With respect to specificity, study enrolment will continue until at least 60 subjects without UGIB are observed. The sample size for specificity

may be increased to a maximum of 120 patients to ensure that at least 60 mITT patients without UGIB are detected if the observed prevalence of UGIB during the trial is different from that assumed (i.e., 30%).

[redacted]

6.4. Analysis Population

a. modified Intent to Treat Population (mITT)

Will include all subjects with PillSense and EGD data. The primary and secondary endpoints will be analyzed based on the mITT Population. Any patients with missing primary endpoint data (either no PillSense Capsule reading or no EGD result) will be excluded from the primary and secondary endpoint analyses; however, we will report on the frequency and reason with which this occurs.

b. Safety Population

Will include all subjects who receive a PillSense capsule. Safety will be analyzed based on the Safety Population.

c. Other Populations

Withdrawals: Patients that fulfill inclusion criteria and have signed informed consent but withdrew after inclusion.

6.5. Handling of Missing and Incomplete data

All attempts will be made to collect all data per protocol, all practical monitoring and follow up steps will be taken to ensure complete and accurate data collection. Any data point that appears to be erroneous or inexplicable based on clinical judgment will be investigated as a possible

outlier. If data points are identified as outliers sensitivity analysis may be performed to examine the impact of including or excluding the outliers. Any substantive differences in these analyses will be reported. It is assumed that all missing data will be random.

In mITT population, subjects with missing data will not be counted in the percentage. Number of missing values will be reported.

In Safety population, for AEs with a missing start date, the AE will be considered treatment-emergent unless there is additional information indicating that the AE started prior to study treatment and AEs for which the relationship is missing, will be considered related

6.6. Poolability

The study is performed in only one site, Development Endoscopy Unit, Mayo Clinic, Rochester MN, therefore there are no issues for site heterogeneity.

6.7. Data Display Characteristics

For continuous data, the minimum and the maximum will use the same decimal accuracy as the raw data.

For categorical data, percentages will be reported to one decimal place.
For all one-sided statistical tests, a 0.025 significance level will be used unless otherwise noted. P-values will be reported to 4 decimal places. P-values less than 0.0001 will be displayed as <0.0001 in the tables.

7. PATIENT ACCOUNTABILITY

7.1. Patient Disposition

Patients' flowchart will be drawn describing the excluded patients from the mITT analysis set along with the reason.

7.2. Demography:

Demographic characteristics will be based on mITT analysis set.
Subjects will be summarized with respect to baseline demographics and physical examination (e.g., age, sex, ethnicity, race ,height, weight…etc), These will be summarized by descriptive statistics, including means, medians, standard deviations, minimums, and maximums.

These will be summarized as follows:

- Age (years): summary statistics
- Sex: Male, Female
- Ethnicity: Hispanic or Latino. Not Hispanic or Latino

- Race: White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian, or other Pacific Islander

7.3. Medical History:

Medical History summaries will be based on the complete and mITT analysis set.
The summary tables for medical history and baseline characteristics will be provided detailing the number and percentage of subjects. The following will be summarized for the complete and mITT cohorts:

- Inclusion/exclusion
- Underlying GI disease
- Height(cm) at baseline: summary statistics
- Weight (kg) at baseline: summary statistics
- BMI derived from height and weight: summary statistics
- Blood pressure (mmHg) at baseline: summary statistics
- Heart rate (bpm) at baseline: summary statistics

Reason for those subjects who were withdrawn will be provided separately.

7.4. Laboratory parameters

Laboratory parameters at baseline will be based on mITT analysis set. Subjects will be summarized with respect to Laboratory assessment. These will be summarized by descriptive statistics, including means, medians, standard deviations, minimums and maximums for continuous variables and frequencies and percentages for categorical variables.

These will be summarized as follows:

- Hemoglobin (g/dL) at baseline: summary statistics
- Hematocrit (%) at baseline: summary statistics
- Platelets (x10 3/uL) at baseline: summary statistics
- PT (secs) at baseline: summary statistics
- INR at baseline: summary statistics
- Pregnancy: Yes/No

7.5. Medications

Concomitant medication will be summarized using mITT analysis set.
The summary tables will be provided detailing the number and percentage of each medication. (Ordered alphabetically). A complete list of all concomitant medications will be provided.

7.6. PillSense Procedure Information

Summary tables will be provided detailing the number and percentage of the following:

- Location of procedures (e.g., endoscopy suite (admitted or not) etc.)

- Total monitoring time
- Device malfunctions (yes/no and type)
- Time between PillSense reading and EGD start time
- PillSense location at time of EGD (stomach or duodenum)
- Other clinically relevant endoscopic findings (yes/no) actual findings will be in listing.
- Additional interventions performed (yes/no) type in listing unless they can be summarized
- Time to PillSense excretion (passage) from the GI tract

8. STATISTICAL METHODOLOGY FOR ENDPOINTS

8.1. Statistical Methods for the Primary Endpoint

The estimate of sensitivity will be provided together with an exact (Clopper-Pearson) 95% confidence intervals for the true sensitivity. The null and alternative hypotheses for sensitivity are as follows:

$$H0: p1 \leq 0.75$$
$$\text{vs.}$$
$$H1: p1 > 0.75$$

where p1 denotes the true sensitivity. A one-sided, continuity-corrected z-test will be used to test the null hypothesis at the 0.025 level of significance.

The estimate of specificity will be provided together with an exact (Clopper-Pearson) 95% confidence intervals for the true specificity. The null and alternative hypotheses for specificity are as follows:

$$H0: p2 \leq 0.60$$
$$\text{vs.}$$
$$H1: p2 > 0.60$$

where p2 denotes the true specificity. A one-sided, continuity-corrected z-test will be used to test the null hypothesis at the 0.025 level of significance.

8.2. Statistical Methods for the Secondary Efficacy Endpoints

Secondary analysis will be performed based on mITT population. Secondary endpoints are for informational purposes only.

- Observed value along with exact (Clopper Pearson) 95% CI of Positive Predicative Value (PPN)
- Observed value along with exact (Clopper Pearson) 95% CI of Negative Predictive Value (NPV)
- Observed value along with exact (Clopper Pearson) 95% CI of Positive Likelihood Ratio (PLR)
- Observed value along with exact (Clopper Pearson) 95% CI of Negative likelihood Ratio (NLR)
- Observed value along with exact (Clopper Pearson) 95% CI of Accuracy.

8.3. Safety Analysis

Safety analysis will be performed based on safety population.

Proportion (Count and percentage (%)) of subjects with the below will be presented:

- at least one TEAE,
- at least one serious TEAE,
- at least one severe TEAE,
- at least one TEAE suspected to be related to the investigational device,
- at least one adverse device effect (ADE),
- at least one serious adverse device effect (SADE),
- at least one unanticipated serious adverse device effect (USADE),
- and any deaths.

Proportion (Count and percentage (%)) of AEs/SAEs Incidence.
Proportion (Count and percentage (%)) of AEs/SAEs type.
Proportion (Count and percentage (%)) of AEs/SAEs characteristics including severity, relationship to procedure, relationship to device, action taken and outcome.

AEs with a related, probable, or possible relationship, or for which the relationship is missing, will be considered related.
TEAEs and serious TEAEs will be summarized at the subject level by MedDRA system organ class (SOC) and preferred term (PT) using frequencies and percentages.
TEAEs will also be summarized at the event level by SOC, PT, and severity and by SOC, PT, and relationship to the investigational device.

9. DERIVED DATA

Adverse event duration will be calculated as (Onset date – Resolution date) + 1.
For partial dates, if day is missing but month is available, the 15th of the month will be used as the date. If both month and day are missing, then January 15th of the year will be used.
PillSense capsule passage will be calculated (Date of passage - Date of procedure)

10. DEVIATION FROM PROTOCOL

The number and percentage of subjects with each type of protocol deviation will be presented. The number and percentage of a corrective action will be presented. A separate listing of protocol deviation type and onset date by subject will be presented.

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