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Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	A prospective single-center pilot study evaluating the technical feasibility of mucosal staining during Colon Capsule Endoscopy (CCE) procedure in Colorectal Cancer (CRC) high risk population, when using MB-MMX (SPICE study)
Clinical Investigation Plan Identifier	MDT20062
Study Product Name	PillCam™ COLON2 Capsule Endoscopy System
Sponsor/Local Sponsor	Given Imaging Ltd., an indirect wholly owned subsidiary of Medtronic plc. ("Medtronic") 2 Hacarmel St. New Industrial Park, P.O. Box 258 Yokneam 2066724, Phone: +972 (4) 909-7700 Local Sponsor (EU legal representative) Covidien Services Europe Ltd, an indirect wholly owned subsidiary of Medtronic plc. Block 3090-3094, Lake Drive Citywest Business Campus, Dublin D24 Xn47 Ireland
Document Version	Ver.4.0
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Confidentiality Statement

1. Investigator Agreement and Signature Page

Study product Name	PillCam™ COLON2 Capsule Endoscopy System
Sponsor	Given Imaging Ltd., an indirect wholly owned subsidiary of Medtronic plc. ("Medtronic") 2 Hacarmel St. New Industrial Park, P.O. Box 258 Yokneam 2066724, Phone: +972 (4) 909-7700
Clinical Investigation Plan Identifier	MDT20062
Version Number/Date	Ver. 4.0/ 16-Jun-2022

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with International Conference on Harmonization Guidelines on Good Clinical Practice, Principles of Declaration of Helsinki (DoH), ISO 14155, Clinical investigation of medical devices for human subjects, 21 CFR Part 11 (Electronic Records, Electronic Signatures)- when applicable, 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), The Clinical Trials Agreement (CTA), The procedures described within this Clinical Investigation Plan, and any local regulations. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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2. Glossary

Term	Definition
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
CA	Competent Authority
CAPA	Corrective and Preventive Action
CCE	Colon Capsule Endoscopy
CIP	Clinical Investigation Plan
CRC	Colorectal Cancer
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency
DoH	Declaration of Helsinki
DR	Data Recorder
eCRF	Electronic Case Report Form
EC	Ethics Committee
EU	European Union
FAP	Familial Adenomatous Polyposis
FD	Financial Disclosure
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference of Harmonization

Term	Definition
IFU	Instructions for Use
MDD	Medical Device Directive
MedDRA	Medical Dictionary for Regulatory Activities
PMDA	Pharmaceuticals and Medical Devices Agency
RA	Regulatory Authority
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SID	Subject Identification
UM	User Manual

3. Synopsis

Title	A prospective single-center pilot study evaluating the technical feasibility of mucosal staining during COLON2 Capsule Endoscopy (CCE) procedure in Colorectal Cancer (CRC) high risk population, when using MB-MMX (SPICE study)
Clinical Study Type	Prospective, single-arm, single-center, non-randomized pilot post-market study
Product Name	PillCam™ COLON2 Capsule Endoscopy System
Sponsor & the funding source	Given Imaging Ltd., an indirect wholly owned subsidiary of Medtronic plc. ("Medtronic") 2 Hacarmel St. New Industrial Park, P.O. Box 258 Yokneam 2066724, Phone: +972 (4) 909-7700
Investigation Purpose	To evaluate the technical feasibility of mucosal staining during CCE in CRC high risk population, when using MB-MMX as a contrast-enhancement technique.
Product Status	PillCam™ COLON2 Capsule Endoscopy System- CE marked since 2009
Primary Objective(s) and/or Endpoint(s)s	**Primary objective:** To demonstrate an effective colonic polyp enhancement during CCE procedure, when using MB-MMX as a contrast- enhancement technique. **Primary endpoints:** • The percent of colonic polyps which have a visible contrast to the healthy colonic mucosa during CCE, as indicated by an experienced reader, using the subjective reader questionnaire *(For each polyp – was there a contrast between the polyp and the healthy mucosa? Yes/No*), out of the examined polyps (Appendix D). • The interference level of detrimental effects on the visualization of the colonic mucosa during CCE, due to use of MB-MMX per colonic segment. Detrimental effect will be considered as any observation, such as an excessive blue dye deposit, dark and dim appearance of the tissue, interfering with tissue visualization and will be evaluated on a scale from 1 (no interference) to 5 (high interference) to evaluate the level of interference, using a subjective reader questionnaire (Appendix D).

Secondary Objective(s) and/or Endpoint(s)	**Secondary objective:** To evaluate the safety of CCE procedure while using MB-MMX. **Secondary endpoint:** All AEs will be reported by number, type, relatedness (device/procedure), seriousness, severity and duration. All AEs will be captured, regardless of severity.
Study Design	Single-center, prospective, non-randomized clinical trial designed to evaluate the technical feasibility during CCE procedure, when using MB-MMX as a contrast- enhancement technique of mucosal staining in CRC high risk population. Subjects will undergo a bowel preparation (single dose, 4L PEG), including 200 mg Methylthioninium chloride, corresponding to eight 25 mg MB-MMX tablets. An experienced Gastroenterologist will read the CCE procedure and complete a subjective questionnaire, to evaluate mucosal enhancement during a CCE procedure, when using MB-MMX as a contrast-enhancement technique.
Sample Size	Up to 15 subjects will be enrolled in 1 site in Spain. This is a pilot study where sample size will not be calculated.
Inclusion/Exclusion Criteria	**Inclusion Criteria:** 1. Male or female adults ages 45-75 years 2. Subject is classified as being at high risk for CRC due to one (or more) of the following risk factors: • A personal history of colorectal polyps • A first-degree family history of colorectal cancer • Family/personal inherited syndrome (Lynch syndrome, Familial adenomatous polyposis {FAP}, other inherited syndromes linked to colorectal cancer) • Subject with currently suspected or diagnosed rectal bleeding, including positive FIT or positive fecal DNA test • Subjects under surveillance for CRC (last OC≥1.5 years) 3. Subject is willing and able to participate in study procedures, understand and sign the informed consent **Exclusion Criteria:** 1. Subject has a previous history or suspicion of inflammatory bowel or Crohn's disease, ulcerative Colitis or indeterminant Colitis

	2. Subject has congestive heart failure or recent myocardial infarction (<3month) 3. Subject with moderate/severe renal disease and/ or severe hepatic impairment 4. Subject has uncontrolled diabetes 5. Subject has a severe, life-threatening disease 6. Subject with known gastrointestinal motility disorders 7. Subject has known delayed gastric emptying 8. Subject has undergone surgery of the luminal gastrointestinal (GI) tract, from esophagus to the rectum, other than uncomplicated appendectomy or cholecystectomy. 9. Subject with any current condition believed to have an increased risk of capsule retention such as suspected or known bowel obstruction or pseudo-obstruction, stricture, or fistula (symptoms such as severe abdominal pain with accompanying nausea or vomiting) 10. Subject with dysphagia, any swallowing disorder, or any major gastrointestinal motility disorder 11. Subject has a history of inadequate bowel preparation for colon imaging with colonoscopy, CTC, CCE, or DCBE (self-reporting) 12. Subject with known or suspected constipation history as defined by the following: as needing the use of medication (prescription or OTC) for management of constipation, or fewer than 3 BM/week regardless of medication use 13. Subject with a cardiac pacemaker or other implanted electromedical device 14. Subject with planned MRI examination within 7 days after ingestion of the capsule 15. The subject is taking antidepressant medicine or a medicine for psychiatric illness, such as: ○ selective serotonin reuptake inhibitor (SSRI)- as fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram and zimeldine; bupropion, venlafaxine, mirtazapine, clomipramine, buspirone ○ medicines classified as Monamine Oxidase Inhibitors (often used for treating depression). 16. Subject has glucose-6-phosphate dehydrogenase (G6PD) deficiency and/or allergic to peanut/soya

	17. Subject consumes any of the medicinal products which interacts with MB-MMX, as per MB-MMX label and Investigator's discretion 18. Subject with allergies or known contraindication to the device, medications or preparation agents used in the procedure as described in the relevant instructions for use/package inserts. 19. Subject use of opioid medication on a regular basis and requires medication to treat opioid induced constipation 20. Subject currently participating in another gastrointestinal clinical study (investigational drug or device) that might interfere with results of study 21. Females who are pregnant or breastfeeding at time of bowel prep 22. Any condition which precludes compliance with study and/or device instructions based on the clinical judgment of the investigator 23. Subject who is considered to be part of a vulnerable population (e.g. prisoners or those without sufficient mental capacity) 24. Medtronic employees
Study Procedures and Assessments	**Day -30 to (-3)-** Screening visit**:** • Obtain written informed consent • Confirm inclusion/exclusion • Medical history+ concomitant medication+ demographics • Vital signs • Urine Pregnancy test (when applicable) • Provide study bowel preparation martials & MB-MMX tablets **Day (-3) - (-2)**- low fiber diet **Day -1:** • Clear liquid diet • Urine Pregnancy test (when applicable) • Bowel prep- 4L PEG+ MB-MMX (in accordance to the MB-MMX IFU): o The first dose of 3 MB-MMX tablets should be taken after drinking at least 1 L of PEG; o The second dose of 3 MB-MMX tablets should be taken 1 hour after the first dose;

	○ The last dose of 2 MB-MMX tablets should be taken 1 hour after the second dose. **Day 0:** • Clear liquid diet • Vital signs • 1 tablet of prucalopride 1mg • CE procedure, including boosts intake. **Day 5-9**: Follow-up phone call
Safety Assessments	Subjects will be asked at each visit, during the PillCam™ CCE procedure and during the follow-up phone call, about changes in their medical condition. All Adverse events and Device Deficiencies (DDs) will be recorded throughout the study period (starting at day -1 prior to the CCE procedure until the follow-up visit).
Statistics	This is a pilot study where no formal sample sizing will be calculated. Up to 15 patients are planned to be enrolled to this study. Demographic and other characteristics will be provided. Summary statistics (arithmetic mean, standard deviation, and range for quantitative variables) will be presented for the total study population. Frequency tables for qualitative data will be provided. For the primary endpoint polyps contrast visibility, - the percent of polyps with visible contrast will be presented with 95%CI. For the primary endpoint of determinantal effects evaluation, the level of interference will be presented as mean, standard deviation, median and range (scale of 1-5; 1 = no interference and 5 = high interference). The percent of cases with at least one AE out of the total cases, will be presented with 95%CI. Any deviation from specified statistical plan will be in addition to “per protocol” analysis and will be reported as such. Post-hoc analysis will be conducted according to the existing data gathered, if necessary.

4. Introduction

4.1. Background

Colorectal Cancer

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, with an estimated 1.8 million new cases in 2018[1]. The incidence of colon cancer has been decreasing steadily since 2001; most recently, incidence declined an average of 3.1% per year between 2005 and 2014[2, 3]. Mortality from colon and rectal cancers also has been declining for the past several decades, with the most rapid declines in the early 2000's, which is likely due to screening [3]. Screening can prevent CRC through the removal of precancerous adenomatous polyps and reduce deaths through early detection and treatment of cancer[4]. However, despite interventions for prevention, early detection and treatment, CRC still remains the third most common cause of cancer death among men and women in the United States and worldwide.[5,6]

PillCam™ Capsule Endoscopy

Capsule Endoscopy (CE) has evolved in recent years and became a first-line, noninvasive diagnostic technique for the small bowel. CE is now being utilized worldwide to assess patients for obscure gastrointestinal bleeding, possible Crohn's disease and small bowel tumors. Alterations and improvements in the CE have led to the development of additional CE systems, namely the PillCam™ UGI, PillCam™ Colon and PillCam™ Crohn's.

The first PillCam™ endoscopy system indicated for the small bowel (SB) was cleared by the US Food and Drug Administration (FDA) in May 2001. Since then, more than 4,000,000 PillCam™ capsules have been sold worldwide in hospitals, outpatient clinics, and physician offices as an ambulatory procedure. After the capsule is ingested, the patient is not restricted to a medical environment.

The PillCam™ COLON capsule

The PillCam™ COLON system received CE mark on October 2006 and was cleared for marketing in the European Union (EU). The advanced generation of the system, the PillCam™ COLON 2 system, received CE mark in the EU on September 2009 and FDA clearance in the US on February 2014, Pharmaceuticals and Medical Devices Agency (PMDA) Japan in July 2013, and TGA approval in Australia in April 2013. Several thousand PillCam™ COLON2 capsules were safely ingested with numerous published clinical studies (please refer to Appendix C for list of clinical studies).

Clinical literature on PillCam™ COLON2 capsule has demonstrated that the device and procedure are safe with very low occurance of adverse events. PillCam™ COLON2 has been clinically proven to serve as an effective alternative diagnostic modality when colonoscopy is incomplete or cannot be performed, and also shows to be preferred in patients who decline a colonoscopy procedure, making another option available to patients who are recommended to undergo a diagnostic evaluation of the colon (EU indication). The general conclusion confirms that the CCE procedure is safe, feasible, has acceptable accuracy rates, provides encouraging data for proposing PillCam™ COLON2 in the armamentarium of tools available for visualization the colon, and offers a more convenient and less risky procedure than other invasive colon exams.

Per-oral Methylene Blue Formulation (MB-MMX):

Widespread application of blue dye to the mucosal surface of the colon has been shown to increase detection of colorectal neoplasia in patients at average or increased risk of CRC due to selective staining of subtle and nonpolypoid lesions (slightly elevated, flat, slightly depressed), both adenomas and sessile serrated adenomas (SSA). COSMO pharmaceuticals have combined methylene blue (MB) with a per-oral, colon-release, pH and time-dependent multimatrix structure (MB-MMX), able to directly deliver the agent in the colon lumen. When orally administered with bowel preparation, MB-MMX tablets may increase the Adenoma Detection Rate (ADR) by staining and contrast-enhancement of the colorectal mucosa[7]. The MB-MMX formulation has been approved for use in EU in August 2020 for the indication- diagnostic agent enhancing visualization of colorectal lesions in adult patients undergoing screening or surveillance colonoscopy. For additional information please refer to the MB-MMX user manual.

MB-MMX has been demonstrated as an efficient agent for polyp enhancement and increased polyp detection rate during Colonoscopy. Further evaluation of its' effect in CCE should be investigated.

4.2. Purpose

Given Imaging Ltd. (an indirect wholly owned subsidiary of Medtronic plc.) is sponsoring the SPICE study, a prospective single-center open-label pilot clinical study. The purpose of this study is to evaluate the technical feasibility of mucosal staining during capsule endoscopy (PillCam™ COLON2) procedure when using MB-MMX as mucosal enhancement technique. The study will be conducted in population with high risk for CRC.

5. Objectives and/or Endpoints

5.1. Objectives

5.1.1. Primary Objective and Endpoints

Primary objective:

To demonstrate an effective polyp enhancement during a Colon Capsule Endoscopy procedure when using MB-MMX as a contrast- enhancement technique.

Primary endpoints:

- The percent of colonic polyps which have a visible contrast to the healthy colonic mucosa during CCE, as indicated by an experienced reader, using the subjective reader questionnaire *(For each polyp – was there a contrast between the polyp and the healthy mucosa? Yes/No*), out of the examined polyps (Appendix D)
- The interference level of detrimental effects on the visualization of the colonic mucosa during CCE, due to use of MB-MMX per colonic segment. Detrimental effect will be considered as any observation, such as an excessive blue dye deposit, dark and dim appearance of the tissue, interfering with tissue visualization and will be evaluated on a

scale from 1 (no interference) to 5 (high interference) to evaluate the level of interference, using a subjective reader questionnaire (Appendix D)

5.1.2. Secondary Objective and Endpoint

Secondary objective:
To evaluate the safety of CCE procedure while using MB-MMX.

Secondary endpoint:
All AEs will be reported by number, type, relatedness (device/procedure) seriousness, severity and duration. All AEs will be captured, regardless of severity.

6. Study Design

This is a single-center, prospective, pilot, non-randomized, open label post-market clinical trial, designed to evaluate the technical feasibility during CCE procedure, when using MB-MMX as a contrast- enhancement technique of mucosal staining in CRC high risk population.

Up to 15 subjects, 45-75 years old, classified as being at high risk for CRC, will be enrolled in 1 site in Spain.

Subjects will undergo a standard bowel preparation (single dose, 4L PEG), including 200 mg Methylthioninium chloride, corresponding to 8 tablets of 25 mg MB-MMX (per product's instructions for use) and will undergo a CCE procedure. An experienced Gastroenterologist will read the CCE procedure and complete a subjective questionnaire, to evaluate mucosal enhancement during a CCE procedure, when using MB-MMX as a contrast-enhancement technique.

6.1. Duration

The expected study duration is up to 13 months from EC/ Competent Authority (CA) approval (the latest). The duration of an individual subject participation will vary based on their enrollment; however, at a minimum, participation of an individual subject can vary for up to 39 days to include all study procedures (up to 30 days from screening to capsule ingestion and additional 5-9 days for the follow up call).

6.2. Rationale

This is a pilot, prospective, single center, open label, non-randomized, uncontrolled clinical study, to evaluate the technical feasibility of mucosal staining during CCE procedure, when using MB-MMX.

MB-MMX oral formulation has been approved for use in EU and been evaluated during colonoscopy procedures. It has been established as an effective technique for colonic contrast enhancement. In this study, this contrast enhancement technique will be evaluated for CCE procedure.

MB-MMX intake in this study is considered a preceding investigational procedure, which is additional for this study and therefore outside standard of care.

The study design is based on clinical review (please refer to Appendix C: List of PillCam™ Colon Clinical Studies) and aligned with risk assessment results, as the product used in the study (PillCam COLON2) is a released CE marked product, which does not require additional risk evaluation, other than the standard risk evaluation process.

The CCE procedure in the study, is the standard procedure performed in conjunction with MB-MMX standard regimen, in subjects at high risk for presence of colonic polyps during the CCE procedure. The study population was set to allow visualization of colonic polyps, under the assumption that the chance of observing colonic polyps in this population is higher comparing to CRC average risk population.

The CCE results will be evaluated by an experience Gastroenterologist for the mucosal stanning outcomes. To evaluate safety, procedure and device-related adverse events will be captured and evaluated.

This is an initial pilot study to generally evaluate polyp visualization during CCE, when using MB-MMX. In case of favorable results, a larger scale study, with a Colonoscopy procedure that follows the CCE, may be considered.

6.3. Study Oversight

No steering committee will be used in this study, due to the nature of this pilot study.

7. Product Description

7.1. General

7.1.1. The PillCam™ Capsule Endoscopy System

The PillCam™ capsule endoscopy system is comprised of four main subunits:

(1) **The ingestible PillCam™ Capsule -** a single-use ingestible video capsule designed to acquire images during natural propulsion through the digestive system. In general, the PillCam™ capsule is designed to withstand the mechanical forces and chemical environment of the digestive system.

(2) **The PillCam™ Recorder -** an external, portable receiving/recording unit that receives and stores the acquired images from the capsule via sensors.

(3) **The PillCam™ Software –** a proprietary software that supports the capsule endoscopy examination in all of its phases.

(4) **The Workstation -** a standard personal computer that is the operational platform for the PillCam™ software.

Figure 1: Data flow of the PillCam™ Colon Capsule Endoscopy System

In general, the PillCam™ capsule has one or two optical heads and acquires images of different parts of the Gastrointestinal (GI) Tract (Esophagus, stomach, duodenum, Small bowel and Colon) during natural propulsion through the digestive system. The Capsule transmits the acquired images via digital radio frequency communication channel and antennas of the Sensor to the PillCam™ Recorder, both located outside the body, which is later downloaded to the workstation that utilizes the PillCam™ software to output an image of the examined gastrointestinal tract (Figure 1**,** for illustration only).

For model numbers details refer to Appendix F.

The CE marked device PillCam COLON2 system will be used in accordance with the intended purpose as described in the approved IFU for which CE mark has been obtained. Thus, the study is classified as a post market study. Note that MB-MMX is used within the intended purpose described in the drug labeling as approved for use in EU.

7.1.2. The PillCam™ COLON 2 Capsule

7.1.2.1. Product Description

The PillCam™ COLON2 capsule is a single-use capsule that has two optical heads (miniature color cameras with a flash), batteries, transmitter, and an antenna to transmit the acquired images. All of these are encapsulated in an ingestible capsule made of biocompatible plastic with a length of up to 32.8 mm and diameter of 11.6 mm.

7.1.2.2. Intended Use

The PillCam™ Capsule Endoscopy System with the PillCam™ COLON2 capsules is intended for the visualization of the colon for diagnosis of colonic disorders.

7.1.2.3. Intended Population

The PillCam™ COLON2 capsule is intended for use in adults and children from 8 years of age.

7.1.3. The PillCam™ Recorder

The PillCam™ Recorder is a portable, external compact battery-operated receiving/recording unit that receives and stores the acquired images from the capsule.

The PillCam™ Recorder is capable of controlling the PillCam™ parameters such as frame rate, light pulse, power and incorporates an integrated LCD screen that supports real time display of images. It receives and stores the image data transmitted by the PillCam™ capsule. Currently PillCam™ recorder DR3 is the standard model commercially available.

The PillCam™ Recorder set consists an antenna array or sensor belt carried in proximity to the body, a receiver, and memory for accumulation of the data during the examination.

The PillCam™ recorder is supplied with a pouch to wear over the shoulder and with an adjustable strap to secure to the waist and worn by the patient during the procedure.

7.1.3.1. Sensor Arrays & Sensor Belt

The PillCam™ sensors are physical receptors that receive data transmission from the PillCam™ capsule and transfer it to the PillCam™ recorder. These sensors are placed on the patient as a sensor belt or a sensor array (in this study sensor belt will be used):

- **PillCam™ sensor belt**: The sensor belt is worn around the patient's waist over a thin shirt.
- **PillCam™ sensor array**: The sensors of the sensor array are attached to the patient's skin. The sensor locations depend on the procedure type. Each sensor consists of a flexible printed circuit board (PCB) and is attached with a disposable, medical adhesive sleeve.

7.1.4. The PillCam™ Software

The PillCam™ software program (v.9), supports the PillCam™ capsule endoscopy procedure by providing access to the different steps in the PillCam™ capsule endoscopy procedure. The software program, used for video creation and interpretation, has several useful incorporated features that aid the physician during diagnosis. For detailed description please refer to PillCam™ Endoscopy System user manual (UM).

7.1.5. The Workstation Unit

The workstation is a standard stand-alone personal computer dedicated workstation that cannot be connected to a network environment. The workstation supports multi-user configuration and intended for use during the interpretation and analysis of the acquired data and for generating PillCam™ reports.

7.2. Dosage Form and Route of Administration

The PillCam™ capsules are administered orally, following a pre-ingestion preparation procedure (see section 10.3) and are swallowed as any other pill with drinking a glass of water. Each subject will ingest one capsule.

7.3. Manufacturer

The PillCam™ Colon Capsule Endoscopy system is manufactured by Given Imaging Ltd., an indirect wholly owned subsidiary of Medtronic plc. (“Medtronic”).

7.4. Packaging

The PillCam™ COLON2 Capsules will be packaged in an appropriate Jewel style package box, using a controlled process that ensures the capsule is activated only when needed.

Each PillCam™ capsule will be packed in a separate Jewel box with an embedded magnet that prevents it from activating when it is handled in the box prior to ingestion.

Standard labeling will reflect the specifications of each PillCam™ capsule, as well as serial number, Lot number tracking, expiration date and will comply with the EU regulatory requirements for study product labeling. The CE-marked devices will be provided with the approved CE-mark labeling. A sticker will be added to the label with the statement "exclusively for clinical investigations" in local language.

7.5. Equipment

Devices under this study do not require any specialized or dedicated maintenance or calibration for the study, hence calibration and maintenance activities will not be documented.

Every equipment used for the study will be tracked to assure it is used as intended.

The following equipment might be used, per investigator's or designee's discretion:

- Abdominal X-ray (will be performed in case of suspected capsule retention)

7.6. Product Use

The PillCam™ COLON2 capsule is dispensed to the subject by the investigator/study coordinator and administered orally, following a pre-ingestion bowel preparation procedure and ingested by the patient as any other pill with drinking a glass of water.

The PillCam™ COLON2 capsule is moving through the patient’s GI tract, propelled by natural peristalsis until it is excreted. The procedure involves intake of bowel preparation and prokinetic agents, in order to propel the capsule agents, and MB-MMX tablets administration, in order to enhance colonic polyp visualization.

The PillCam™ sensor belt that receives data transmission from the PillCam™ COLON2 capsule and transfer it to the PillCam™ recorder, is worn around the patient’s waist over a thin shirt.

For further information, refer to the PillCam™ UM.

7.7. Product Training Materials

All investigators and clinical team personnel involved in conducting the PillCam™ endoscopy procedures throughout the study period, are knowledgeable with the PillCam™ endoscopy system and procedures and are well trained on performing the study procedures.

All the investigators and clinical team personnel will further be instructed and trained by the sponsor (or designee) on all relevant Clinical Investigation Plan (CIP) specific aspects and related documents, to a level that enables them to perform their delegated tasks appropriately, according to the study specific training plan and their training will be documented. Per ISO14155, the training/experience should be based on the risk assessment.

Only trained team members with a signed training record and proper documented delegation, will be allowed to perform their delegated tasks as part of this study.

7.8. Product Receipt and Tracking

The sponsor will initiate product(s) shipment from the sponsor to the site upon obtaining CA and EC approval for study conduct and fully executed Clinical Trial Agreement (CTA). Both sponsor and site will maintain all shipment documentation and tracking, which will include dates, quantities received, lot/serial numbers and expiration dates, as applicable. Prior to any shipment, the site will be informed by the sponsor regarding the upcoming shipment, expected arrival date and content of the shipment. All products shipments will be supported by delivery and return notes.

"Product Accountability Log" will be managed and maintained by the site, filed in the Investigator Site File (ISF) at the site and monitored by the study Monitor(s). Products receipt & return processes, as well as products' identifying information will be documented in the log.

For each dispensed capsule, the following information should be recorded, at minimum: subject's ID, date dispensed, capsule ID number. At the termination of the study, all unused study material must be returned with the corresponding documentation as directed by the Sponsor.

7.9. Product Storage

The supplied PillCam™ COLON2 capsules will be stored in a locked, secured area with limited access only to approved study staff. The capsules should be stored in a dry place, at a temperature below 25°C (77°F) and away from any magnetic source. To prevent capsule activation, the PillCam™ capsules will be kept in their original containers until use. Even when stored in their original containers and according to recommendations, the PillCam™ COLON2 capsules can be kept for a limited period, only as indicated by the expiration date of the container label.

Minimum/ Maximum temperature log will be maintained on site to ensure that the PillCam™ COLON2 capsules are stored at the correct temperature.

It is the responsibility of the investigator to correctly handle, store, and track the study products maintained at the study site and the study products will be used only in the clinical study according to the CIP.

7.10. Product Return

Subjects are not required to return the PillCam™ COLON2 capsules following capsule excretion. At the end of the study, all unused study material must be returned with the corresponding documentation as directed by the Sponsor. Any capsule that reaches its expiration date before it has been dispensed should be returned to the Sponsor or destroyed on site; with proper documentation in either scenario.

7.11. Product Accountability

The study site team is responsible for maintaining tracking of the PillCam™ system and components during the study. In order to maintain current and accurate inventory records for documentation of the receipt, dispensing and safe return (when applicable) of study product, 2 device accountability logs will be used- 1 for non-disposable PillCam™ system components (i.e. workstation, DRs) and 1 for disposable PillCam components (i.e. capsules). The logs will be monitored by the study Monitor, assigned by the Sponsor. For each dispensed capsule, the following information should be recorded: The subject study ID, capsule's serial number/ lot number, expiration date, received date, the date dispensed and the initials of the person dispensing the capsule, date/reason for return or disposal (when applicable).

If upon arrival of the product at site, the product supply appears to be damaged, the investigator and/or the study coordinator will report this to the study Monitor immediately and follow the instructions provided.

The product will be kept under the recommended storage conditions until administered to the subject and only authorized study personnel will have access to the study product.

The Bowel preparation agents , as well as the MB-MMX tablets required for the capsule pre-ingestion preparation, will be provided to enrolled subjects by the site study team during the screening visit. Prucalopride & Prokinetic agents will be provided to enrolled subjects by the site study team during the CCE procedure visit.

At the termination of the study, all unused study materials must be safely returned/destroyed per local regulations. Accountability log will be updated accordingly and reviewed by the Sponsor.

The investigator shall make sure that all study products will be stored in such a manner as to be easily identifiable. If the study device cannot be identified, the device shall not be used.

8. Study Site Requirements

8.1. Investigator/Investigation Site Selection

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation, as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation.
- Be a qualified practitioner (experienced gastroenterologist) and experienced in the field of application and trained in the use of PillCam™ CE System.
- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results.

- Be able to demonstrate that the proposed investigational study site:
  - Has the required number of eligible subjects needed within the recruitment period.
  - Has one or more qualified investigators, a qualified investigational study site team and adequate facilities for the foreseen duration of the clinical investigation.

Study site personnel training will be completed and documented prior to participation in this study.

8.2. Study Site Activation

During the activation process (prior to subject enrollment), the Sponsor will train study site personnel on the clinical investigation plan, on relevant standards and regulations, informed consent, and on data collection and reporting tools. If new members join the study site team, they will receive training on the applicable study requirements relevant to their role before contributing to the study.

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- EC approval (and voting list, as required by local law) of the current version of the CIP and Informed Consent (IC).
- CA approval or notification (as required per local law)
- Fully executed CTA
- Financial disclosure
- CV of investigators and key members of the investigation study site team (as required). The signature on the CV must be dated within 3 years prior to the date of activation of the study site.
- Documentation of delegated tasks
- Documentation of study training
- Additional requirements imposed by local regulations, the EC and CA shall be followed, if appropriate.

In addition, all participating study site staff must be trained on the current version of the CIP as well as on the applicable study requirements depending on their role and must be delegated by the principal investigator to perform study related activities.

The Sponsor will provide the study site with documentation of study site/investigator readiness- a site activation letter; this letter must be received prior to performing any study related activities.

8.3. Role of the Sponsor Representatives

In addition to performing monitoring and auditing activities, Sponsor representatives may provide support to the study site, as required for the study, under the supervision of the Principal Investigator, including but not limited to:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities

9. Selection of Subjects

9.1. Study Population

Up to 15 subjects at high risk for CRC (as defined by inclusion criterion #2) will be enrolled to this study.

9.2. Subject Enrollment

Written ICF will be obtained from each subject prior to performing any screening assessments. Once ICF is obtained, subjects will be screened to ensure they meet all of eligibility criteria prior to study enrollment. A subject is considered enrolled in the study once the ICF is signed and it is determined that all eligibility criteria are met.

9.3. Inclusion Criteria

1. Male or female adults ages 45-75 years
2. Subject is classified as being at high risk for CRC due to one (or more) of the following risk factors:
    - A personal history of colorectal polyps
    - A first-degree family history of colorectal cancer
    - Family/personal inherited syndrome (Lynch syndrome, Familial adenomatous polyposis {FAP}, other inherited syndromes linked to colorectal cancer)
    - Subject with currently suspected or diagnosed rectal bleeding, including positive FIT or positive fecal DNA test
    - Subjects under surveillance for CRC (last OC≥1.5 years)
3. Subject is willing and able to participate in study procedures, understand and sign the informed consent

9.4. Exclusion Criteria

1. Subject has a previous history or suspicion of inflammatory bowel or Crohn's disease, ulcerative Colitis or indeterminant Colitis
2. Subject has congestive heart failure or recent myocardial infarction (<3month)
3. Subject with moderate/severe renal disease and/ or severe hepatic impairment
4. Subject has uncontrolled diabetes
5. Subject has a severe, life-threatening disease
6. Subject with known gastrointestinal motility disorders
7. Subject has known delayed gastric emptying

8. Subject has undergone surgery of the luminal gastrointestinal (GI) tract, from esophagus to the rectum, other than uncomplicated appendectomy or cholecystectomy.

9. Subject with any current condition believed to have an increased risk of capsule retention such as suspected or known bowel obstruction or pseudo-obstruction, stricture, or fistula (symptoms such as severe abdominal pain with accompanying nausea or vomiting)

10. Subject with dysphagia, any swallowing disorder, or any major gastrointestinal motility disorder

11. Subject has a history of inadequate bowel preparation for colon imaging with colonoscopy, CTC, CCE, or DCBE (self-reporting)

12. Subject with known or suspected constipation history as defined by the following: as needing the use of medication (prescription or OTC) for management of constipation, or fewer than 3 BM/week regardless of medication use

13. Subject with a cardiac pacemaker or other implanted electromedical device

14. Subject with planned MRI examination within 7 days after ingestion of the capsule

15. The subject is taking antidepressant medicine or a medicine for psychiatric illness, such as:

    - selective serotonin reuptake inhibitor (SSRI)- as fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram and zimeldine; - bupropion, venlafaxine, mirtazapine, clomipramine, buspirone; -

    - medicines classified as Monamine Oxidase Inhibitors (often used for treating depression).

16. Subject has glucose-6-phosphate dehydrogenase (G6PD) deficiency and/or allergic to peanut/soya

17. Subject consumes any of the medicinal products which interacts with MB-MMX, as per MB-MMX label and Investigator's discretion

18. Subject with allergies or known contraindication to the device, medications or preparation agents used in the procedure as described in the relevant instructions for use/ package inserts

19. Subject use of opioid medication on a regular basis and requires medication to treat opioid induced constipation

20. Subject currently participating in another gastrointestinal clinical study (investigational drug or device) that might interfere with results of study

21. Females who are pregnant or breastfeeding at time of bowel prep

22. Any condition which precludes compliance with study and/or device instructions based on the clinical judgment of the investigator
23. Subject who is considered to be part of a vulnerable population (e.g. prisoners or those without sufficient mental capacity)
24. Medtronic employees

10.Study Procedures

The study consists of a screening – enrollment phase, bowel preparation phase, including MB-MMX tablets administration, followed by the PillCam™ Colon endoscopy procedure visit and a post procedure telephone follow up visit, as described in Table 1- Schedule of events and data collection:.

10.1. Schedule of Events & Data collection

The study assessment in table 1 indicates the observations/ assessments/ data collection to be conducted throughout the study period.

Table 1- Schedule of events and data collection:

	Screening/ Enrollment	Preparation	Procedure Visit	Follow Up Visit
⇓ **Procedure** **Visit** ⇒	**V1**		**V2**	**V3**
Time Schedule (Days)	(-30)-(-3)[1]	(-3)-0[2]	0	7±2
Inform consent	X			
Eligibility criteria	X			
Demographic data	X			
Medical History	X			
Concomitant medication	X		X	
Vital Signs and height/weight measurements	X		X	
Urine Pregnancy test (when applicable)	X	X[3]		
Provide Preparation materials (including MB-MMX) and subject instructions form	X			
Low Fiber Diet		X		
Bowel Preparation intake		X		
MB-MMX intake		X[4]		
Bowel preparation and MB-MMX compliance verification			X	
Prucalopride administration			X	
CCE administration			X	
Device Deficiencies			X	X
Study Deviations	X	X	X	X
AEs collection		X	X	X
Study exit				X

[1] Screening/enrollment process may start 3-30 days prior to visit 2.

[2] Preparation starts 3 days prior to visit 2

[3] Urine Pregnancy test must be performed at day (-1) prior to the bowel prep/MB-MMX intake (when applicable).

[4] MB-MMX is administrated at day (-1).

10.2. Subject Screening (visit 1)

All subjects that are considered for the study should be included on the study screening log. The reason for non-eligibility, as determined by the Investigator, should be recorded on the study screening log. The screening log serves as a method for the Sponsor to assess selection bias in the trial.

During the screening visit, the investigator will obtain patient's written informed consent, after the subject had an ample time and opportunity to read and understand the ICF, verify that the subject does not have any contraindications for the PillCam™ Capsule Endoscopy procedure, and assess each subject for eligibility based on the inclusion/exclusion criteria.

To determine subject eligibility, baseline information will be collected as outlined in Table 1- Schedule of events and data collection:. Informed consent, vital signs, medical history, concomitant medications, urine pregnancy test (performed in women with childbearing potential) and demographic information will be collected during the visit. Study medications required for the pre-ingestion procedure will be provided to eligible subjects during this visit.

Data of screen failure subjects will not be captured within the Electronic Case Report Form (eCRF). Their signed ICF and Inclusion-Exclusion criteria evaluation will be kept on site.

10.3. PillCam™ Capsule pre-ingestion preparation procedure

The pre-ingestion preparation procedure is similar to colonoscopy or capsule endoscopy standard preparation and is performed in accordance to the labeling of the agents which are being used. In this study MB-MMX tablets will be also administrated to evaluate colonic polyps staining during the CCE procedure. Use of MB-MMX will be according to the product's label.

The preparation procedure will begin with a low fiber diet at days (-3)- (-2) before the CCE, followed by a clear liquid diet, starting from the day before capsule ingestion. At day (-1) prior to the CCE, a urine pregnancy test will be performed (as applicable and prior to prep/MB-MMX administration) and bowel preparation agent will be administrated (single dose) as well as administration of MB-MMX tablets (in accordance to the product's IFU). At the day of CCE procedure, 1 tablet of prucalopride (i.e. Resolor) 1mg will be administrated Prior to the CCE procedure. The subject will be required to consume additional bowel preparation & prokinetic agents during the CCE procedure.

Prior to the CCE procedure, the subjects will be given detailed instructions regarding the preparation regimen, as specified in the subject instructions form that will be provided to the subject during the screening visit.

10.4. PillCam™ CCE Procedure (visit 2)

On the morning of the scheduled CCE procedure, the subject will be requested to arrive to the site. Compliance to the bowel prep and MB-MMX intake will be recorded, vital signs will be taken and prucalopride tablet will be consumed. The subjects will then undergo the PillCam™ CCE procedure within defined timelines. During the CCE procedure subjects will comply with the prokinetic agents & bowel preparation regimen as described in Appendix A- SPICE Study- Bowel Preparation/MB-MMX

administration Schedule. Subjects will be allowed to drink clear liquids and eat upon clinical team instructions.

Following capsule ingestion and intake of the 2nd bowel preparation boost, the subjects might be dismissed to continue the procedure at home, upon physician decision. In such case, the data recorder and sensor belt will be removed according to the clinical team instructions and up to 12 hours from ingestion.

Prior to discharge, the subject will be instructed to contact the study physician/ team in any case of an adverse event. In case a subject didn't excrete the capsule during the CCE procedure, he/she will be instructed to attempt to verify that the capsule exited the body and to inform the study team on the exit time, if possible.

10.5. Phone Call Follow-up Visit (visit 3)

5 to 9 days after the CCE procedure (after visit 2), each subject will be contacted by the study team over the phone, to verify that there have been no changes in their well-being following the procedure. In addition, capsule excretion will be verified.

An acceptable indication for safe excretion of the PillCam™ is capsule entry to the colon as visualized in the CCE video. The risk for retention may be considered null when the capsule enters the colon.

Subjects who didn’t report capsule excretion until the phone call follow up visit, and the capsule didn’t reach the Colon during the CCE procedure, as observed in the CCE video, will be evaluated for a need to perform abdominal x-ray to verify capsule exit, based on the investigator’s judgment.

Should a subject miss a visit or the visit fall outside the pre-specified window of 5-9 days following the CE procedure, a study deviation must be reported. A subject will be considered as lost to follow-up if at least three attempts to contact the subject are unsuccessful. The method of attempt will be documented in subject’s records.

10.6. CCE Procedure Video

The nature and purpose of this pilot study is an initial assessment and not medical evaluation. The raw data from the CCE procedure will be sent to the Sponsor for customized video compilation, which will allow reading of the CCE procedure in conjunction with the MB-MMX. All of the videos are read and analyzed by an experienced gastroenterologist. In cases the video is eligible for reading and allows assessment, a report will be generated and provided to the subject.

10.7. Medication Compliance

All enrolled subjects will receive detailed bowel preparation/MB-MMX administration instructions for the CCE procedure. Compliance to the bowel preparation/MB-MMX intake will be captured and documented on a dedicated subject instructions form.

10.8. Optional X-ray Procedure

If needed, the progress/excretion of the capsule may need to be verified by an abdominal x-ray. The expected radiation exposure from an abdominal x ray is approximately 0.7mSV. This may be compared to the annual exposure of an individual of 3mSV in background radiation or a chest radiograph of 0.4 mSV**.**

10.9. Subject Consent

Informed consent is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular study, after information has been given and explained to the subject on all aspects of the study that are relevant to the subject's decision to participate. This process includes obtaining an IC form that has been approved by the study site's EC and signed and dated by the subject and investigator.

Prior to enrolling subjects, the ICF must be approved by the EC. The ICF must be controlled (i.e. versioned and dated) to ensure it is clear which version was approved by the EC. Any adaptation of the sample ICF must be reviewed and approved by the Sponsor and the EC reviewing the application prior to enrolling subjects.

The investigator must notify the subject of any significant new findings about the study that become available during the course of the study, which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study. If relevant, re-consent may be requested from subjects to confirm their continued participation.

Prior to initiation of any study-specific procedures, IC must be obtained from the subject. The IC process must be conducted by the principal investigator or an authorized designee, and the IC Form must be given to the subject in a language he/she is able to read and understand. The process of IC must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other study site personnel. The IC process shall not waive or appear to waive subject's legal right. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the IC form, to inquire about details of the study, and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the study, the ICF must be signed and personally dated by the subject and investigator or authorized designee, as required, and ensured by the principal investigator or his/her authorized designee.

A copy of the ICF, signed and dated as required by law, must be provided to the subject.

Per ISO14155, in the event the subject cannot read and/or write, the IC process shall be obtained through a supervised oral process. An independent and impartial witness must be present during this process. The ICF and any other information must be read aloud to the prospective subject. Whenever possible, the subject shall sign and personally date the informed consent form. The witness signs and personally dates the IC attesting that the information was accurately explained and that informed consent was freely given.

The original of the signed ICF must be filed on site with the subject's study documents.

The ICF (and any subsequent version) will be submitted for ECs/ CA approval, as required per local regulations.

The IC must be available for monitoring and auditing and the study monitor must be able to review the subject's signed and dated ICF and verify its completeness.

Consistent with the Declaration of Helsinki (DoH), vulnerable adults (i.e. those subjects mentally incapable of giving consent) are excluded from this protocol. Any subjects with mental incompetence (e.g. Alzheimer's, dementia, psychiatric disorders, developmental disorders) should be assessed for vulnerable status. If the ICF is signed by an individual other than the subject, the monitor may discuss whether the Investigator believes the subject meets the definition of a vulnerable adult. This protocol defines vulnerable adult as those subjects mentally incapable of giving consent, in the Investigator's opinion. The Investigator should consider the definition of vulnerable adult per ISO 14155, which defines vulnerable adults as: "individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of a retaliatory response". For example, this could include Individuals with loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving IC. Other vulnerable subjects could include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

10.10. Enrollment

Written ICF will be obtained from each subject prior to performing any screening assessments. Once ICF is obtained, subjects will be screened to ensure they meet all of eligibility criteria prior to study enrollment. A subject is considered enrolled in the study once the ICF is signed and it is determined that all eligibility criteria are met. A log of all subjects enrolled in the study will be maintained and the date the subject signed the ICF will be documented in the subject's medical records.

10.11. Assessment of Efficacy

Please refer to Section 13- Statistical Design and Methods for further information regarding assessment of efficacy.

10.12. Assessment of Safety

AEs information is collected in this study.

To monitor safety in this study, subjects will be asked at each visit about any changes in their medical condition/well-being. All adverse events will be recorded throughout the study, from start of Bowel preparation (1 day prior to the CCE procedure) until the end of the follow up call. AEs should be assessed in terms of their seriousness, type, relatedness (device/procedure), severity and duration. All anticipated adverse events will be collected. Subjects will be able to contact the investigator at any time during the study, if they notice any change in their medical condition/well-being.

The data regarding severity, seriousness, timing, relatedness (device/procedure), duration and type of procedure as well as AE outcome will be observed and documented. See Section 12 for further information on the collection of AEs and safety information.

10.13. Recording Data

This study will utilize an electronic eCRF database. All data requested on the eCRF are considered required. All entries made in the eCRF must be verified against source documents. For each complete case, the Principal Investigator or designee must ensure the accuracy and completeness of the recorded data and then provide an electronic signature on the appropriate eCRFs. The Investigator's electronic signature for specific eCRFs will be documented in compliance with local regulations.

The source documents must be made available for monitoring or auditing by Sponsor's representative or representatives of the CA and other applicable regulatory agencies.

Visual and/or computer data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Oracle remote RDC system and will be issued to the site for appropriate response.

eCRFs are recommended to be entered into the electronic system within no later than 10 days of the completion of the protocol-specified visit, or sooner, as required by the CIP and local regulations.

Data points not collected and/or recorded will be considered deviations unless otherwise specified. Procedures used for data review, database cleaning, and issuing/resolving data queries will be included in the Data Management Plan.

The study eCRF is an FDA CFR title 21 Part 11 compliant electronic data capture system.

The investigator must ensure the availability of source documents from which the information on the eCRFs was derived. The type and location of source documents should be documented. Where printouts of electronic medical records, are provided as source documents, or where copies of source documents are retained as source documents, those should be certified. Certification must contain (1) the signature of the individual making the copy, (2) the date the copy was made and (3) a statement attesting to the accuracy and completeness of the copy.

Data generated from using the device will be stored on an external hard drive provided by the Sponsor in accordance to local data protection laws. This data will remain confidential and identified only by subject's code. The data will be available to the monitor and will be considered as source data. De-identified videos and raw data from the CCE procedure will be sent to the Sponsor for analysis using an encrypted device. Additional data collection may apply. In case that following the CCE procedure, the subject is referred to a colonoscopy procedure, de-identified colonoscopy report and images/videos may be collected. All data sent to the Sponsor will not include any subject identifying information.

10.14. Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the CIP or the CTA. Use of waivers from the CIP is prohibited.

Prior written approval by the Sponsor is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a

deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from the Sponsor is required for such situations.

All study deviations must be reported on the eCRF regardless of whether medically justifiable, pre-approved by the Sponsor, an inadvertent occurrence, or taken to protect the subject in an emergency. Multiple deviations of the same type at the same visit may be reported on one case report form.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the EC as well as the Sponsor within 5 working days.

Reporting of all other study deviations should comply with EC policies and/or local laws and must be reported to the Sponsor as soon as possible upon the study site becoming aware of the deviation. Reporting of deviations must comply with EC policies, local laws, and/or CA requirements. Refer to Investigator Reports, Table 7: Investigator reports for geography-specific deviation reporting requirements and timeframes for reporting to the Sponsor and/or RAs.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and study site, and in some cases, may necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. If further escalation is needed, it may result in Corrective and Preventive Action (CAPA), suspension, or termination. If it is determined that there is investigator fraud, or strong evidence of fraud, the course of action may include, but is not limited to: potential exclusion from analyses, site closure, notification of the responsible EC of the actions to be taken, notification of key stakeholders and/or study team of the actions to be taken, notification of appropriate CA and/or restrictions on future participation in clinical studies. The Sponsor will provide reports to investigator summarizing information on deviations that occurred at the investigational study site on a periodic basis.

Major deviations are defined as deviations with respect to:

- Failure to obtain proper IC
- Subject's eligibility criteria not met

Bowel preparation related deviations are common and expected. Deviations related to bowel preparation consumption/MB-MMX intake will be specifically defined for the study and captured accordingly in the eCRF. For further details please refer to Appendix B: Bowel Preparation/MB-MMX administration Deviations.

10.15. Subject Exit, Withdrawal or Discontinuation

A study exit eCRF is required for all subjects. The reason for study exit, including screen failure, will be documented on the applicable eCRF and in the subject file. The Sponsor must be informed of each withdrawal case. Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing device and/or procedure related AEs are resolved or unresolved with no further actions planned. At the completion of the follow-up visit, the subject will be exited from the study. A follow-up eCRF and a Study Exit eCRF will to be completed. Upon exiting from the study, no further study data will be collected, or study visits will occur for the subject, unless the subject has been referred to a colonoscopy procedure post the CCE procedure (de-identified colonoscopy report and images/videos may be collected) and/or AE follow up is required.

Subjects will be informed that they have the right to withdraw from the study at any time, without prejudice to their medical care, and are not obliged to state their reasons.

If the subject wishes to exit from the study (i.e. the subject revokes consent), the study site is required to document the reason for exit on the Exit eCRF. In addition, study site shall follow the regulations set forth by the governing EC. Per ISO14155 guidance, permission may be requested to follow up with the subject outside of the study, due to withdrawal based on issues related to the investigational feature safety or performance.

The investigator may withdraw a subject from the assigned study at any time if any of the following situations arise:

1. Subject did not provide consent/ withdrawal of informed consent by the subject
2. The Principal Investigator deems that it is in the subject's best interest to withdraw from the study for subject's safety.
3. Subject's death
4. Occurrence of a Serious Adverse Device Effect (SADE), or severe side effects
5. Presence or appearance of any of the exclusion criteria/inclusion criteria not met
6. A significant CIP violation, as determined either by the sponsor or the investigator
7. Subject noncompliant with study procedures/visits

Every effort will be made to determine the reason for the subject dropping out of the study. Any withdrawal must be fully documented and recorded including the reason for withdrawal on the study termination page on the study eCRF and in the subject file.

Subjects removed from the study because of a Serious Adverse Device Event or Serious Adverse Event will be followed-up until the adverse event has resolved or study closure, whichever occurs first.

The eCRF will be completed for withdrawn subjects and will include all available information including: Demographics, medical information, all parts of the procedures that were performed, safety information, reason for end of study etc.

10.16. Lost to Follow-up

A subject is considered to be lost to follow-up if at least three attempts to contact the subject are unsuccessful. The method of attempt (e.g., three phone calls) must be documented in the subject's medical record. In addition, regulation set forth by the governing EC must be followed, if any. Subjects replacement will not be performed in this study.

11.Risks and Benefits

11.1. Potential Risks

Device related risks:

The Sponsor follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance. Per ISO 14155, the risk analysis process for the SPICE Study, product- PillCam™ COLON2, is being performed in accordance with ISO 14971, and will ensure that the level of risk is acceptable prior to starting the study.

Based on the literature evaluation, clinical trials, PillCam User Manual, the risk assessment reports, and post market vigilance, potential adverse events associated with the use of PillCam™ capsules may include: Adverse events associated with difficulty and/or inability to swallow the capsule (i.e. choking), Symptomatic/asymptomatic capsule retention (including delayed excretion of the capsule), aspiration (extremely rare risk), obstruction, perforation, and mucosal injury or bleeding. In some instances, intervention was required to remove the capsule.

The clinical investigation has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects, and both the risk threshold and the degree of distress are specifically defined in the clinical investigation plan and constantly monitored.

For complete risk assessment and further information (i.e. foreseeable AEs), please refer to the PillCam COLON risk file and the PillCam system manual.

Procedure related risks:

Bowel preparation risks:

As the study procedure involves bowel preparation, additional risks are anticipated.

Some bowel-cleansing preparation agents may involve risks of dehydration (loss of body water) and/or imbalance in the levels of salts in the bloodstream. These risks may be further avoided by strictly following the instructions, such as carefully drinking the amounts of fluids required before and during the capsule preparation procedure.

Due to bowel preparation the subject might experience abdominal pain, headache, vomiting, nausea, gagging, bloating, significant anal burning/irritation, hemorrhoids bleeding, dizziness, fatigue, which are anticipated symptoms, mostly mild, that could be related to the bowel preparation procedure. Another risk is possible allergic reaction to bowel preparation agents.

For further information and complete list of adverse events, please refer to the bowel preparation agents' leaflets/manuals for use.

MB-MMX related AEs:

The most common reported adverse events related to the MB-MMX intake include Chromaturia and discolored feces. These are temporary events, mostly mild in nature which are related to the presence of a vital dye in the drug formulation. For the complete list of AEs, please refer to MB-MMX UM.

There are no known incremental risks introduced to the subject as a result of participation in this study.

For possible interaction with concomitant medical treatments, complete list of adverse events and additional information, please refer to the PillCam™ Endoscopy system UM, Bowel Preparation materials leaflets and MB-MMX UM.

11.2. Risk Minimization

The potential risks associated with the CCE were identified and have been successfully mitigated, as described in the PillCam COLON2 risk assessment file/documents. The overall residual risk has been determined to be acceptable. Any potential risks associated with this study are further minimized by selecting qualified and experienced investigators and training study personnel on the CIP.

In addition, investigators will be actively involved in the follow-up of the subjects undergoing the CCE procedure. Risks will be minimized by careful assessment of each subject prior to, during, and after the procedure.

The Sponsor has further minimized the possibility of risks by providing guidelines for subject selection and evaluation and providing adequate instructions and labeling.

The risks for CCE procedure, as noted, will be minimized by excluding subjects who have evidence of complicated medical or surgical histories that would otherwise preclude them from participating. In addition, subjects with sensitivity to substances used during the preparation for the CCE procedure will be excluded. Furthermore, training on the CIP screening, procedures, and follow-up will be given to all investigators and personnel included in the study.

Retention of the CCE capsule will be minimized since capsule will be administered only to those subjects who have no prior history of strictures, GI surgeries/diseases or major motility disorders. In addition, subjects with swallowing disorders are excluded to avoid the risk of capsule aspiration or inability to swallow the capsule.

Table 2- Potential risks and risk minimization for study subjects

Potential risk	Risk Minimization
Capsule retention/bowel obstruction	Capsule retention is a known complication of CE. Physicians are trained to identify those patients who may be at increased risk for retention, including some who may be covered by the contraindication for CCE with suspected or known bowel obstruction. All subjects with prior GI histories, including surgeries, strictures, prior obstructions, or who are otherwise at risk or contraindicated for CCE will be excluded per the exclusion criteria.
Capsule aspirated instead of swallowed	Aspiration of the capsule has been reported as rare complication of CE. This risk is mitigated by the contraindication to use of the device with any patient with a swallowing disorder. In addition, ingestion of the capsule is usually performed under medical supervision.

11.3. Potential Benefits

The study participation may offer no direct benefit, as this is a pilot study, which does not include medical evaluation. Subject would be contributing to future knowledge and potential improvement in colonic polyp identification in the future during CCE procedure.

For the specific type of population included in the study (high risk for CRC), there might be a benefit related to the frequency of their standard of care CRC surveillance. The CCE procedure in between their surveillance Colonoscopy procedures, may offer additional information such as visualization of lesions which were missed during Colonoscopy and/or visualization of small lesions which might have malignancy potential. This is a non-invasive procedure which does not involve sedation nor bowel insufflation.

Due to the use of MB-MMX in conjunction with the CCE procedure, an additional benefit to the subject could be considered, as the MB-MMX has been found potentially effective in colonic polyp enhancement.

11.4. Risk-Benefit Rationale

CCE procedure is considered as a safe, feasible, procedure for visualization of the colon, and offers a more convenient with relatively low risks than other invasive colon exams.

PillCam™ capsule and the corresponding endoscopy systems, have been cleared for marketing in many countries world-wide, including USA, EU, Canada, Japan and Australia. All capsules are considered as class IIa devices in Europe. Risk assessment has been performed and no major or intolerable risks were found.

All the mitigations as biocompatibility test, electrical safety and electromagnetic safety were documented according to ISO 14971. In addition, sponsor facilities have been certified to relevant medical device quality system requirements. The risk management summary demonstrates that the

risks associated with the tested device are well mitigated and the residual risks are as low as reasonably practicable as defined by the applicable standards.

To conclude, the risks to subjects participating in this study would be similar to the expected risks for CRC surveillance subjects in standard medical practice, while the subjects can potentially benefit from better colonic polyps enhancement and the data gathered from this study could contribute to future knowledge and potential improvement in colonic polyps identification in future CCE procedures.

12.Adverse Events and Device Deficiencies

12.1. Adverse Events

AEs definitions are provided in Table 3- Adverse Event and Device Deficiency Definitions.

Adverse Events will be collected for all enrolled subjects at the start of the bowel preparation, at day (-1), until the follow-up phone call (visit 3). Medical care will be provided, as defined in the informed consent, for any AE related to study participation, if needed.

Reporting of these events to the Sponsor will occur on an AE Form. Each event must be reported separately. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. Also, Diarrhea<24h after the CCE and mild anal burning/irritation are considered as the expected outcome of the bowel preparation process and shall not be recorded as Adverse Events, as long as the event does not require any medical intervention. Incidental findings observed during CCE video analysis will not be considered as AEs and will not be reported as such. In addition, in case of discovering a pregnancy during the course of the study, it will not be considered as an AE and will not be reported as such.

Per ISO14155:2020, it is required to collect all AEs and DDs. Non-subject AEs are not expected in this study, thus are not collected.

For AEs that require immediate reporting, initial reporting may be done by phone, fax, or on the eCRF completing as much information as possible. The completed AE eCRF must be submitted to the Sponsor as soon as possible.

Any medication/treatment associated with the treatment of an AE must be reported.

Subject deaths are also required to be reported. Refer to Section 12.6 for Subject Death collection and reporting requirements.

12.2. Device Deficiency (DD)

The DD definition is provided in Table 3. DD information will be collected throughout the study and reported to Medtronic. Note that DD that result in an AE to the subject should be captured as an AE only.

DD that did not lead to an AE but could have led to a SADE (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting (

Table 6: Reporting Requirements).

12.3. Processing Updates and Resolution

For any changes in status of a previously reported adverse event or DD (i.e. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE or DD form. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject dies or exits the study, or until study closure, whichever occurs first.

If the subject is exited from the study prior to study completion, all efforts should be made to continue following the subject until all unresolved device or procedure related AEs, as classified by the investigator, are resolved, unresolved with no further actions planned, or study closure, whichever occurs first.

At the time of study exit, all collected adverse events that are unresolved must be reviewed and an update to the original AE must be reported.

12.4. Definitions/Classifications

For the list of anticipated adverse events and anticipated adverse device effects, please refer to section 11.

Table 3- Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators. (ISO 14155:2020, 3.2)
Adverse Device Effect (ADE)	AE related to the use of an investigational medical device NOTE 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. NOTE 3: this includes 'comparator' if the comparator is a medical device. (ISO 14155:2020, 3.1)

Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. NOTE 1: DD include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling. NOTE2: This definition includes device deficiencies related to the investigational medical device or the comparator. (ISO 14155:2020, 3.19)
Relatedness	
Device Related	An AE that results from the presence or performance of any component of the device. Device-related: An AE that results from the presence or performance (intended or otherwise) of the device.
Procedure Related	An AE that occurs due to any procedure related to the CCE procedure (other than device). The preparation procedure for the CCE procedure in the study includes consumption of bowel preparation materials and MB-MMX tablets (non-MDT products).
Seriousness	
Serious Adverse Event (SAE)	AE that led to any of the following a) death, b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic disease, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function, c) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE. (ISO 14155:2020, 3.45)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2020, 3.44)

Serious Health Threat	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons NOTE 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals. (ISO 14155:2020, 3.46)

12.5. Reporting of Adverse Events

Please refer to below for a list of the minimum AE reporting requirements for Investigators. If local regulations or EC require faster reporting, then the Investigator will adhere to those requirements. Reporting of all safety events to the Sponsor will be completed through Investigator submission of the AE eCRF in the remote data capture system.

Events will be reviewed by the Sponsor to determine any reporting obligations to the CA. Reporting will occur within the timelines per local regulations and requirements. The Principal Investigator is responsible to report the events to the EC.

Event's relatedness to the study device and procedure will be assessed according to the following levels of causality:

Causal relationship- the serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that-
    - o the investigational device or procedures are applied to;
    - o the investigational device or procedures have an effect on;
- the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

Probable- The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

Possible- The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

Not related- Relationship to the device, comparator or procedures can be excluded when:
- the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
- the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure when clinically feasible and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
- the event involves a body-site or an organ that cannot be affected by the device or procedure;
- the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

Event's Severity will be defined according to the following criteria:

Mild	Event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (e.g., insomnia, mild headache).
Moderate	Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (e.g., fever requiring antipyretic medication).
Severe	Event results in significant symptoms that prevents normal daily activities may require hospitalization or invasive intervention (e.g., anemia resulting in blood transfusion).

An AE can be classified as severe and not deemed an SAE. Similarly, an SAE is not automatically severe in nature. Severity will be assessed by the Investigator.

Regardless of severity, all AEs occurring during the study must be recorded in the subject's eCRF. The following information and assessments should be documented:

- Type of event (AE term)
- Subject number
- Date of AE onset

- Date of resolution
- Seriousness
- Severity degree: mild / moderate / severe
- Relationship to study device and procedure: causal relationship/ probable/ possible/ not related
- Measures taken
- Outcome of event:
  - not recovered/ not resolved
  - recovered/resolved
  - recovered/ resolved with sequelae
  - recovering/ resolving
  - unknown
  - fatal

The sponsor shall immediately conduct an evaluation of any unanticipated events if determined that the events presents an unreasonable risk to subjects and report the results of such evaluation per the local requirements.

In case of SAEs and SADEs, the following emergency contact may be approached:

Table 4: Emergency contacts

Clinical Affaires	Medical Affairs
Inbal Eyal Senior Manager, Clinical Affairs Medtronic, GI Solutions POB 258, 20692 Yoqneam, Israel 2 Hacarmel St. New Industrial Park POB 258 20692 Yoqneam, Phone: +972 (4) 909-7774 Mobile: [redacted] Fax: +972 (73) 250-1533 Email: inbal.eyal@medtronic.com Roslana Fox Clinical Trials Leader Medtronic, GI Solutions POB 258, 20692 Yoqneam, Israel 2 Hacarmel St. New Industrial Park POB 258 20692 Yoqneam, Phone: +972 (73) 250-1552 Mobile: [redacted] Email: roslana.fox@medtronic.com	Ari Bergwerk MD Medical Advisor, Medical Affairs Medtronic, GI Solutions New Industrial Park POB 298, 20698 Yoqneam, Israel Phone +972 (4) 909-7822 Mobile [redacted] Fax +972 (73) 250-1537 Email: Ari.Bergwerk@medtronic.com

Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements.

12.5.1. Adverse Event and Device Deficiency Classification

All AE and DD will be reviewed by a Sponsor representative. AEs will be classified according to the definitions provided.

Upon receipt of AE at the Sponsor, a representative will review the AE/DD for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. The Sponsor will utilize MedDRA, to assign a MedDRA term for each AE based on the information provided by the investigator.

Regulatory reporting of AEs and DDs will be completed according to local regulatory requirements. Refer to

Table 6 for a list of required investigator and Sponsor reporting requirements and timeframes. It is the responsibility of both investigators and Sponsor, to abide by any additional AE reporting requirements stipulated by the EC responsible for oversight of the study.

For emergency contact regarding SAE and/or SADE, contact a study representative immediately (refer to the study contact list provided in the study site's study documents binder/investigator site file or refer to the Sponsor contact information provided on the title page).

AEs and Deaths will be classified according to the standard definitions as outlined below.

Table 5:Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Device, Procedure
	Sponsor	Device, Procedure
Seriousness	Investigator	SAE, DD with SADE potential
	Sponsor	SAE, DD with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator

12.5.2. Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and DDs will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator and the sponsor to abide by the AE reporting requirements stipulated by local law and the study site's EC.

Table 6: Reporting Requirements

SAEs	
Investigator shall submit to:	
Sponsor	Report to the sponsor, immediately, all serious adverse events and no later than 3 calendar days after investigator first learns of the event.
CA	Submit to CA per local reporting requirement.
EC	Submit to EC per local reporting requirement.
Sponsor shall submit to:	
CA	Submit to CA per local reporting requirement.
EC	Submit to EC per local reporting requirement.
ADEs	
Investigator shall submit to:	
Sponsor	Submit without unjustified delay, after the investigator first learns of the effect.
CA	Submit to CA per local reporting requirement.
EC	Submit to EC per local reporting requirement.
Sponsor shall submit to:	
CA	Submit to CA per local reporting requirement.
EC	Submit to EC per local reporting requirement.
SADEs	
Investigator shall submit to:	
Sponsor	Submit immediately after the investigator learns of the event or of new information in relation to an already reported event, and no later than 3 calendar days after the investigator first learns of the effect.
CA	Submit to CA per local reporting requirement
EC	Submit to EC per local reporting requirement.
Sponsor shall submit to:	
CA	Submit to CA per local reporting requirement.
EC	Submit to EC per local reporting requirement.
Investigators	Submit per local reporting requirement.

All other reportable AEs	
Investigator shall submit to:	
Sponsor	Submit without unjustified delay after the investigator first learns of the event.
CA	Submit to CA per local reporting requirement.
EC	Submit to EC per local reporting requirement.
DDs with SADE potential	
Investigator shall submit to:	
Sponsor	Submit immediately, and no later than 3 calendar days after the investigator first learns of the effect.
CA	Submit to CA per local reporting requirement.
EC	Submit to EC per local reporting requirement.
Sponsor shall submit to:	
CA	Submit to CA per local reporting requirement.
EC	Submit to EC per local reporting requirement.
All other Device Deficiencies	
Investigator shall submit to:	
Medtronic	Submit without unjustified delay after the investigator first learns of the deficiency.
CA	Submit to CA per local reporting requirement.
EC	Submit to EC per local reporting requirement.

12.6. Subject Death

All subject deaths must be reported by the investigator to Medtronic on an AE form (AE with outcome of fatal) as soon as possible after the investigator first learns of the death. In case of death, there should be one AE with the outcome of fatal.

Local laws and procedures must be followed where applicable. If any system component is returned to the Sponsor, internal return product reporting systems may be used to gather additional information about the returned device/component.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Sponsor clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records, if available should be sent to the Sponsor clinical study team. If an autopsy is conducted, a copy of the autopsy report should also be sent to the Sponsor clinical study team if available and allowed by state/local law. When the death occurs at a remote study site, it is the investigative study site's responsibility to attempt retrieval of information about the death. Additionally, device disposition information should be updated.

In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to device and procedure
- Device disposition information
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law)

12.7. Product Complaint Reporting

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by the Sponsor, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. The Sponsor will notify the RAs (e.g. CA) as applicable for the following incidents immediately upon learning of them and is not limited to AEs and DDs only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
  - Life-threatening illness or injury
  - Permanent impairment of a body function or permanent damage to a body structure
  - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

13.Statistical Design and Methods

This is a single-center, prospective, non-randomized clinical trial designed to evaluate the technical feasibility (descriptive) of mucosal staining during CCE procedure, using MB-MMX, in CRC high risk population. As a result, no formal sample size was calculated and up to 15 patients are planned to be enrolled to this study. No interim analysis is planned.

As a result, the methods for analysis will be descriptive in nature (frequency and percent as well as distribution measures such as: mean, standard deviation, median and range). 95% confidence intervals will be presented as well.

Primary objective:

To demonstrate effective polyp enhancement during a COLON2 Capsule Endoscopy procedure when using MB-MMX as a contrast- enhancement technique.

Primary endpoints:

- The percent of colonic polyps which have a visible contrast to the healthy colonic mucosa during CCE, as indicated by an experienced reader, using the subjective reader questionnaire *(For each polyp – was there a contrast between the polyp and the healthy mucosa? Yes/No*), out of the examined polyps
- The interference level of detrimental effects on the visualization of the colonic mucosa during CCE, due to use of MB-MMX per colonic segment

Detrimental effect will be considered as any observation, such as an excessive blue dye deposit, dark and dim appearance of the tissue, interfering with tissue visualization and will be evaluated on a scale from 1 (no interference) to 5 (high interference) to evaluate the level of interference, using a subjective reader questionnaire.

Secondary objective:

To evaluate the safety of CCE procedure while using MB-MMX.

Secondary endpoint:

All AEs will be reported by number, type, relatedness (device/procedure) seriousness, severity and duration. All AEs will be captured, regardless of severity.

This section presents statistical considerations for the study design and provides a high-level description of planned analysis and reporting. More details will be given in a separate Statistical Analysis Plan (SAP) that will be approved before data freeze or lock. Any deviation to the pre-specified statistical analyses will be noted in the study report.

13.1. General Aspects of Analysis

Data analysis will be performed by the sponsor and/or designee.

The analysis will include all of the available information. Demographic and other characteristics will be provided. Summary statistics (arithmetic mean, standard deviation, and range for quantitative variables) will be presented for the total study population. Frequency tables for qualitative data will be provided. All confidence intervals will be presented as 95% confidence intervals unless otherwise stated. For each of the objectives the available data will be summarized, and missing data will be discussed. The main analysis of the study objectives will be based on available data and missing data will not be imputed.

Two analysis sets will be used for the statistical analysis. The definition of each is defined below:

Full Analysis Set (FAS). FAS includes all enrolled subjects:

- Who signed the informed consent and
- Who satisfied the eligibility criteria
- Ingested the PillCam™ COLON2 capsule

FAS will be used for subject disposition, population and procedures description, for performance and for Safety analyses.

Per Protocol Analysis Set (PPAS): PPAS is a subset of the FAS, which includes only subject who have demonstrated all of the following:

- Subjects' compliance to the bowel prep regimen/MB-MMX administration is ≥75% according to each of the following criteria:
    - Total volume of bowel prep material (PEG) consumed is ≥3L (out of 4L in total)
    - Intake of ≥6 MB-MMX tablets (out of total of 8 tablets)
- No major deviations related to Eligibility Criteria and/or Informed Consent
- The capsule reached the colon during the procedure
- Raw data has been generated for the CE procedure

Any deviation from specified statistical plan will be in addition to “per protocol” analysis and will be reported as such. Post-hoc analysis will be conducted according to the existing data gathered, if necessary.

13.2. Interim Analysis

No interim analyses are planned for this study.

13.3. Primary Objective(s)

Primary Objective - to demonstrate effective polyp enhancement during a Colon Capsule Endoscopy procedure when using MB-MMX as a contrast- enhancement technique.

As this is a descriptive pilot study, no formal hypothesis was formulated. In any case of post hoc analysis which will include statistical testing, P-value<0.05 will be considered significant.

The primary objective will be measured via a subjective questionnaire, at the polyp level and at the case level:

Primary endpoint at the polyp level – the reader will answer for each polyp the following question: "*was there a contrast between the polyp and the healthy mucosa? Yes/No*". The endpoint refers to the percent of colonic polyps which have a visible contrast to the healthy colonic mucosa during CCE, as indicated by the reader (i.e. the reader marked "Yes"), out of the examined polyps. the percent of polyps with visible contrast will be presented with 95% confidence level (95%CI)

Primary endpoint at the case level – for each case the reader will be asked to mark the level of interference form a 5-point scale (1 =no interference to 5= high interference). The level of interference refers to the detrimental effects on the visualization of the colonic mucosa during CCE, due to use of

MB-MMX per colonic segment (detrimental effect will be considered as any observation, such as an excessive blue dye deposit, dark and dim appearance of the tissue, interfering with tissue visualization). Analysis of this endpoint will include summary statistics (arithmetic mean, standard deviation, median and range) as well as frequency and percent of each scale level.

All of the available information will be analyzed according to the CIP criteria (inclusion, exclusion, deviations etc.).

13.4. Secondary Objective

Secondary Objective - To evaluate the safety of CCE procedure while using MB-MMX.

As this is a descriptive pilot study, no formal hypothesis was formulated.

All AEs will be reported by number, type, relatedness (device/procedure), seriousness, severity and duration. All AEs will be captured, regardless of severity.

The percent of cases with at least one AE out of the total cases, will be presented with 95%CI.
All of the available information will be analyzed according to the CIP criteria (inclusion, exclusion, deviations etc.).

13.5. Sample Size Determination

This is a pilot study where no formal sample size will be calculated.
As this is the first time that MB-MMX is being used during a CCE procedure, the chosen sample size includes small number of subjects, which allows visualization of colonic polyps and evaluation of their contrast to the healthy mucosa, under the assumption that not all subjects will have colonic polyps presence during the CCE procedure. Up to 15 patients are planned to be enrolled to this study.

14.Ethics

14.1. Statement(s) of Compliance

- The study shall be conducted in accordance with the protocol and ethical principles that have their origin in the DoH. All principles of the Declaration of Helsinki have been implemented in this clinical study by means of the patient informed consent process, EC approval, clinical study training, clinical study registration, publication policy.
- The study will be conducted in compliance with the protocol, International Conference on Harmonization Guidelines on Good Clinical Practice (GCP), EU MDR 2017/745 as of Date of Application (where applicable), Medical Device Directive (MDD) 93/42/EEC and ISO 14155:2020.
- The clinical study will not begin until the EC and regulatory authority approvals/ notification, as required by the local regulations, are received. This also applies to the continuing review of an ongoing study, and approval of any subject facing materials, including the ICF. Approval of the CIP and CIP amendments is required from the following entities prior to any study procedures at a study site:

  - Medtronic
  - Principal Investigator (where required by local law/regulations)
  - Geography-specific regulatory authorities (if regulatory approval is required)
  - An independent EC
- Similarly, approval of subsequent revisions to the CIP is required at the study site from the above-mentioned entities prior to implementation of the revised CIP at the study site.
- The SPICE study was designed to reflect the GCP principles outlined in ISO 14155:2020 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with ISO 14155, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation. AE and DD handling in the SPICE study is ISO 14155:2020 compliant, other than collection of Non-subject AEs, which are not expected in this study, thus are not collected. As this is a post-market study, USADE will also not be collected.
- The study is sponsored by All Given Imaging, an indirect wholly owned subsidiary by Medtronic plc and all financial aspects are outlined in the clinical investigation site agreement (CTA).
- Written informed consent is mandatory and must be obtained from each subject prior to his/her participation in this trial and screening procedures are initiated. Any additional requirements imposed by the EC or regulatory authority will be followed.
- By signing the ICF, the subjects will acknowledge that the video originated from the CCE procedure may be of a poor quality, or otherwise unsuitable for examination or interpretation. Subjects shall be further advised that the CCE report provided for the CCE procedure may be incomplete or inaccurate and may not identify the actual condition of the subject's digestive tract. Subjects will acknowledge that the procedure and any results stemming therefrom, including any reports provided with respect thereto, are not substitute for a medical exam and must not be relied upon.
- The PillCam™ endoscopy capsules and the other parts of the PillCam™ Endoscopy system does not incorporate any medicinal product, human blood derivative or tissues of animal origin.
- All Given Imaging, an indirect wholly owned subsidiary by Medtronic plc. products fully comply with all safety and radio standards worldwide.
- Given Imaging Ltd, is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local

law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the EC. All subjects participating in the study will have insurance coverage by the sponsor, which is in line with the applicable laws and/or local regulations for Clinical Trials.

- The study will be publicly registered prior to in accordance with the 2007 FDA act and DoH on http://clinicaltrials.gov (PL 110-85, section 810(a)). In addition, the study may be registered in local regulatory databases where required by local law.
- The study will also comply (when applicable) with 21 CFR Part 11 for use of electronic Records and electronic Signatures and 21 CFR Part 54 for collection and handling of Financial Disclosure by Clinical Investigators.

15. Study Administration

15.1. Monitoring

It is the responsibility of the sponsor to ensure proper monitoring of this study.

Trained sponsor personnel or delegates appointed by the Sponsor may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the CTA, and the applicable regulatory and local requirements. Sponsor, or delegates, must therefore be allowed direct access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the IC and CTA. The principal investigator or designee should also be available during monitoring visits.

15.1.1. Monitoring Visits

Frequency of monitoring visits may be based upon subject enrollment, study compliance, number of adverse events, number of deviations, observations from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents will be reviewed at each study site. Monitoring for the study, including site qualification visits (if applicable), site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance to the study-specific monitoring plan.

Monitoring visits may be conducted periodically to assess study site progress, the investigator's adherence to the CIP, regulatory compliance including but not limited to EC approval and review of the study, maintenance of records and reports, and review of source documents against subject eCRFs in accordance to the study-specific monitoring plan. Monitors review study site regulatory and study compliance by identifying observations of non-compliance and communicating those observations along with recommendations for preventative/corrective actions to study site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular study site.

15.2. Data Management

Data will be collected using an electronic data management system. eCRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by the Sponsor.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by the Sponsor or a third party designated by the Sponsor in a key coded form.

Procedures in the CIP require source documentation. Source documentation will be maintained at the study site. Source documents, which may include worksheets, subject medical records, programmer printouts, and interrogation files, must be created and maintained by the investigational study site team.

Per ISO14155, the investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation.

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing.

Data generated from using the device will be stored on site on a dedicated secured storage device provided by the Sponsor in accordance to local data protection laws. This data will remain confidential and identified only by subject's code. The data will be available to the monitor and will be considered as source data. De-identified videos and raw data from the CCE procedure will be sent to the Sponsor for analysis using an encrypted device. The data will not include any subject identifying information.

15.3. Direct Access to Source Data/Documents

The Sponsor may conduct audits at participating study sites. The purpose of an audit is to verify the performance of the monitoring process and the study conduct, independently of the personnel directly involved in the study. CAs/RAs, such as the FDA, may also perform inspections at participating study sites. The investigator and/or institution shall permit the Sponsor, ECs and RAs direct access to source data and documents during monitoring, audits and regulatory inspections.

15.4. Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique study ID to each subject. Records of the subject/ Subject Identification (SID) relationship will be maintained by the study site. The SID number is to be recorded on all study documents to link them to the subject's medical records at the study site. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. To maintain confidentiality, the subject's name or any other identifying information should not be recorded on any study document other than the ICF and study identification

log. In the event a subject's name is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel. Data relating to the study might be made available to third parties (for example in case of an audit performed by CA/RA), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

15.5. Liability/Warranty/Insurance Information

Given Imaging Ltd. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the EC.

15.6. CIP Amendments

Any revisions or amendments to the CIP or ICF, along with a statement of justification for the changes, will be submitted to all affected CA and governing ECs, according to applicable regulations. All amendments to the CIP shall be agreed upon between the Sponsor and the principal investigator. Approval by regulatory agencies (when applicable) and EC must be obtained prior to implementing a CIP revision at the study site.

15.7. Record Retention

All study-related documents must be retained at the clinical investigation site for a period of at least 25 years after completion or early termination of the clinical investigation. The Sponsor will inform the investigator/study site when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement between the Sponsor and the investigator. The investigator should take measures to prevent accidental or premature destruction of documents. Should the investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to Medtronic.

The Sponsor will retain the study records according to Sponsor's corporate policy and record retention schedule.

15.7.1. Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. eCRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after product approval or the date on which the investigation is terminated or the date that the records are no longer required for purposes of supporting a pre-market approval application.

- All essential correspondence between the EC, sponsor, monitor, CA and the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
  - Signed and dated ICF (signed by subject and investigator)
  - Observations of AEs/ADEs/DDs
  - Medical history
  - Documentation of the dates and rationale for any deviation from the protocol
- Financial Disclosure (FD)
- Subject screening log & ID log
- All approved versions of the CIP, ICF
- Signed and dated CTA
- CV (signed and dated) of principal investigators and key members of investigation study site team.
- Documentation of delegated tasks.
- EC approval documentation. Written information that the investigator or other study staff, when member of the EC, did not participate in the approval process. Approval documentation must include the ECs composition, where required per local law.
- CA notification, correspondence and approval, where required per local law.
- Study training records for study site staff.
- Insurance certificate
- Any other records that local regulatory agencies require to be maintained.
- Final Study Report including the statistical analysis.

15.7.2. Sponsor Records

The sponsor shall maintain the following accurate, complete, and current records:

- All correspondence which pertains to the investigation
- Study device traceability record containing serial numbers/ID of devices, shipping date and name and address of person that received shipped device, location (if different than person shipped to), transfer and receipt by the Sponsor dates.
- Sample of label attached to study device
- Signed Investigator Trial Agreements, Financial Disclosure and current signed and dated CV of principal investigator and key members of the investigation study site team (as required by local law), delegated task list
- All signed and dated case report forms submitted by investigator, including reports of AEs, ADEs and DDs

- All approved ICF templates, and other information provided to the subjects and advertisements, including translations
- Copies of all EC approval letters and relevant EC correspondence and EC voting list/roster/letter of assurance
- Names of the institutions in which the study will be conducted
- CA correspondence, notification and approval as required by national legislation
- Insurance certificates
- Names/contact addresses of monitors
- Monitoring visit reports
- Statistical analyses and underlying supporting data
- Final report of the study
- The CIP, study related reports, and revisions
- Study training records for study site personnel and Sponsor personnel involved in the study
- Any other records that local regulatory agencies require to be maintained.

The Sponsor records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in stored in secured file cabinets at the Sponsor during the course of this study.

After closure of the study Medtronic will archive records and reports indefinitely.

15.8. Reporting Requirements

15.8.1. Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by an EC with respect to this study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in Section 12. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 7: Investigator reports

Report	Submit to	Description/Constraints
Withdrawal of EC approval	Sponsor and CA (when applicable)	The investigator must report a withdrawal of approval by the reviewing EC of the investigator's part of the investigation within 5 working days.
Progress Report	Sponsor and EC	Provide if required by local law or EC.

Study Deviations	Sponsor and when applicable to EC and CA	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. Per ISO 14155:2020- when relevant, ethics committee, or the appropriate RAs should be informed.
Failure to obtain IC	Sponsor and ECs	ICF shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. (ISO 14155:2020)

15.8.2. Sponsor Reports

The Sponsor shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, the Sponsor shall, upon request of the reviewing EC or CA, provide accurate, complete and current information about any aspect of the investigation. Safety data Sponsor reporting requirements are listed in section 12.

Table 8: Sponsor reports

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, EC and CA (when applicable)	Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2020)
Withdrawal of EC approval	Investigators, EC and CA (when applicable)	Investigators, ECs and CAs (when applicable) will be notified only if required by local laws or by the EC.
Withdrawal of CA approval	Investigators, EC and CA (when applicable)	Investigators, ECs and CAs (when applicable) will be notified only if required by local laws or by the EC.
Progress Reports	EC and CA (when applicable)	This will be submitted to the EC/CA only if required by the local regulations.
Final report	Investigators, CA and EC (when applicable)	The final report shall be submitted within 12 months of study completion or termination. The investigator shall have the opportunity to review and comment on the final report and the signature of the principal Investigator will be obtained.

Report	Submit to	Description/Constraints
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the eCRFs and the final report of the clinical investigation. (ISO 14155:2020) Study site specific study deviations will be submitted to investigators periodically.

15.9. Publication and Use of Information

Publications from the SPICE Study (if applicable) will be handled according to Standard Operating Procedures and as indicated in the CTA.

The Sponsor Publication and Authorship Policy is aligned with the International Committee of Medical Journal Editors (ICMJE) recommendations (www.icmje.org). the Sponsor may seek to publish, in appropriate peer-reviewed journals and scientific conferences, results of clinical studies where human subjects are involved, regardless of outcome. Information regarding the study will be made available on clinicaltrials.gov. Additionally, the results of this study may be submitted for publication in an appropriate journal. While study results are owned by the Sponsor, all data on which a potential publication is based will be made available to all authors as required for their participation in the publication process.

Furthermore, data may be published or used by study investigators, with written approval by the Sponsor, provided that such publication or use is in accordance with this this protocol, the Sponsor Publication and Authorship Policy, and the Clinical Investigation Agreement. Investigators must submit a copy of all manuscripts and/or abstracts to the Sponsor for review and comment 30 days prior to planned submission. The Sponsor acknowledges that its right to review and comment shall relate solely to the proprietary, licensing, and/or confidential rights The Sponsor may have in such proposed publication, rather than whether such results and/or opinions are favorable to the Sponsor.

15.9.1. Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Sponsor personnel, must at a minimum meet all of the conditions below:

- Substantial contributions to conception and design of the work, or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The Sponsor involvement in a publication (e.g., funding of the study; sponsor of the study; collection, analysis, and interpretation of data; professional writing assistance) must be disclosed according to journal-specific policies, submission requirements, and prevailing editorial standards, in addition to those specified by ICMJE. Authors must ensure that an acknowledgement/disclosure statement is included in the body of the manuscript for the Sponsor to review for accuracy. All authors must also disclose financial or personal affiliations that could be considered conflicts of interest as per journal/conference requirements.

Decisions regarding authorship and contributor-ship will be made by the Sponsor. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All investigators not listed as co-authors will be acknowledged as the "Sponsor SPICE Study Investigators" and will be individually listed according to the guidelines of the applicable scientific journal when possible and affiliation. Any other contributors will be acknowledged by name with their specific contribution indicated.

15.9.2. Transparency

Transparency of clinical study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to the investigator, ECs and CAs of participating countries when required.
- Registering and posting the study results on a publicly accessible database, e.g., ClinicalTrials.gov based on the posting rules stipulated
- Disclosing conflicts of interest (e.g., financial)

15.10. Suspension or Early Termination

15.10.1. Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a study that occurs when the Sponsor requirements have been satisfied per the CIP and/or by a decision by the Sponsor or CA), whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing EC oversight is required until the overall study closure process is complete. Refer to section 10.14 for additional information regarding study exit procedures.

15.10.2. Early Termination or Suspension

Early Termination is the closure of a study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single study site Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single study site.

The Sponsor reserves the right to discontinue the study at any stage, with suitable written notice to all investigators and reviewing ECs. The appropriate sites and ECs will be notified of discontinuation

of the study for any reason no later than 5 working days after the sponsor makes this determination. In addition, ECs can decide whether the study is to be terminated and will notify the Sponsor.

Similarly, investigators may withdraw from the study at any time, subject to providing written notification to the Sponsor prior to the date they intend to withdraw, as described in the CTA. However, the Sponsor and investigators will be bound by their obligation to complete the follow-up of subjects already participating in the study. The subjects must be followed according to the clinical Investigation Plan, and information obtained during subject follow-up shall be reported to the Sponsor on the appropriate eCRF.

15.10.2.1.1. Study-wide termination or suspension

Possible reasons for considering study-wide suspension or termination of the study include but are not limited to:

- AEs associated with the product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by the Sponsor or CA
- Technical issues during the manufacturing process

15.10.2.2. Investigator/study site termination or suspension

Possible reasons for investigator or study site termination or suspension include but are not limited to:

- Failure to obtain initial EC approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance to regulations and the terms of the CTA (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring observations in a timely manner, etc.)
- EC suspension of the study site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

15.10.3. Procedures for Termination or Suspension

15.10.3.1. Sponsor-initiated and regulatory authority-initiated

- The Sponsor will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the RAs where required
- In the case of study termination or suspension for reasons other than a temporary EC approval lapse, the investigator will promptly inform the EC

- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by the Sponsor
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

15.10.3.2. Investigator-initiated

- The investigator will inform the Sponsor and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the EC
- Per ISO1415, the investigator will promptly inform the regulatory authorities
- The investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

15.10.3.3. Ethics Committee-initiated

- The investigator will inform the Sponsor and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with EC policy or its determination that an overriding safety concern or ethical issue is involved
- The investigator will inform his/her institution (where required per local requirements)
- The investigator will promptly inform the subjects and/or the personal physician of the subjects, with the rationale for the study termination or suspension
- Per ISO14155, the investigator will promptly inform the CA

16.References

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8. ANNEX I- Summary of Product Characteristics, Methylthioninium Chloride Cosmo 25 mg prolonged-release tablets

9. PillCam™ Capsule Endoscopy User Manual

17.Appendices

Appendix A: SPICE Study- Bowel Preparation/MB-MMX administration Schedule

PEG --> Citrafleet/Picosalax			
Time		**Activity**	
Day (-3)	All day	Low-fiber diet	No nuts, seeds, granola, fruit with skin or seeds, any type of legume, whole grains, anything with red or purple dye, vegetables as Corn, potatoes with skin, tomatoes, cucumbers with seeds and peel, etc.
Day (-2)		Low-fiber diet	
	All day	Water	At least 10 glasses
Day (-1)	All Day	Clear liquid diet	No solid food
	18:00-19:00	Bowel prep	1L of PEG solution (i.e. Solución evacuante)
	19:00-20:00	Bowel prep	1L of PEG solution
	20:00	MB-MMX 1st dose	3 MB-MMX tablets after drinking at least 1L of PEG
	20:00-21:00	Bowel Prep	1L of PEG solution
	21:00	MB-MMX 2nd dose	3 MB-MMX tablets 1h after the 1st dose
	21:00-22:00	Bowel Prep	1L of PEG solution
	22:00	MB-MMX 3rd dose	2 MB-MMX tablets 1h after the 2nd dose
	All day	Clear liquid diet	No solid food
Day 0	07:00-	Tablet	1 Prucalopride (i.e. Resolor) tablet of 1 mg
	08:00	PillCam™ capsule	45 – 90 min after Prucalopride consumption
	08:45 - 09:15 DR alert #1	Boost 1 (G2SB) *	1 sachet of Citrafleet/Picosalax, diluted with water-150ml
	09:15 - 10:15	Water	1L water- through 1h duration after DR alert #1
	11:45-12:00 DR alert #2	Boost 2	1 sachet of Citrafleet/Picosalax, diluted with water-150ml, 3h after alert #1
	12:00-13:00	Water	1L water- Through 1h duration after DR alert #2
	13:45 DR alert #3	Suppository	Bisacodilo/ Contalax 10 mg (Bisacodyl) 2h after alert #2
	15:45 DR alert #4	Meal	Light meal 2h after alert #3

* Time of G2S is estimated. 10 mg Metoclopramide (i.e. Primperan/ Pramin will be administrated in case the capsule fails to enter SB within 1h from ingestion (alert 0)

Appendix B: Bowel Preparation/MB-MMX administration Deviations

Activity	Deviation specifications
Diet restrictions	Complete deviation if: • Low-fiber diet was not followed at day 2 and day 3 prior to CCE procedure • Clear liquid diet was not followed 24h prior to and during the CCE procedure
Bowel prep & MB-MMX schedule and volume	Complete deviation if: • MB-MMX intake is less than 8 tablets. If less than 6 tablets- **Exclude from the analysis** • MB-MMX is taken after less than 1L of PEG. • MB-MMX timing of intake for 2nd and 3rd doses is ±10 min from the allowed intervals (as described in Appendix A) • PEG volume consumed is less than 3.5L. • PEG volume consumed is less than 3L.: **Exclude from the analysis.** • PEG volume consumed is less than 2.5L: **No ingestion** • PEG consumed during more than 5h/ less than 2h. • Bowel prep consumed prior to Day (-1)– **cancel/postpone the procedure**.
Prucalopride Intake	Complete deviation if Prucalopride tablet was not administrated prior to capsule ingestion.
Capsule ingestion	Complete deviation if the capsule was ingested less than 45m or more than 90m from Prucalopride intake.
Boosts schedule/ volume	Complete deviation if: • Boost consumption started more than 15m from alert** • Complete deviation if less than entire volume was consumed***
* In case of a PEG volume deviation s, it should be reported as 1 deviation. **In case a boost consumption was not started within the regimen timelines and a capsule was excreted within 30 minutes from alert, it will not be considered as a deviation. ***In case a capsule is excreted during boost consumption, partial volume of boost consumption will not be considered as a deviation.	

Appendix C: List of PillCam™ COLON2 Clinical Studies

Several Clinical investigations with the PillCam™ COLON2 capsule have been conducted in major academic and experienced clinical research centers and have established the safe use and performance capability of the PillCam™ COLON2 capsule endoscopy system. The main clinical studies for the PillCam™ COLON2 capsule endoscopy system sponsored by Medtronic are listed below:

#	NCT Number	Title
1	NCT01372878	Evaluation of Capsule Endoscopy with PillCam® COLON 2 in Visualization of the Colon
2	NCT01269372	Evaluation of Capsule Endoscopy with PillCam® COLON2 in Visualization of the Colon
3	NCT01185002	Evaluation of PillCam® COLON2Capsule Endoscopy Regimen
4	NCT01063231	Evaluation of PillCam® COLON2 in Visualization of the Colon
5	NCT01087528	Evaluation of PillCam® COLON2 in Visualization of the Colon
6	NCT02481219	Optimization of the Bowel Preparation Regimen for the PillCam® COLON2 Capsule Endoscopy Procedure
7	NCT01575093	Safety Evaluation of Bowel Cleansing Regimen for PillCam® COLON2 Capsule Endoscopy
8	NCT01576120	Evaluation of a PillCam Colon Bowel Preparation Regimen in Crohn's Disease Patients
9	NCT00884624	Evaluation of the PillCam® COLON Capsule -2 System
10	NCT01631435	PillCam Platform with the PillCam Crohn's Disease Capsule
11	NCT02754661	Colon Capsule Endoscopy (CCE) Versus Computed Tomographic Colonography (CTC) in the Identification of Colonic Polyps in a Screening Population. (TOPAZ)

Appendix D: Subjective Assessment Questionnaire (filled by the CCE reading physician)

SPICE Clinical Study

Subjective Assessment Questionnaire

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Subject ID: | | | | | | |

Based on subject's PillCam video review, please fill-out the following subjective assessment questionnaire:

Polyps visualization:

1. Were any colonic polyps visualized during the CCE procedure? ☐Yes ☐No

If yes, please indicated the number of polyps: _____

2. For each of the visualized polyps, please indicate the following:

	Location	Size (mm)	Contrast between polyp and healthy mucosa due to MB-MMX?	Flat polyp?
Polyp#1	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#2	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#3	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#4	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#5	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#6	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#7	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#8	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No

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Polyp#9	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#10	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#11	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#12	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#13	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#14	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#15	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#16	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#17	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#18	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#19	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#20	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#21	Cecum/ Ascending/ Transverse/ Descending-Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No

Polyp#22	Cecum/ Ascending/ Transverse/ Descending- Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#23	Cecum/ Ascending/ Transverse/ Descending- Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#24	Cecum/ Ascending/ Transverse/ Descending- Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No
Polyp#25	Cecum/ Ascending/ Transverse/ Descending- Sigmoid/Rectum		☐Yes ☐No	☐Yes ☐No

Level of MB-MMX interference Evaluation:

3. Please rate the level of interference, which is related to determinantal effects on the visualization of the colonic mucosa, during the CCE, due to use of MB-MMX per each colonic segment. Detrimental effects are considered as any observation, such as an excessive blue dye deposit, dark and dim appearance of the tissue, interfering with tissue visualization. 1 =no interference to 5= high interference:

Cecum:

1	2	3	4	5

Ascending:

1	2	3	4	5

Transverse:

1	2	3	4	5

Descending-Sigmoid:

1	2	3	4	5

Rectum:

1	2	3	4	5

Comments: _____

_____

_____

Evaluation Date: _____/_____/_____

Evaluated by (Print name): _____

Signature: _____

Appendix E: list of participating sites/investigators:

Name of the site	Hospital de Navarra, Department of Gastroenterology
Address of the site	Pamplona, Spain ZIP 31008
PI's name	Dr. Ignacio Fernandez-Urien
PI's professional position	Gastroenterologist

Appendix F: System components' model numbers

PillCam™ Recorder	
FGS-0347	PillCam™ recorder, DR3
PillCam™ Recorder accessories including Sensor Belt	
Sensor Belts	
FGS-0325	PillCam™ sensor belt, DR2, SB
FGS-0443	PillCam™ sensor belt, DR3 C2
FGS-0508	PillCam™ sensor belt 2, DR3 SB3
FGS-0568	PillCam™ sensor belt 2T, DR3 SB3
FGS-0590	PillCam™ sensor belt, Small Bowel
FGS-0605	PillCam™ sensor belt, DR3 C2 Crohn's
FGS-0666	PillCam™ Sensor Belt disp kit – 5pk
Accessories	
FGS-0214	PillCam™ recorder pouch, DR2C
FGS-0355	PillCam™ recorder cradle, DR3
ASM-0355-01	PillCam™ recorder accessories, DR3
FGS-0362	PillCam™ recorder accessories, DR3

FGS-0431	PillCam™ sensor belt cover, DR3
FGS-0448	PillCam™ sensor belt, C2 sleeves
FGS-0452	PillCam™ sensor sleeves, 5-pack
FGS-0453	PillCam™ sensor sleeves,10-pack
FGS-0496	PillCam™ sensor belt cover, DR3, SB3
FGS-0509	PillCam™ sensor belt 2 cover, DR3, SB3
FGS-0510	PillCam™ sensor belt 2 disp kit, 5-pk
FGS-0475	PillCam sensor belt cover, DR3, C2
FGS-0575	Data Recorder 3 Software Upgrade v28D
FGS-0619	PillCam™ recorder DR3 SW upgrade
FGS-0664	PillCam™ Recorder DR3 SW upgrade
FGS-0435	SD Card for PillCam™ recorder DR3
FGS-0581	Velcro sleeve, downlink antenna
FGS-0686	DR3 Firmware upgrade for UGI
RAPID®/PillCam™ Software workstations	
FGS-0595	RAPID® WS, Dell T5810 V8.0 WW
FGS-0480-01	RAPID® SW kit, v8.0 SCA WS
FGS-0598	RAPID® WS, Dell T5810 V8.3 WW
FGS-0594	RAPID® WS, Dell T5810 V8.5 WW
FGS-0533	RAPID® SW kit, v8.5 WS OUS
FGS-0616	PillCam™ WS, Dell T5810 WW
FGS-0673	RAPID® WS, V8.3 WW
FGS-0675	PillCam™ WS, WW
RAPID®/PillCam™ Software	
FGS-0396	RAPID® Access SW kit, v7.0
FGS-0399	RAPID® SW upgrade, v7.0

FGS-0478-01	RAPID® SW kit, v8.0 SCA
FGS-0479-01	RAPID® SW upgrade, v8.0 SCA
FGS-0601	RAPID® SW kit, v8.3 WW
FGS-0603	RAPID® SW kit, V8.3 WW WS
FGS-0604	RAPID® SW upgrade, v8.3 WW
FGS-0531	RAPID® SW kit, v8.5 OUS
FGS-0532	RAPID® SW upgrade, v8.5 OUS
FGS-0614	PillCam™ SW Kit, WW
FGS-0615	PillCam™ SW Upgrade Kit, WW
FGS-0626	PillCam™ Software v9.0, WW WS
FGS-0676	PillCam™ Software Kit V9.0E, WW
FGS-0677	PillCam™ Software upgrade kit V9.0E, WW
RAPID®/PillCam™ Software (Web)	
FGS-0587	PillCam™ Software V1, OUS
FGS-0623	PillCam™ Web Software v9.0, WW
PillCam™ Software (Remote Reader)	
FGS-0665	PillCam™ Remote Reading Software
PillCam™ COLON2 Capsule	
FGS-0517	PillCam™ COLON2 Capsule, 1-pack
FGS-0518	PillCam™ COLON2 Capsule, 5-pack
FGS-0519	PillCam™ COLON2 Capsule, 10-pack

18.Version History

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
1.0	Not Applicable- initial release				Roslana Fox/ CSM
2.0	1. Throughout the document- updated study classification to post-market study, including replacing study classification as “feasibility study” to “pilot study” 2. Study name- SPICE has been added to the title 3. Sec. 6.1- “the latest” has been added 4. Throughout the document- changes according to CIP template Ver. C. 5. Throughout the document- information re USADE not being collected was updated 6. Sec. 6.2 added “MB-MMX intake in this study is considered a preceding investigational procedure, which is additional for this study and therefore outside standard of care.	1. Following AEMPS (Spanish RA) decision that the study is not classified as a pre-market study 2. N/A 3. Clarification of the study expected duration 4. for template C version adherence 5. Update as USADEs are not collected in a post market study. 6. to comply with MDR requirements	1. N/A 2. N/A 3. N/A 4. N/A 5. N/A 6. N/A	1. ICF- language to be updated. 2. N/A 3. N/A 4. N/A 5. Safety plan 6. N/A	Roslana Fox/ CSM

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
3.0	1. Part 11 compliant signature- added *when applicable* 2. Throughout the document- morning bowel preparation was removed and 2L of PEG were moved to day -1. 3. Prucalopride tablet was added to the regimen 4.Exclusion criteria #17- added *per Investigator's discretion* 5. Appendix B: Deviations table was updated 6. Appendix D: Subjective Assessment Questionnaire was updated 7. Section 12 was updated	1. Added to reflect that this regulation is not applicable in the study geography (EU) and the documents signed under the study are not submitted to the FDA 2. This change reflects the change in bowel prep regimen- single PEG dose at day -1, instead of spit dose. 3. Added as an agent to support to capsule movement in the colon. 4. Added for clarification 5. Was updated to reflect the current CIP deviations 6. Appendix D: Subjective Assessment Questionnaire was updated to include more rows for polyps (up to 25) 7. for better alignment with ISO 14155:2020 language	1.N/A 2.N/A 3.N/A 4.NA 5.N/A 6.N/A 7.N/A	1.N/A 2.ICF 3.ICF 4.NA 5.N/A 6.N/A 7.N/A	Roslana Fox/ CSM
4.0	1. Section 6.1- study duration was extended to 13 months	1. Duration was extended to allow study procedures completion	1. NA	1. NA	Roslana Fox/ CSM