CLINICAL INVESTIGATIONAL PLAN (CIP)

Protocol Number: CIP-019-03 NCT05385224

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)

Brief Title: DETECT-1 Study

Version: 4.0

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7 INVESTIGATIONAL PLAN

7.1 Study Design

The DETECT-1 study was a prospective, single-center, single-arm comparative clinical investigation designed to evaluate safety and effectiveness of the PillSense System when used for the detection of blood in subjects suspected to have an Upper Gastrointestinal Bleed (UGIB). PillSense System performance for blood detection was compared with EGD performed within 4 hours of the PillSense System reading. The investigators performing the EGD were blinded to the results provided by the PillSense system.

Subjects were monitored for Capsule passage during hospitalization. An X-ray was taken before discharge if PillSense Capsule passage was not confirmed. As required, subjects were provided with a Capsule Retrieval Kit and were instructed to monitor their stools. A follow-up visit was performed within 7 days of Capsule administration. If Capsule passage was confirmed (either via return of the Capsule or photographic evidence of passage) the subject was exited from the study. Otherwise, the subject was required to return for another visit between Day 8 and Day 21. During this visit, if Capsule passage was not confirmed, an X-ray was to be performed before the subject was exited from the study. During hospitalization and at each in-person visit and telephone follow-up, occurrence of adverse events was assessed by verbally asking subjects if they have had any problems or symptoms since their last assessment. Upon discharge, the Subject was reminded to contact site staff immediately in the case of any discomfort and/or abdominal pain.

The complete final (Rev. 04) clinical protocol can be found in Appendix 16.1.

7.2 Discussion of Study Design, Including the Choice of Reference Group

The DETECT-1 study was designed as a prospective single-arm cohort study with the aim of evaluating safety and effectiveness of the PillSense System by comparing the sensitivity and specificity (and accuracy) of the PillSense System for detecting blood to the widely accepted reference standard; EGD. The Sensitivity and Specificity endpoints were compared with prespecified performance goals of 75% and 60% respectively.

The performance goals (PG) were developed based on a literature review of capsule endoscopy (CE) as the CE device represents the best comparator for the PillSense System as both the PillSense and CE are capsule technologies used for the detection of blood in the upper gastrointestinal tract. In a meta-analysis performed by Shah and colleagues [12], sensitivity among 5 studies evaluating CE for diagnosing UGIB ranged from 62% to 100% with a pooled sensitivity of 78% (lower 95% CI of 58%). Within this same meta-analysis, the specificity was documented to range from 64% to 100% with a pooled specificity of 74.8% (lower 95% CI of 68%). Of the two endpoints/performance goals, sensitivity was seen as the more important characteristic and therefore the PG was set higher for sensitivity than it was for specificity and on par with values observed for CE. Although the specificity for the PG in the PillSense protocol is slightly lower than the lower range documented in the literature for CE, the lower value is justified on the following basis:

- The PillSense reading is immediate, providing a “reading at the moment”; therefore, it is very possible that when the EGD was performed hours after the PillSense reading, that

bleeding may no longer be present, which may present as a “false positive” for the PillSense device.
- Since the PillSense detects the presence of fluids that are indicative of bleeding, there may be remnants of blood in the stomach even if there is no active bleeding, providing a false positive response.
- The risks associated with a false positive is minimal in that once the confirmation EGD is performed the patient’s treatment pathway would be reaffirmed within hours of the PillSense procedure.

The appropriateness of the study design and suitability of the PG values were reviewed with and accepted by FDA via review of a pre-submission Q210522.

7.3 Study Objectives

The study objectives are the following:

- to demonstrate the PillSense System can detect blood in the stomach in clinically relevant scenarios and heterogeneous 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.

7.4 Selection Of Study Population

7.4.1 Inclusion Criteria

Subjects who met all the following criteria were eligible for participation in the study:

1. Age ≥ 18 years
2. Ability to provide informed consent
3. Clinical suspicion of UGIB based on initial physical evaluation and intake history e.g., prior episodes of UGIB, presence of comorbid illnesses or medications associated with UGIB, laboratory data and symptom assessment, and subject is a candidate for endoscopy

7.4.2 Exclusion Criteria

Subjects who met any of the following criteria were excluded from participation in the study:

1. Based on the 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 esophageal 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. Subjects 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. The presence of a known gastric bezoar
14. History of Crohn's disease
15. History of small or large bowel obstruction
16. Suspected or previously diagnosed obstructing gastrointestinal tumor
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
21. Presence of other concurrent conditions or known history that in the opinion of the Investigator would compromise subject safety or study objectives

7.4.3 Withdrawal Of Subjects from Therapy or Assessment

In accordance with the 21 CFR Part 50, each subject had the right to withdraw his/her consent to participate in the trial at any time, for any reason, and without prejudice to his future medical care by the physician or at the investigational site.

The investigator also had the right to withdraw patients from the study for any legitimate reason, such as patient non-compliance with study procedures.

If a subject decided to withdraw from the study, or if a subject was withdrawn from the treatment or study, the date of and the reason for discontinuation was recorded on the electronic case report form (eCRF). All efforts were made to complete the end of treatment (EOT) evaluations at a time agreed by the patient and investigator, and observations/assessments were recorded as thoroughly as possible.

All patients were to be followed until it was determined that the capsule had passed via photographic evidence provided by the subject or with a confirmatory x-ray performed within 21 days (about 3 weeks) to confirm capsule passage, as necessary. Reasons for not evaluating a subject through the follow-up period included:

1. Subject Lost to Follow-Up: Unable to locate the subject despite documented attempts to notify the subjects via three telephone calls and one registered letter.
2. Subject Withdrawal: The subject requested to terminate his/her involvement in the study. To the extent possible, an exit interview was conducted with each subject to determine if the capsule had passed and to assess the subject's specific reason(s) for study withdrawal.

Full documentation was made of any withdrawals that occurred during the study. The Investigator documented the date of the withdrawal and results of any assessments made at this time

7.5 Study Procedures

7.5.1 Subject Informed Consent

All subjects provided written informed consent before participation in the study. The informed consent form detailing the investigational nature of the device and the procedures involved in the study including aims, methodology, potential risks, and anticipated benefits. The consent process was documented in the subject's medical chart prior to the performance of any research related assessments.

7.5.2 Screening Assessment

The following procedures or documentation was to be obtained as part of screening.

- Review and signing of the informed consent
- Identification number assignment
- Review of inclusion and exclusion criteria
- Obtaining a medical history and demographic data
- Record medication history and concomitant medication (limited to medications that affect the gastrointestinal tract or coagulation status, such as proton pump inhibitors, antiplatelets or anticoagulants)
- Urine or blood-based pregnancy test (for women of childbearing potential)

7.5.3 Pre–recording procedures

The following procedures or documentation was to be obtained prior to administration of the PillSense Capsule.

- Confirmation of inclusion and exclusion criteria
- Record of medical history
- Record of concomitant medications (limited to medications that affect the gastrointestinal tract or coagulation status, such as proton pump inhibitors, antiplatelets or anticoagulants).
- Physical examination
- Vital signs (pulse, blood pressure, body temperature)
- All laboratory tests routinely performed in case of a GI bleeding as a standard of care at the investigation site (no investigation-specific lab tests were needed)
- The subject had fasted for 2 hours for intake of only clear liquids or 4 hours for PO intake other than clear liquids

7.5.4 Recording procedures

The following procedures or documentation was to be obtained at the time of PillSense Capsule administration.

- The Investigator ensured that the Subject had been fasting at least 2 hours if intake of only clear liquids or 4 hours for PO intake other than clear liquids
- The Investigator paired the PillSense Capsule to its Receiver Unit in accordance with the Instructions for Use (see Appendix 16.4)
- The Investigator provided the PillSense Capsule to the Subject which was ingested with approximately 150mL of water
- The Subject was asked to lie on their left side on a bed
- The PillSense Receiver was placed next to the Subject
- The PillSense Receiver recording was initiated once the Subject was comfortable
- The PillSense Receiver was monitored, and the output recorded on the Case Report Form and a photograph taken of the monitor screen to document the result, i.e., “Blood detected” or “No blood detected”

Subjects that could not or refused to swallow the capsule were withdrawn. Reason for withdrawal was documented on the End of Study form.

7.5.5 Post-recording procedure

The following procedures or documentation was to be obtained at the time within approximately 4 hours after PillSense Capsule administration.

- An EGD was completed within 4 hours after PillSense Capsule administration to confirm the result achieved with PillSense System. The EGD procedure was conducted according to the site standard of care procedure. The endoscopist was not told the result of the PillSense Capsule evaluation.
- The EGD result was recorded on the Case Report Form
- After the sequence of examinations had been completed, the Subject was brought back to the recovery ward.
- The Subject was informed to check their stool for passage of the PillSense Capsule and bring it to the next on-site visit, if possible, or to document passage via a photograph and notify the study coordinator or PI. The subject received a Stool Collection Kit and instructions to check for the passage of the PillSense Capsule.
- The Subject could be admitted to the hospital depending on the severity of the symptoms of the illness and duration of the investigation procedures or if clinically indicated.

7.5.6 Follow-up Contact (visit 2): Within 7 days

A phone call or on-site follow up was to take place within 7 days after the PillSense Capsule administration. If the Subject was still in the Hospital the Subject was reviewed by the investigation staff or if the Subject had already been discharged, they were contacted by investigation staff via phone to:

- Perform AE/SAE review
- Determine whether the PillSense Capsule had passed since the intervention:

  - if the PillSense Capsule had not passed or there was no evidence / record, the Subject was scheduled for a confirmatory X-ray examination between 2 and 7 days.
  - if the Subject confirmed by submitting a photograph documenting that the PillSense Capsule passed, a subsequent follow-up visit could be planned earlier upon Investigator´s and Subject´s agreement if deemed necessary or eliminated altogether.
- The Subject was reminded to contact site staff immediately in the case of any discomfort and/or abdominal pain.

7.5.7 Discretionary On-site or phone follow-up (visit 3): Between Day 8 and Day 21

A phone call or on-site follow up was to take place between 8 and 21 days after the PillSense Capsule administration to:

- Perform AE/SAE review
- Perform confirmatory X-Ray examination to ascertain the passage status of the PillSense Capsule if there was no confirmation that the PillSense Capsule has passed through the GI tract prior to this timepoint

This visit was considered the final visit in the investigation if the Investigator does not have a medical reason to carry out any further follow-up visits with the Subject for the purpose of the investigation.