CLINICAL INVESTIGATIONAL PLAN

PROSPECTIVE, OPEN LABEL, PIVOTAL STUDY OF THE ACCURACY OF THE CAPSOCAM® COLON (CV-3) IN DETECTING COLONIC POLYPS, USING COLONOSCOPY AS THE REFERENCE

PIVOTAL CLN-CVI-5794

Revision M

August/2024

CapsoVision
18805 Cox Avenue, Suite 250
Saratoga, CA 95070

Principle Investigator's Statement and Signature

I agree to conduct this study following this protocol. Modifications to this protocol not permitted without agreement from CapsoVision and must be documented through the document control process.

Investigator Name (Print): _____

Investigator Signature: _____

Date: _____

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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with the appropriate sections of the following:

- United States (US) Code of Federal Regulations (CRF) applicable to clinical studies (21 CFR 812, 21 CFR Part 50and 21 CFR Part 56)

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes to the study are implemented. All IRB requested changes to the consent form will be approved by the study Sponsor prior to subject enrollment. In addition, all changes to the consent form occurring as a result of protocol amendments will be IRB-approved.

1. INVESTIGATIONAL PLAN

1.1 Protocol Synopsis

Sponsor	CapsoVision, Inc., Saratoga, CA
Title	Prospective, Open Label, Pivotal Study of the Accuracy of the CapsoCam® Colon (CV-3) in Detecting Colonic Polyps, Using Colonoscopy as the Reference
Study device	CapsoCam® Colon (CV-3)
Design	Prospective, open-label, non-significant risk, multicenter study comparing the polyp detection of the study device to that of the colonoscopy reference. The study device videos will be read in a crossover design, both with and without computer assisted detection (CADe), so that the benefit of CADe can be assessed.
Purpose	The purpose of this study is to evaluate the safety and effectiveness of CapsoCam® Colon (CV-3) endoscope system for the detection of colonic polyps and to show that AI-based CADe improves the polyp-detection accuracy and efficiency of capsule video readers. It is anticipated that the data from this clinical trial will be used to support marketing authorizations to commercialize the CapsoCam® Colon (CV-3).
Study Population	Subjects referred for colonoscopy.
Clinical Sites	Up to 30 US clinical sites will participate in the study.
Inclusion Criteria	1. 45-75 years of age 2. Committed to undergo a colonoscopy. 3. Choose to participate and must have signed the IRB-approved informed consent document and agreed to release colonoscopy images and results report to Sponsor
Exclusion Criteria	1. Colonoscopy or CT-colonography within the past 5 years that demonstrated no polyps 2. Has contraindication for capsule endoscopy or colonoscopy 3. Subject is suspected or diagnosed with familial adenomatous polyposis, hereditary non polyposis colon cancer, or any high-risk genetic syndrome 4. Subject is suspected or diagnosed with inflammatory bowel disease such as ulcerative colitis or Crohn's disease 5. History of incomplete colonoscopy 6. Type I or uncontrolled II Diabetes (Uncontrolled defined as HbA1C>6.4 within the past 3 months and/or with history of constipation or gastroparesis). 7. Impaired cardiac function assessed as greater than NYHA Class II

	8. History of small- or large-bowel obstructive condition 9. Known history of swallowing disorder, and/or ischemic bowel disease neuropathies and/or radiation enteritis 10. Known history of NSAID enteropathy and stricture resulting from taking NSAIDs on a regular basis that, in the opinion of the Investigator, would put the subject at greater risk for capsule endoscope retention 11. Known allergy to ingredients used in bowel preparation and boosters 12. Daily and/or regular narcotic use 13. Decompensated cirrhosis 14. Prior abdominal radiation therapy 15. Diagnosis of anorexia or bulimia 16. History of or suspicion of any of the following: strictures, volvulus or intestinal obstruction, or internal hernias or abdominal surgeries that the Investigator believes should exclude the patient from study participation 17. Known or suspected megacolon 18. Scheduled to undergo MRI examination within 7 days after ingestion of the capsule 19. Has known slow gastric-emptying time or confirmed diagnosis of gastroparesis 20. Pregnant or nursing or of child-bearing potential and does not agree to practice medically acceptable methods of contraception. Women of child bearing potential (WOCBP) must have a negative urine pregnancy test at screening. 21. Unable to follow or tolerate fasting, bowel preparation, and other study procedures 22. Any documented medical or psychological condition or significant concurrent illness which, in the Investigator's opinion, would make it unsafe for the subject to participate in this research study or would affect the validity of the study results 23. Are currently enrolled in an interventional clinical study or currently enrolled in or within the last 30 days, a pharmaceutical clinical study 24. Chronic constipation as defined by <3 bowel movements per week, or the use of routine laxatives (other than fiber) to attain regular bowel movements
Pre-Enrollment Screening	Eligible subjects who have been referred for colonoscopy will adhere to the following protocol procedures: <u>Screening (Day -14 to -3)</u>: • Informed consent completion and verification of eligibility • Detailed medical history and medications, including assessment of GI health • Site will dispense bowel prep regimen along with detailed dosing instructions <u>Pre-Procedure Preparation (Day -2 to 0)</u>: • Subject starts the pre-determined bowel prep that has been provided • Adhere to dietary requirements
Intervention and Follow-up Periods	<u>Procedure (Day 0)</u>: • Confirmation of adherence to pre-procedure prep via bowel prep visual aid (subject reported) o Subjects that do not report acceptably clean bowel preparation (picture 1 or picture 2 on visual aid) will be considered screen failures or will be permitted to re-attempt bowel preparation and capsule swallow described in detail in section 3.5.4. • Recording of Anticipated Observations/Adverse Events • Ingestion of pro-kinetic medication 30 – 60 minutes prior to ingestion of capsule • Ingestion of capsule

	• Post-procedure instructions provided to study subject:
	  ○ Very clear liquid diet until capsule is excreted or until 8:00am the next day, whichever comes first, or as directed by a Principal Investigator (PI)
	  ○ Booster regimen until capsule is excreted or 8 hours post ingestion, whichever comes first
	  ○ Suppository use at bedtime and next morning if capsule hasn't been excreted within the first hour of arising
	  ○ Retrieval kit and instructions to return CapsoCam® Colon (CV-3) to the Sponsor who will download the CapsoCam® images to a secure server. All image readings and interpretations will be performed by independent colonoscopists /endoscopists.
	  ○ Discharge from clinic upon confirmed understanding of at-home instructions
	
	Follow-up Phone Call (Day 3 +/- 2 days):
	• Excretion of capsule and retrieval of CapsoCam® Colon (CV-3) verification
	• Instruct subject to return CapsoCam® Colon (CV-3) to Sponsor (if not yet completed)
	• Assessment of adverse events related to capsule ingestion
	
	Colonoscopy – (Day 1 or Day 21-42):
	• **Day 21-42 option:** Colonoscopy will be performed from 3-6 weeks following CapsoCam® Colon (CV-3) ingestion.
	• **Day 1 option**: Only if it is in the best interest of the subject, as determined by the Investigator, a study subject may have colonoscopy the day after CapsoCam ingestion. See section 3.5 for further details.
	• Recording of Anticipated Observations

Coprimary Effectiveness Endpoints	• Positive Percent Agreement (PPA) of the study device with computer assisted detection (CADe) for detecting the presence in a subject of the largest polyp detected by optical colonoscopy (OC) if that polyp is ≥ 6 mm, where a match is considered to have occurred if a polyp detected by the device is assessed as having a size within plus or minus 50% of the size of the polyp detected by OC and as having a location within the same or an adjacent colon segment. • Negative percent agreement (NPA) of the study device with CADe for not detecting any polyp ≥ 6 mm in a subject for whom OC did not detect any polyp ≥ 6 mm.
Secondary Effectiveness Endpoints	• Study-device PPA with a random reader relying on CADe versus not using CADe for detecting the presence in a subject of the largest polyp detected by optical colonoscopy (OC) if that polyp is ≥ 6 mm, where a match is considered to have occurred if a polyp detected by the device is assessed as having a size within plus or minus 50% of the size of the polyp detected by OC and as having a location within the same or an adjacent colon segment. • Study-device NPA with a random reader relying on CADe versus not using CADe for not detecting any polyp ≥ 6 mm in a subject for whom OC did not detect any polyp ≥ 6 mm. • Sensitivity of the study device with CADe for detecting in a subject an advanced neoplasia (AN) detected by OC and histopathology, defined as an adenoma ≥ 10 mm, or containing villous growth or high-grade dysplasia, or cancer, where a lesion in the subject detected by the device is assessed to be at least 6 mm in size.

	• Specificity of the study device with CADe for not detecting any lesion ≥ 6 mm in a subject for whom OC detected no polyps ≥ 6 mm and no AN of any size. • Specificity of the study device with CADe for not detecting any lesion ≥ 6 mm in a subject for whom OC detected no polyps. • PPA of the device with CADe for detecting the presence in a subject of the largest polyp detected by optical colonoscopy (OC) if that polyp is ≥ 10 mm, where a match is considered to have occurred if a polyp detected by the device is assessed as having a size within plus or minus 50% of the size of the polyp detected by OC and as having a location within the same or an adjacent colon segment. • NPA of the device with CADe for not detecting any polyp ≥ 10 mm in a subject for whom OC did not detect any polyp ≥ 10 mm. • PPA of the device with CADe for detecting the presence in a subject of the largest polyp detected by optical colonoscopy (OC) if that polyp is ≥ 6 mm and < 10 mm, where a match is considered to have occurred if a polyp detected by the device is assessed as having a size within plus or minus 50% of the size of the polyp detected by OC and as having a location within the same or an adjacent colon segment. • Sensitivity of the device with CADe for detecting the presence of a polyp ≥ 6 mm in a subject with OC as the reference (without regard to polyp matching). • Sensitivity of the device with CADe for detecting the presence in a subject of a polyp ≥ 10 mm with OC as the reference (without regard to polyp matching). • PPA of the device with CADe for detecting the presence in a subject of the largest sessile serrated polyp (SSP) detected by OC if that polyp is ≥ 6 mm, where a match is considered to have occurred if the size of a polyp detected by the device is assessed as having a size within plus or minus 50% of the size of the polyp assessed by OC and as having a location within the same or an adjacent colon segment. • Sensitivity of the study device with CADe for detecting in a subject a SSP detected by OC and histopathology, where a polyp in the subject detected by the device is assessed to be at least 6 mm in size. • PPA of the device with CADe for detecting the presence in a subject of a cancerous polyp biopsied by OC and diagnosed by histopathology, where a match is considered to have occurred if the size of a polyp detected by the device is assessed as having a size within plus or minus 50% of the size of the cancerous polyp assessed by OC and as having a location within the same or an adjacent colon segment. • Sensitivity of the study device with CADe for detecting in a subject a cancer detected by OC and histopathology, where a lesion in the subject detected by the device is assessed to be at least 6 mm in size. • The above secondary endpoints will also be assessed for the device without CADe. • The paired within-subject difference in video reading time with and without CADe (time with CADe – time without CADe).
Safety Assessment	All adverse events (AEs) including serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) will be assessed and reported at all visits. To ensure the accurate capture of device related events, side effects from bowel preparation, prokinetic booster and colonoscopy will be recorded as “Anticipated Observations” on the adverse event form. Incidence of all AEs for the discreet interval of capsule ingestion through excretion will be recorded and analyzed for seriousness, severity, and relatedness to the device.

Exploratory Endpoints	• Accuracy of the detected polyp morphology assessed by the device.
Hypotheses	Secondary Endpoint #1 – The null hypothesis is that "true" difference in PPA for detecting polyps ≥ 6 mm with CADe versus without CADe (PPA with CADe – PPA without CADe) is ≤ 0. The alternative hypothesis is that this difference is > 0. Secondary Endpoint #2 – The null hypothesis is that "true" difference in NPA for detecting polyps ≥ 6 mm with CADe versus without CADe (NPA with CADe – NPA without CADe) is ≤ -10%. The alternative hypothesis is that this difference is > -10%. Secondary Endpoint #3 – The null hypothesis is that the sensitivity for detecting advanced neoplasia with CADe is < 65%. The alternative hypothesis is that it is ≥ 65%.
Analysis Populations	Evaluable population: This population will consist of all subjects who have both an evaluable colonoscopy and an evaluable CapsoCam® Colon (CV-3) exam, as defined in section 4.1. This population will be used for all effectiveness analyses. Safety population: This population will consist of all subjects who ingested the capsule and those who attempted but were unsuccessful at swallowing the capsule. It will be used for all safety analyses.
Study Success Criteria	The study will be considered a success if • The observed value of the PPA primary effectiveness endpoint with CADe is greater than or equal to the performance goal of 65.0%. • The observed value of the NPA primary effectiveness endpoint with CADe is greater than or equal to the performance goal of 75.0%.
Sample Size Estimate	A minimum of 700 evaluable subjects, of whom at least 192 have at least one ≥ 6 mm polyp and at least 432 do not, as determined by optical colonoscopy, and who meet the study eligibility criteria and consent to participate, will be enrolled in this study.
Duration of Study	It is expected to take approximately 12-24 months to complete enrollment.

2. INTRODUCTION

2.1 Background

The CapsoCam® Colon (CV-3) (hereinafter referred to as CapsoCam® or the study device) is intended to provide visualization of the colon and the detection of colon polyps in adults.

The CapsoCam® is a capsule endoscope system that captures and stores image data onboard for subsequent download and review. The system does not require the placement of external data receivers or a data recorder on the subject. *In vivo* image data are stored within the capsule, and it is retrieved by the subject after excretion and returned to a specified site for data download. A physician reviews the video on a computer using the CapsoView software, makes a diagnosis, and creates a report.

The literature indicates colon capsule endoscopy safe and a tolerable method for visualization of the large intestine.[1-3] Most of the adverse events that have occurred in colon capsule endoscopy (CCE) studies have been associated with bowel preparation and not with the CCE itself.[4] CCE's high acceptability by subjects in various settings,[3,5,6] coupled with the potential for out-of-clinic use,[7] could increase patient adherence to CRC screening guidelines when offered as an alternative screening method.[8] The main, but still rare, complication of capsule endoscopy is capsule retention.[2,3,9] In the clinical studies reviewed, the incidence of capsule retention requiring endoscopic or surgical removal depended on the indication of the study and varied from 1-2% in subjects referred for obscure gastrointestinal bleeding (OGIB) to 2-5% for subjects with known Crohn's disease.[10,11] Capsule retention requiring endoscopic or surgical intervention may be beneficial since it often leads to a definitive diagnosis and therapy for the underlying cause of the retention, a tumor for example, that might have gone undetected without the capsule procedure.

CCE provides a thorough visualization of the colon and is less invasive and more convenient for patients than optical colonoscopy (OC). It is especially suitable for patients at elevated risk for colonoscopy or associated sedation. The CapsoCam® has several potential advantages relative to existing capsule endoscopes. It includes an attached balloon, which adjusts buoyancy to speed the colon transit; a panoramic imaging system that presents a more direct view of the mucosa with potentially less chance of missing features of interest due to obscuration or poor illumination; a 3D sensing system which allows the size of polyps to be measured; and AI-based computer aided detection (CADe) of colon polyps.

2.2 CapsoCam® Colon (CV-3) System

The overall system consists of the ingestible device, the capsule data access system (CDAS), the image-review and CADe workstation software CapsoView® (CVV), the retrieval kit (CVR), and CapsoCloud® (CLD), a cloud-based system allowing physicians to access and read videos online. Five unique design attributes of this system are: 1) it does not employ wireless communication technology (e.g. a radio transmitter) while *in vivo* and does not generate significant electromagnetic interference, so subjects with implanted medical devices such as pacemakers and hearing aids may safely use the CapsoCam®, 2) it utilizes a panoramic imaging system rather than a camera on each end of the capsule, with the intent to provide complete colon visualization and short video review times, 3) it

includes hardware and software which enable the measurement of polyp diameter, 4) it includes an inflatable balloon attached to the capsule to quicken transit through the colon, and 5) it includes AI-powered software for computer assisted detection (CADe) of polyps.

2.3 Device Description

The CapsoCam® is an ingestible capsule, Figure 1. The video capsule contains a panoramic color digital video camera, two silver-oxide watch batteries, white-LED illumination sources, a laser diode for data download, and system-control and nonvolatile flash-memory data-storage electronics. The video camera capsule saves data in the on-board flash memory as it traverses the GI tract. The CapsoCam® is a capsule endoscope that uses non-wireless technology to capture and store images. The CapsoCam® is less than 12.4 x 32.6 mm in size and has four (4) lateral-facing cameras, providing a 360° circumferential view. The capsule does not require placement of external sensors or a data recorder on the subject.

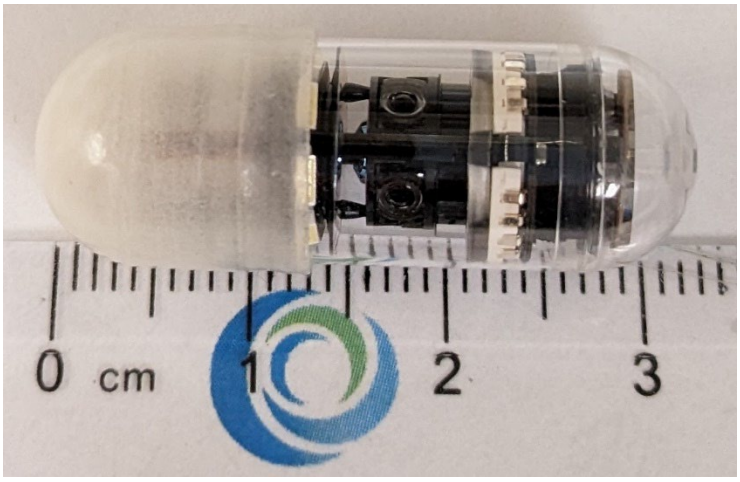

Figure 1 *Photograph of CapsoCam® Colon (CV-3) (as swallowed)*

The CapsoCam® has an *in vivo* feature-size measurement tool. The modified capsule has a projector that projects beams of light onto surrounding surfaces within the camera field of view (FOV). When an *in vivo* object is within the FOV of the camera, bright spots from these projected beams appear in the captured images. As the distance between the object and CapsoCam® changes, the spot positions change, since the projector and the camera pupil are not coincident. Using software to determine which spot comes from which beam and accounting for the distortion of the camera lens, the object distance is determined at every spot. These data can be displayed as a 3-dimensional (3D) mesh showing the surface profile of the object. The clinician can measure the size of polyps using the graphical user interface (GUI) of the CapsoView software.

Unlike other capsule endoscopy devices, the CapsoCam® does *not* employ wireless communication technology (*e.g.* a radio transmitter) and does not generate significant electromagnetic interference. Subjects with implanted medical devices such as pacemakers and hearing aids may safely use the CapsoCam®.

The CapsoCam® consists of a capsule camera attached to a self-inflating balloon encapsulated inside a dissolvable outer shell. The outer shell is intended to make swallowing the device easier. The inflatable balloon helps to stabilize the capsule transit through the gastrointestinal tract. Inside the balloon is an effervescent formulation that reacts to produce CO_2 gas once it contacts trace amounts of water that diffuse into the balloon through the balloon membrane, Figure 2.

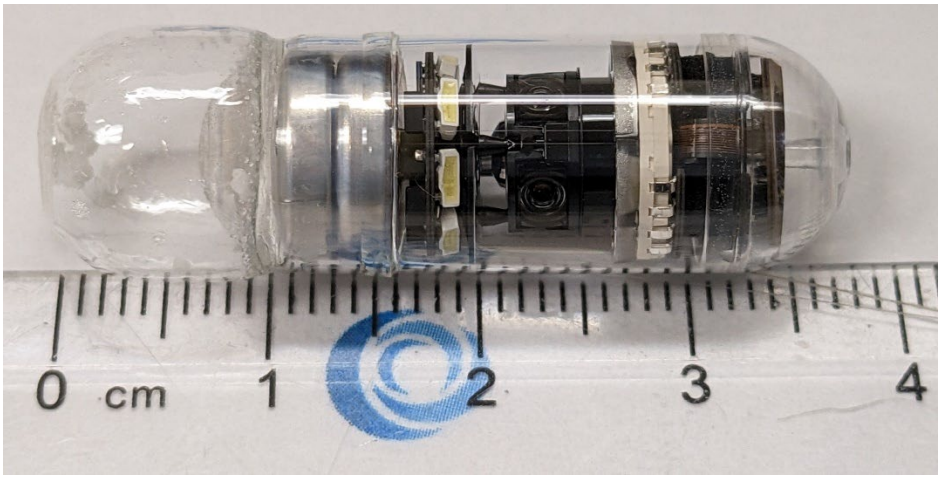

Figure 2 *Photograph of an inflated CapsoCam® Colon, (CV-3)*

The CO_2 inflates the balloon and the specific gravity of the device is reduced to about 1, which means that the capsule achieves neutral buoyancy and can more readily move through the intestines with flowing liquid, increasing the likelihood of a complete colon visualization.

As the CapsoCam® passes through the GI tract, it captures and saves images and other data in the on-board flash memory. Following retrieval of the CapsoCam®, the capsule images are downloaded using the Capsule Data Access System (CDAS) (Figure 3) and read by a study investigator (reader) using the CapsoView® Software (CVV). The software includes computer-assisted detection (CADe) of polyps using an artificial intelligence (AI) algorithm developed by deep learning. The software highlights CADe-detected polyps with a bounding box in the video frame as the reader reviews the entire video of the colon.

Figure 3 *Capsule Data Access System*

2.4 Proposed Indications for Use

The CapsoCam® Colon capsule endoscopy system is intended to provide visualization of the colon.

It may be used for detection of colon polyps in patients after an incomplete optical colonoscopy with adequate preparation, and a complete evaluation of the colon was not technically possible.

In addition, it is intended for detection of colon polyps in patients with major risks for colonoscopy or moderate sedation, who could tolerate colonoscopy and moderate sedation in the event a clinically significant colon abnormality was identified on capsule endoscopy.

The object-size measurement tool is intended to measure the size of anatomical features, including polyps.

The computer-assisted polyp detection software (CADe) is intended to highlight regions in the capsule endoscopy video which contain visualized polyps to aid endoscopists in detecting colon polyps.

2.5 Early Clinical Investigations

A complete Report of Prior Clinical Investigations relevant to the CapsoCam® is provided in **Appendix A.**

2.5.1 Safety

Interim results support a positive safety profile of the CapsoCam®. To date, there have been no serious or unanticipated adverse events reported. There were no capsule retentions, defined as subjects retaining the capsule after resuming post-procedural food ingestion. All capsules ingested in the studies were excreted. In all cases, the deflated balloons remained securely attached to the capsules upon excretion.

To date, there have been no device-related AEs reported. However, a small number of anticipated bowel preparation and booster regimen adverse events were reported: nausea, limited episodic vomiting, and modest abdominal discomfort (for full details see **Appendix A**). These bowel preparations-related adverse events are known to be possible whenever bowel preparations are administered and are well characterized in the drug manufacturers' prescription information.

2.5.2 Effectiveness

As outlined in **Appendix A**, the CapsoCam® has demonstrated the ability to capture quality images throughout the colon, provided the subject follows the bowel preparation and booster regimen instructions. For recent versions of the study device, the operational time has been adequate for the capsule to capture images of the entire colon in most procedures. Recorded images were successfully downloaded using the Capsule Data Access System (CDAS) and were then available for physicians to review and interpret.

2.6 Rationale for This Study

Colon capsule endoscopy (CCE) has significant advantages for visualization of the colon and polyp detection. The procedure is less invasive than conventional optical colonoscopy (OC) and does not require sedation. However, significant, potentially precancerous, polyps detected by CCE must be subsequently removed by OC. Unlike stool or blood tests, CCE provides visual evidence and size measurement of pathology to assess its risk and motivate patients to get follow-on colonoscopy when appropriate. CCE has been shown to have positive predictive value comparable to computed tomography colonography (CTC), another common alternative to conventional colonoscopy.[14,15]

Currently, one CCE device, the PillCam COLON 2 (Medtronic) is marketed and indicated for visualization of the colon for patients who have had an incomplete colonoscopy or those with evidence of lower GI bleeding who are at major risk for colonoscopy or moderate sedation but who could tolerate colonoscopy and moderate sedation should CCE identify clinically significant abnormality. A multicenter study evaluated CCE compared to OC for agreement on the absence or presence of colon polyps 6 mm or larger in each subject and found 68.8% positive percent agreement (PPA) and 81.3% negative percent agreement (NPA).[12]

To improve CCE's utility, it should accurately identify those patients with potentially dangerous polyps who should undergo polypectomy and those at lower risk for developing colorectal cancer (CRC) who may not require immediate polypectomy. Since the precancerous potential of polyps is strongly correlated to their size, accurate size measurement would greatly assist in this identintification.[13] Better accuracy in early polyp detection could reduce the number of unnecessary and costly colonoscopies and the associated risks. The CapsoCam Colon system includes a polyp size measurement to accurately measure polyp size, a feature the PillCam lacks.

A challenge for CCE is the long video reading time and the risk that readers overlook polyps in the video, especially those captured in only a few frames. The PillCam produces two disjoint videos—one by the front- and one by the back-facing camera—increasing the reading time relative to a single-camera system. The CapsoCam Colon has four cameras, but their images are

stitched into a single coherent panoramic video, potentially reducing the reading time relative to the PillCam.

To both reduce reading time and improve polyp-detection accuracy, the CapsoCam is the first CCE system to utilize artificial intelligence (AI), implemented as a convolutional neural network (CNN), for computer assisted detection (CADe) of polyps. The PillCam COLON 2 system (K123666) has a software feature dubbed "Top 100" which shows "the 100 most clinically relevant images in a PillCam COLON capsule study, focused on frames containing lesions, bleeding, and polyps." (Quick Reference Guide, Reading a PillCam COLON 2 capsule study in PillCam software v9, US1600035(1) © 2019 Medtronic). However, its polyp-detection accuracy has not been published, and the device does not have an FDA-cleared indication for this feature.

This study is designed to show that readers relying heavily on CADe (not reading the entire video) will achieve positive-percent agreement (PPA) and negative percent agreement (NPA) with a colonoscopy that exceed performance goals and, when compared to the same readers not using CADe (reading the entire video), superior PPA and noninferior NPA. Since readers can reject false-positive CADe detections, the negative percent agreement (NPA) is not expected to decrease significantly when CADe is used, but the study will assess this risk.

2.7 Purpose and Objectives of the Investigation

The purpose of this pivotal study is to establish the safety and effectiveness of the study device in the visualization of the colon and in the detection and size measurement of colonic polyps and to show the benefit of the CADe. The capsule video for each subject will be read by the same reader twice, separated by a washout period: once with and once without access to the CADe polyp detections. When performing the CADe read, the reader will review all the frames with CADe polyp detections segregated from the full video, only referring to the full video as much as necessary to identify landmarks, rate the colon cleanliness, review the CADe findings in the context of nearby frames, localize the polyps by bowel segment, and measure the polyps' sizes. The study will compare the readers' polyp detection with and without CADe.

Cancerous lesions in the colon, often called tumors or cancerous polyps, will be referred to as cancerous polyps in this protocol. Some of the polyps detected by the CapsoCam® may be cancerous polyps, and, although the CapsoCam® cannot provide a diagnosis of cancer, detection of a polyp which is cancerous is considered a positive finding for detection of a cancerous polyp.

The ***primary objective*** of this study is to compare the study device with CADe polyp detection to optical colonoscopy (OC) for agreement on the presence or absence of colon polyps ≥ 6 mm.

Secondary objectives of this study are to compare the study device both with and without CADe to OC for agreement on the presence or absence of the colon of lesions of various types and sizes. Additional secondary objectives are to compare the video reading times with and without CADe and to show that CADe, when used in a clinically realistic manner with random readers, improves the polyp detection accuracy.

2.8 Study Endpoints

2.8.1 Coprimary Endpoints

- Positive Percent Agreement (PPA) of the device with CADe for detecting the presence in a subject of the largest polyp detected by optical colonoscopy (OC) if that polyp is ≥ 6 mm, where a match is considered to have occurred if a polyp detected by the device is assessed as having a size within plus or minus 50% of the size of the polyp detected by OC and as having a location within the same or an adjacent colon segment.
- Negative percent agreement (NPA) of the device with CADe for not detecting any polyp ≥ 6 mm in a subject for whom OC did not detect any polyp ≥ 6 mm.

2.8.2 Secondary Endpoints

- Study-device PPA with a random reader relying on CADe versus not using CADe for detecting the presence in a subject of the largest polyp detected by optical colonoscopy (OC) if that polyp is ≥ 6 mm, where a match is considered to have occurred if a polyp detected by the device is assessed as having a size within plus or minus 50% of the size of the polyp detected by OC and as having a location within the same or an adjacent colon segment.
- Study-device NPA with a random reader relying on CADe versus not using CADe for not detecting any polyp ≥ 6 mm in a subject for whom OC did not detect any polyp ≥ 6 mm.
- Sensitivity of the study device with CADe for detecting in a subject an advanced neoplasia (AN) detected by OC and histopathology, defined as an adenoma ≥ 10 mm, or containing villous growth or high-grade dysplasia, or cancer, where a lesion in the subject detected by the device is assessed to be at least 6 mm in size.
- Specificity of the study device with CADe for not detecting any lesion ≥ 6 mm in a subject for whom OC detected no polyps ≥ 6 mm and no AN of any size.
- Specificity of the study device with CADe for not detecting any lesion ≥ 6 mm in a subject for whom OC detected no polyps.
- PPA of the device with CADe for detecting the presence in a subject of the largest polyp detected by optical colonoscopy (OC) if that polyp is ≥ 10 mm, where a match is considered to have occurred if a polyp detected by the device is assessed as having a size within plus or minus 50% of the size of the polyp detected by OC and as having a location within the same or an adjacent colon segment.
- NPA of the device with CADe for not detecting any polyp ≥ 10 mm in a subject for whom OC did not detect any polyp ≥ 10 mm.
- PPA of the device with CADe for detecting the presence in a subject of the largest polyp detected by optical colonoscopy (OC) if that polyp is ≥ 6 mm and < 10 mm, where a match is considered to have occurred if a polyp detected by the device is

assessed as having a size within plus or minus 50% of the size of the polyp detected by OC and as having a location within the same or an adjacent colon segment.

- Sensitivity of the device with CADe for detecting the presence of a polyp ≥ 6 mm in a subject with OC as the reference (without regard to polyp matching).
- Sensitivity of the device with CADe for detecting the presence in a subject of a polyp ≥ 10 mm with OC as the reference (without regard to polyp matching).
- PPA of the device with CADe for detecting the presence in a subject of the largest sessile serrated polyp (SSP) detected by OC if that polyp is ≥ 6 mm, where a match is considered to have occurred if the size of a polyp detected by the device is assessed as having a size within plus or minus 50% of the size of the polyp assessed by OC and as having a location within the same or an adjacent colon segment.
- Sensitivity of the study device with CADe for detecting in a subject a SSP detected by OC and histopathology, where a polyp in the subject detected by the device is assessed to be at least 6 mm in size.
- PPA of the device with CADe for detecting the presence in a subject of a cancerous polyp biopsied by OC and diagnosed by histopathology, where a match is considered to have occurred if the size of a polyp detected by the device is assessed as having a size within plus or minus 50% of the size of the cancerous polyp assessed by OC and as having a location within the same or an adjacent colon segment.
- Sensitivity of the study device with CADe for detecting in a subject a cancer detected by OC and histopathology, where a lesion in the subject detected by the device is assessed to be at least 6 mm in size.
- The above secondary endpoints will also be assessed for the device without CADe.
- The paired within-subject difference in video reading time with and without CADe (time with CADe – time without CADe).

2.8.3 Safety Assessment

All adverse events (AEs) including serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) will be assessed and reported at all visits. Side effects from bowel preparation, prokinetic medications, boosters and colonoscopy will be recorded as "Anticipated Observations" on the Adverse Event Form. Incidence of all AEs for the discreet interval of capsule ingestion through excretion, will be recorded and analyzed for seriousness, severity, and relatedness to the device.

2.8.4 Exploratory Endpoints

- Sensitivity for AN and specificity for AN and polyps ≥ 6 mm as a function of the polyp size cutoff for capsule positivity.
- Accuracy of the detected polyp morphology assessed by the device.

2.9 Study Design

This is a prospective, open-label, non-significant risk, multicenter study designed to determine the PPA and NPA of the investigational CapsoCam® capsule endoscope, using colonoscopy as

the reference in detecting colonic polyps. Subjects who meet the entry criteria will ingest CapsoCam®, and undergo a colonoscopy procedure. The capsule videos are read both with and without CADe in a crossover design, where each video is read by one reader in each mode, separated by a washout period. When reading with CADe, the readers will rely on the CADe and not read the entire video. The performance with and without CADe will be compared in a multi-reader multi-case (MRMC) analysis with a case-nested-within-reader split plot structure,[18, 19] using sufficient readers to generalize the results to a population of random readers.

2.10 Duration and Extent of Investigation

Enrollment will be competitive and subjects will be screened by up to 30 clinical trial sites until a minimum of 700 evaluable subjects, of whom at least 192 have at least one ≥ 6 mm polyp and 432 have none. It is anticipated that the enrollment period will last 12-18 months. Subject trial participation may be for a duration of up to 8 weeks (−2 weeks prior to capsule ingestion to 6 weeks following capsule ingestion for colonoscopy).

All subjects will remain enrolled in the study until 6 months after the initial colonoscopy or when the Sponsor informs the site that the subject can be exited from the study following review of the second capsule report as defined in section 3.11.1, whichever comes first.

3. CLINICAL PROTOCOL

3.1 Site Selection

Up to thirty (30) investigational sites will participate in the study. Sites will be selected based on the availability of the subject pool, the Investigator's experience and familiarity with colonic polyp detection and diagnosis and the staff's availability.

3.2 Number of Subjects

This study will continue to enroll subjects until there are at least 700 evaluable subjects, of whom at least 192 subjects have at least one polyp ≥ 6 mm and 432 have none.

3.3 Subject Population

The target population for this study are patients who have been referred for a colonoscopy. The eligibility criteria aim to exclude subjects for whom capsule endoscopy is contraindicated. Potential study subjects will be identified by the study site Investigator or Sub-Investigator with assistance from qualified research staff.

3.4 Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. 45-75 years of age
2. Committed to undergo a colonoscopy.
3. Choose to participate and must have signed the IRB-approved informed consent document and agreed to release colonoscopy images and results report to Sponsor.

Exclusion Criteria:

1. Colonoscopy or CT-colonography within the past 5 years that demonstrated no polyps.
2. Has contraindication for capsule endoscopy or colonoscopy.

3. Subject is suspected or diagnosed with familial adenomatous polyposis, hereditary non-polyposis colon cancer, or any high-risk genetic syndrome.
4. Subject is suspected or diagnosed with inflammatory bowel disease such as ulcerative colitis or Crohn's disease.
5. History of incomplete colonoscopy.
6. Type I or uncontrolled type II Diabetes (Uncontrolled defined as HbA1C >6.4 within the past 3 months and/or with history of constipation or gastroparesis).
7. Impaired cardiac function assessed as greater than NYHA Class II.
8. History of small- or large-bowel obstructive condition.
9. Known history of swallowing disorder, and/or ischemic bowel disease neuropathies and/or radiation enteritis.
10. Known history of NSAID enteropathy and stricture resulting from taking NSAIDs on a regular basis that, in the opinion of the Investigator, would put the subject at greater risk for capsule endoscope retention.
11. Known allergy to ingredients used in bowel preparation and boosters.
12. Daily and/or regular narcotics use.
13. Decompensated cirrhosis.
14. Prior abdominal radiation therapy.
15. Diagnosis of anorexia or bulimia.
16. History of or suspicion for: strictures, volvulus or intestinal obstruction; internal hernias or abdominal surgeries that the Investigator considers as an exclusion.
17. Known or suspected megacolon.
18. Scheduled to undergo MRI examination within 7 days after ingestion of the capsule.
19. Has known slow gastric-emptying time or confirmed diagnosis of gastroparesis.
20. Pregnant or nursing or is of child-bearing potential and does not practice medically acceptable methods of contraception. WOCBP must have a negative urine pregnancy test at screening.
21. Unable to follow or tolerate fasting, bowel preparation, and other study procedures.
22. Any documented medical or psychological condition or significant concurrent illness which, in the Investigator's opinion, would make it unsafe for the subject to participate in this research study.
23. Are currently enrolled in an interventional clinical study or currently enrolled in or within the last 30 days, a pharmaceutical clinical study.
    Chronic constipation as defined by < 3 bowel movements per week, or the use of routine laxatives (other than fiber) to attain regular bowel movements.

3.5 Study Procedures

3.5.1 Subject Consent

Potential study subjects will be provided with the IRB approved consent detailing the study device, participation requirements, risks and benefits and subject's rights. Written documentation, following Good Clinical Practice (GCP) must be obtained prior to initiating any study activities.

3.5.2 Screening/Baseline (Day -14 to -3)

- Informed consent completion and verification of eligibility
- Medical history including medications and assessment of GI health
- Review of colon preparation requirements and administration of prep
- Pregnancy test when applicable
- Dispense:
    - Bowel Prep Regimen and instructions on use
    - Instructions on diet requirements and restrictions
    - Schedule return date and time for CapsoCam® swallow

3.5.3 Pre-procedure Prep (Day -2 to 0)

- Two days prior to capsule ingestion through the day of ingestion, participant will begin prescribed bowel prep regimen and adhere to dietary requirements

3.5.4 Day of Procedure – Capsule Ingestion (Day 0)

- Confirm completion of prep
- Assess bowel prep with Bowel Prep Visual Aid
    - If subject does not confirm bowel cleanliness with image 1 or 2 on the Visual Aid, the subject will be considered a screen failure or will be permitted to re-attempt bowel preparation as follows:
        - If the subject has been scheduled for Day 1 colonoscopy, and does not indicate adequate bowel preparation per image selection, this subject will be considered a screen failure
        - If the subject has been scheduled for Day 21-42 colonoscopy, they may be permitted to perform another bowel preparation and capsule swallow attempt so long as **at least** 2 weeks elapse between bowel preparations such as:
            - Initial attempt→2 weeks→bowel preparation for capsule→capsule swallow→2 weeks→bowel prep for colonoscopy
            - Initial attempt→21-41 days→bowel preparation for capsule→capsule swallow→Day 1 colonoscopy
- Administer prokinetic medication 30-60 minutes prior to capsule ingestion
- Anticipated Observation review/reporting
- Capsule ingestion (30-60 minutes after prokinetic)
- Dispense/review (can be done while subjects wait to ingest capsule after prokinetic medication consumed):
    - Booster/suppository (if needed) regimen following capsule ingestion Instructions on clear liquid diet
    - Subject diary to record booster use
    - CapsoRetrieve® Kit
    - Instruct return of CapsoCam® to CapsoVision
- Discharge from clinic

3.5.5 Follow-Up Phone Call (Day 3 ± 2 days)—can be completed in office if subject has opted for Day 1 Colonoscopy

- Verify capsule excretion and retrieval
- AE review
- Confirm return of CapsoCam® to CapsoVision

3.5.6 Colonoscopy (Day 1 or Day 21-42)

- Perform colonoscopy
- Capture images of polyps with and without Napoleon measuring tool in frame
- Record colonoscopy
- Unmask capsule results (if available)
    - Immediate 2nd look colonoscopy if potentially significant polyps are noted on the CapsoCam report that were not seen during colonoscopy and if it's in the best interest of the subject
- Boston Bowel Prep Scale score recorded for all colon sections
- Anticipated Observation capture
- Upload images and video to secure server

3.5.7 2nd-look Colonoscopy (when warranted as described in section 2.10)

- Perform colonoscopy to seek potentially missed polyp
- Capture video images of polyp with and without measurement tool, as was completed for initial colonoscopy
- Boston Bowel Prep Scale score
- Anticipated Observations
- Complete colonoscopy
- Enter data from newly discovered polyps, if applicable, into EDC.

3.5.8 Capsule retrieval and return

The subject collects the capsule after it is excreted using the retrieval system and then returns it to the Sponsor-affiliated download center in the provided vial from the CapsoRetrieve® Kit, where the video will be processed into video format for distribution to be read by an independent reader. The processing includes application of the polyp CADe to the image data, so that the detection area coordinates are encoded into the video metadata. If the capsule is retrieved during colonoscopy, the site will return the capsule to the download center for this processing.

Table 1.1: Schedule of Assessments

Study Visit	Screening Baseline	Pre-Procedure	Pre-Procedure	Day of Procedure	Follow up Phone Call	Colonoscopy*	Colonoscopy*
Study Day	-14 to -3	-2	-1	0	+1 to +3	+1	+21 to 42
Informed Consent	**X**						
CapsoCam®/Colonoscopy Instruction	**X**						
Demographic	**X**						
Medical History	**X**						
Medication Use	**X**			**X**			**X**
Pregnancy Test	**X**						
Prep Regimen/Prokinetic Drugs		**X**	**X**	**X**			
Capsule Ingestion				**X**			
After Capsule Swallow; Booster Regimen/Suppository as needed				**X**			
Clear Liquids				**X**			
First Full Meal (if having day 1 colonoscopy)						**X**	
Follow up					**X**		
Anticipated Observation/ Adverse Event Assessment				**X**	**X****	**X**	**X****
Colonoscopy						**O***	**O***

***0=Day 1 or Day 21-42 option**: if it is in the best interest of the subject, as determined by the investigator, a study subject may have colonoscopy the day after CapsoCam® ingestion. For all others, colonoscopy will be performed from 21-42 days following CapsoCam® ingestion.

****Anticipated observations**: Events captured prior to capsule ingestion (bowel prep related to capsule ingestion) and after excretion (bowel prep related to colonoscopy, colonoscopy related events)

3.6 Moment of Enrollment

Subjects will be considered enrolled in the study when they have successfully ingested the capsule without regurgitating it. Subjects who attempt swallow but are not successful will be withdrawn from the study but remain in the safety analysis population. Subjects that screen fail as a result of poor bowel prep who are not given another opportunity to complete bowel preparation, will be considered screen failures and will not be included in any analysis.

3.7 CapsoCam® Video Reading

CapsoVision will download image data from the capsules, and each subject will be assigned without bias to one independent video reader from a pool. Two versions of the video will have been created at the download center, one for the CADe read and one the non-CADe read. The reader will be blinded to the correspondence between video and subject and will be randomly assigned to read either the non-CADe version first (sequence A) or the CADe version first (sequence B), with the second reading following a washout period of at least three (3) weeks. The two crossover sequences are summarized below.

Sequence A:

1. The reader first reviews the entire video without exposure to the CADe output and annotates all polyps detected, including measured size and location (colon segment). Anatomical landmark frames and bowel cleanliness ratings are recorded.
2. Following a washout period of at least three weeks, the same reader reviews a secondary video that only includes frames with CADe polyp detections that are highlighted with a bounding box around the detection area. The reader can switch from the secondary video to the main video to view nearby frames. For CADe detections assessed to be a true polyp, and for any additional polyps detected in the main video, the reader annotates the polyp, including measured size and location (colon segment). Anatomical landmark frames and bowel cleanliness ratings are recorded. The reader is instructed to review the main video only to the extent necessary to make these assessments and not to read it in its entirety.

Sequence B:

1. The reader first reviews a secondary video that only includes frames with CADe polyp detections that are highlighted with a bounding box around the detection area. The reader can switch from the secondary video to the main video to view nearby frames. For CADe detections assessed to be a true polyp, and for any additional polyps detected in the main video, the reader annotates the polyp, including measured size and location (colon segment). Anatomical landmark frames and bowel cleanliness ratings are recorded. The reader is instructed to review the main video only to the extent necessary to make these assessments and not to read it in its entirety.
2. Following a washout period of at least three weeks, the same reader reviews the entire video without exposure to the CADe output and annotates all polyps

detected, including measured size and location (colon segment). Anatomical landmark frames and bowel cleanliness ratings are recorded.

For each read, the reader will rate the bowel cleanliness in the left colon (cecum and ascending), transverse colon, and right colon (descending/sigmoid, and rectum) using the CC-CLEAR method and the overall colon cleanliness will be determined adequate or inadequate from these ratings using a standardized validated method.[18] For each identified polyp, at least one annotated frame number (time stamp) will be documented on the report. The size of the polyp will be measured using the size measurement tool. When necessary, readers will have the option to use the software measurement function of combining measurements, for polyps that are too large to be captured in a single frame, or using the output of the size-measurement tool to inform an estimated final value, for example by averaging multiple measurements or by measuring a fraction of a polyp and scaling the value by the inverse of the fraction. In other instances, the size measurement tool may not be able to make a measurement for reasons such as excessive bubbles or turbidity and the reader shall make a best estimate of the size and select the final image(s) that support the final measurement for each polyp. The polyp size will be recorded in millimeters to one decimal place (*e.g.* 11.2 mm or 8.0 mm).

Only those findings which the reader records, not the CADe output, are included in the CCE subject clinical dataset for comparison to the OC reference. There will be at least 9 and up to 16 central readers trained by CapsoVision to read the capsule videos. Each central reader is a board-certified gastroenterologist in good standing and experienced with capsule endoscopy and colonoscopy. The readers are independent reviewers that will have been trained on the reading of video captured by the study device using the CapsoView® software. Financial disclosures will be collected on all readers in accordance to 21 CFR Part 54. To the extent practical, the readers will all review an approximately equal number of subject videos.

3.8 **Colonoscopy and Biopsy** (follow these procedures for initial and/or repeat colonoscopy)

The Sponsor will identify, train, and qualify physicians with reported adenoma-detection rates (ADRs) of at least 25% for both male and female. The colonoscopy and biopsy will be performed according to the clinic's standard of care by trained Study Investigators. Instructions on polyp measurement and photography requirements will be provided by the Sponsor. Study Investigators must agree to video record the entire colonoscope withdrawal for every study subject. Each OC performed on study subjects must have a withdrawal procedure time of at least 6 minutes. Polyps will be resected per the site's standard of care.

The Boston Bowel Preparation Scale (BBPS) will be used to rate bowel cleanliness of three colon sections (right, transverse, and left) during the colonoscopy on the standard scale of 0 to 3. The overall colon cleanness will be rated inadequate if the BBPS score for any of the three colon sections is 0 or the total BBPS score (scale of 0 to 9) is less than 5.

Colonoscopy will be performed during the period starting 3 weeks after capsule ingestion and ending 6 weeks (+2 weeks window) post-ingestion, or, if it is in the best interest of the subject, as determined by the Investigator, a study subject may instead have colonoscopy the day after CapsoCam ingestion, but must be scheduled more than 26 hours post-capsule-ingestion to allow the capsule to finish recording if it has not been excreted. In the event the capsule is seen during

the colonoscopy, it is recommended that the physician retrieve the capsule and return it to the Sponsor. If the capsule is retrieved in the cecum, there is no need for the physician to perform steps 3, 5 and 6 listed below and the capsule video will not need to be read by the independent reader.

Subjects will be prepared for colonoscopy according to Investigator instructions.

The following procedures are specified for significant polyps, where significant polyps are defined as those estimated to be ≥ 4 mm. In addition, all suspected advanced neoplasia, including cancers, will be considered significant polyps.

1. The entire colonoscope withdrawal will be video recorded.
2. The colonoscopist will estimate the size of detected polyps.
3. A measurement reference tool will be imaged with the polyps and used as a reference for a later final polyp size determination by independent readers.
4. The colonoscopist will capture at least one photograph showing an unobstructed view of each significant polyp.
5. The colonoscopist will capture at least one photograph of each significant polyp with the measurement tool in frame. If the entire polyp cannot be captured in a single image, multiple images of the polyp with the measurement tool should be captured. These photographs will be analyzed to determine the ground-truth polyp size.
6. Each resected significant polyp will be placed in a separate vial for biopsy labeled to match the polyp to the subject and to the polyp diagnosis, including the polyp photographs, size estimate, and the colon-segment location.
7. The location of each significant polyp is recorded by segment: cecum, ascending colon, transverse colon, descending/sigmoid colon, or rectum.

The histopathology report is referred to to determine if a subject has CRC or an advanced precancerous lesion, defined as an adenoma with at least one of the following characteristics:

- Size ≥ 10mm
- Villous growth (a tubulovillous or villous adenoma)
- High-grade dysplasia (HGD).

Sessile serrated polyps (SSPs) are counted as adenomas. Advanced neoplasia is considered either cancer or an advanced precancerous lesion.

Immediately after the colonoscope pull-back is complete, the first CapsoCam® read results, if available, will be unmasked. The results list the size, morphology, and colon segment of all polyps detected, and include at least one capsule image of each. If the Investigator suspects that a significant CapsoCam® polyp was missed by OC, but especially if the CapsoCam® results include a polyp ≥ 6 mm or suspected cancer and no OC polyp of size estimation ≥ 4 mm was detected in the same or adjacent colon segment, the colonoscopist should repeat the colonoscopy at least in the indicated colon segments and those adjacent to it, if it is in the best interest of the subject. The prior photography procedures should be repeated for each new significant polyp found and the record should indicate which OC polyps were found after unmasking.

3.9 Second-colonoscopy determination and subject exit from study

If, based on either the CADe or no-CADe capsule report, it is determined that a significant finding, including a polyp assessed at 6mm or larger, may have been missed during OC (and confirmed by a member of the CEC as defined in section 3.11.1), this determination will be conveyed to the PI. If a second colonoscopy is decided to be in the best interest of the subject and is performed within 6 months of the original colonoscopy, any additional significant polyps will be added to the Polyp Measurement Log case report form for analysis and marked as found during 2nd colonoscopy. The subject can be exited from the study at this point.

For subjects that complete next-day "Day 1" colonoscopy, capsule results will not be available the day of the colonoscopy. In these cases, once a capsule report (either with or without CADe) is available and reviewed, if it is determined that a polyp assessed at 6mm or larger may have been missed during OC (and confirmed by a member of the CEC as defined in section 3.11.1), this determination will be conveyed to the PI. The physician and subject may choose to repeat the colonoscopy. If repeat colonoscopy is decided to be in the best interest of the subject and is performed within 6 months of the original colonoscopy, any additional significant polyps will be added to the Polyp Measurement Log case report form for analysis and marked as found during 2nd colonoscopy.

In both colonoscopy scenarios, subjects completing a second colonoscopy will be exited from the study following the second colonoscopy or within 6 months after colonoscopy, whichever occurs first. Sites will be informed of negative CapsoCam results after both the CADe and non-CADe reports are reviewed and may then exit the subject from the study.

For subjects that were exited from the study prior to the introduction of CADe, they will not be considered for reconsenting. However, both their capsule reports will be reviewed as defined in section 3.11.1. Any positive findings will not be collected for analysis.

3.10 Reference Polyp Size Determination

The video record of the colonoscopy and photographs taken during the OC procedure, showing the measurement tool proximal to the polyps, will be collected from the clinical sites and distributed to two independent physicians to determine the polyp sizes. Provided that the measurements of both readers are within 1 mm, the measurements will be averaged and treated as ground truth for a particular polyp. When the discrepancy between the two size measurements exceeds the greater of either 1 mm or 10% of the larger measurement and the largest measurement is > 6 mm, a third reader will evaluate and measure the polyp in question. In cases where one reader selects the CRF option "< 6 mm" and the other reader provides a numerical measurement > 6 mm, a third measurer will also be asked to measure the polyp. For polyps with three measurements, the median will be used as the final measurement.

The physician measures the polyps in the photographs using a measurement software application, which may include a graphical user interface (GUI) which allows the user to draw one line across the measurement tool and another line across the long axis of the polyp. The software calculates the polyp size from the length of these lines and the known size of the measurement tool. The polyp size will be recorded in millimeters to one decimal place (*e.g.* 11.2 mm or 8.0 mm).

If a single photograph is deemed inadequate to make a measurement, either because the entire polyp or a sufficient portion of measurement tool is not visible, then the reader should refer to all

photographs of the polyp, the colonoscopist's polyp-size estimation, and the video record of the colonoscopy and make a size determination, adjudicating discrepant size values. If the reader cannot confidently estimate the polyp size but can confidently classify it as < 6 mm, then this classification should be recorded. Otherwise, the size should be recorded as indeterminate, and, if no other polyp is found in the subject ≥ 6 mm to serve as the reference polyp, then the subject should be excluded from the endpoint analyses due to "missing size measurement data."

3.11 Adverse Events (AEs)

An adverse event (AE) is defined as any untoward medical occurrence, independent of its association with the study device.

Adverse events that start on the day of capsule ingestion (Procedure) through excretion will be recorded on the appropriate CRF. All side effects from bowel preparation, pro-kinetic medication, boosters or anything related to colonoscopy (e.g., anesthesia) will be recorded as anticipated observations on the adverse event CRF. Subjects discontinuing prematurely from the study due to an AE that has not yet been stabilized will be managed by their treating physician.

Adverse events that occur during the study will be recorded on the Adverse Event CRF. Data to be collected will include the description of the adverse event, onset and resolution date (or whether the adverse event is ongoing), severity, management/treatment, outcome, and determination of the relationship to the study device and/or procedure (i.e., Prep, Pro-kinetics, or Booster). In general, AEs should be reported and classified by the Investigator using a diagnosis rather than symptoms.

The relationship of the AE will be coded as follows:

- **Not related**: The AE is due to an underlying or concurrent illness or effect of another device, drug or intervention and is not related to the study device or device procedure.
- **Possibly related**: The causal and/or temporal relationship to the study device or device procedure is equally or less likely than other plausible explanations.
- **Probably related:** The causal and/or temporal relationship to the study device or device procedure is likely or significantly more likely than other plausible explanations.
- **Definitely related**: A clinical event that can only be attributed to the study device or device procedure.

Severity will be coded as to the degree of severity as follows:

Mild: The AE is transient and easily tolerated by the subject, even if it causes discomfort

Moderate: The AE causes the subject discomfort and interrupts the subject's usual activities.

Severe: The AE causes considerable interference with the subject's usual activities; may be incapacitating and may require hospitalization.

All adverse events that occur in the study population (including Serious Adverse Events and Unanticipated Adverse Device Effects) will be tabulated and summarized. In addition, the incidence of all types of adverse events will be reviewed during the course of the study for any indications that use of study device confers any unanticipated significant risk. An unanticipated

adverse device effect (UADE) is defined by the FDA as *"any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem with a device that relates to the rights, safety, or welfare of subjects."* Should any unanticipated adverse device effects occur during the course of the study, the Investigator is required to report the events to the Sponsor as soon as possible after learning of the event but no later than 10 working days after learning of the event. The Investigator must report to the governing IRB per IRB reporting requirements. The Sponsor, will conduct an evaluation of such effects. In addition, the study Sponsor will report the UADE to FDA and participating Investigators within 10 working days after the Sponsor first receives notice of the effect. Following the evaluation, if the Sponsor determines that an unanticipated adverse effect presents an unreasonable risk to subjects, the investigation will be terminated as soon as possible. Termination shall occur no later than five working days after the Sponsor makes the determination and no later than 15 working days after the Sponsor receives notice of the unanticipated adverse device effect. FDA and IRB approval will be obtained prior to resuming a terminated investigation.

A serious adverse event (SAE) is any AE that:

- led to a death,
- led to a serious deterioration in the health of the subject that:
- resulted in a life-threatening illness or injury,
- resulted in a permanent impairment of a body structure or a body function,
- required in-patient hospitalization or prolongation of existing hospitalization,
- resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function
- or led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note that an elective or pre-planned hospitalization for a condition that did not worsen during the study is not an AE.

ALL SAEs and UADEs should be reported to the Sponsor within 24 hours of the knowledge of the event and reported to the respective IRB per their requirements. In the event of subject death, a copy of death records, medical records pertaining to the events leading up to the death, and an autopsy report (if performed) should be sent to the Sponsor as soon as possible. All subject identifiers other than the subject number should be removed from the documents submitted to the Sponsor.

3.11.1 Clinical Events Committee (CEC)

The CEC will consist of one to three independent physicians. The CEC will adjudicate all reported SAEs. The CEC will be responsible for review, adjudication, and validation of all

reported SAEs that occur over the course of the study and subsequent classification of these complications as related to the study device, procedure, or other. If the CEC's classification differs from the Investigator, Investigator will be notified of the determination. The CEC's adjudication is final for all SAEs. In addition, the CEC will review all deviations that may affect the study endpoints. The CEC will meet as needed based on the rate of reported events. Members will be provided data summaries from the clinical study.

The CEC will also review both capsule report results with the colonoscopy reports for subjects that have colonoscopy on Day 1 as described in section 3.8. The CEC will be provided with all images/video and report documentation from the capsule report and the colonoscopy report when a polyp ≥4 mm is identified on the capsule report that is not reflected in the colonoscopy report. The committee will review the documentation independently and submit their recommendation regarding repeat colonoscopy. When the committee is in agreement, the site will be notified of the final recommendation. If a repeat colonoscopy is recommended, the final decision to repeat the exam will be the responsibility of the Principal Investigator and subject. In the event of a disagreement between the committee members, a live meeting will be held to discuss the case. If a unanimous agreement cannot be reached, the site will be notified of the conclusion from all members of the committee to better inform their decision regarding repeat colonoscopy.

3.12 Device Malfunction

Throughout the study, the Investigator and study staff will report and document all study device deficiencies and malfunctions related to the identity, quality, durability, reliability, safety or performance of the study device.

This includes reporting of study device deficiencies/malfunctions that did not lead to an AE but could have if:

1) suitable action or intervention had not been taken, or

2) if intervention had not been made or

3) circumstances had been less fortunate.

If possible, the Investigator should return study devices suspected of deficiency or malfunction to the Sponsor for analysis.

All malfunctions of the study device observed during capsule administration or at the download center must be documented on the Device Malfunction/Performance Case Report Form within 24 hours of the knowledge of the event. If possible, study devices should be returned to the Sponsor for analysis. All performance issues and malfunctions will be reported in the final report. Instructions for returning the study device are included in the Instructions for Use.

3.13 Subject Withdrawal

Subjects will be advised that they may voluntarily withdraw from the study at any time and will be instructed to notify the Investigator immediately if they choose to withdraw. Subjects may choose to withdraw for any reason and are not obligated to reveal their reason(s) for withdrawal. Should subjects withdraw prior to the Final Visit, the site will communicate with the subject and exit them from the study. In addition, subjects may be involuntarily withdrawn by the Investigator if the Investigator believes it is in the best interest of the subject (e.g., adverse event)

or if the subject needs re-intervention. AEs that are study device related (onset after ingestion and prior to excretion) and ongoing at study exit will be followed for 30 days or until resolved, whichever comes first.

3.14 Data Collection and Reporting

Electronic Case Report Forms (eCRFs) will be used to capture patient data in the clinical trial. The Principal Investigator consents to visits by the staff of the Sponsor and its authorized representatives and the U.S. Food and Drug Administration or any other governmental body to review the study subjects' medical records including any test or laboratory data.

3.14.1 Reporting of Protocol Deviations:

A Protocol Deviation Form must be completed for each study protocol deviation (e.g., failure to obtain informed consent, enrolling a subject who does not meet inclusion/exclusion criteria, not performing required testing, subject not following the prep regimen, missed follow-up window, etc.). Deviations involving subjects' rights, safety or welfare should be reported to the Sponsor as soon as the Investigator or other study staff are made aware. IRB's may require the reporting of protocol deviations. The site Investigator and study staff are responsible for knowing and adhering to their IRB requirements.

Deviations will be reviewed regularly by the Sponsor and corrective actions may be implemented if required to assure data integrity and the protection of study subjects.

3.14.2 Confidentiality of Data:

All information and data sent to the Sponsor, Contract Research Organizations, or the CEC concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject.

3.14.3 Lost to Follow Up

If a subject is lost to follow up, the End of Study eCRF will be completed. If a subject fails to comply with the follow up evaluations, the study site will attempt to contact the subject at least three times, and retain documentation of contact attempts.

In order to minimize loss to follow-up, at the baseline evaluation visit, the Study Coordinator will ensure accuracy of contact information for the study subjects. It is recommended that the research site obtain contact information for at least one individual to serve as an alternate contact for the participant. The contacts will be utilized in the event that the subject relocates or cannot be reached by mail or telephone. This information will be treated as confidential and for use by the investigative site only.

3.14.4 Quality Assurance of the Data

Subject case report forms will be reviewed for completeness and accuracy as well as for any evidence suggesting subject risk. Where any discrepancies are noted, they will be resolved with the Investigator and/or an individual designated by the Investigator. Where the data are incomplete, attempts will be made to obtain the missing data.

3.15 Study Termination

If new information is discovered during the study that indicates that the study device provides an

unreasonable risk to subjects, study enrollment will be suspended or discontinued. Enrollment will only be resumed once the risk has been appropriately mitigated and authorization to resume is obtained from FDA and the IRB.

Regardless of ability to resume the study, all subjects may undergo the planned colonoscopy.

4. STATISTICAL CONSIDERATIONS

4.1 Analysis Population

Evaluable population. This population will consist of all subjects who have both an evaluable colonoscopy and an evaluable CapsoCam®. This population will be used for all effectiveness analyses.

The following circumstances contribute to procedures that are not evaluable and therefore such subjects will be excluded from all effectiveness analyses:

1. Subjects who fail to undergo either the capsule or OC procedure.
2. Subjects for whom the capsule did not leave the cecum in 24 hours post-ingestion.
3. Subjects for whom the capsule did not reach the colon within 24 hours post-ingestion.
4. Subjects with incomplete colonoscopies.
5. Subjects whose bowel cleanness was rated as inadequate for either the colonoscopy or capsule procedures.
6. Subjects with capsule malfunction resulting in more than approximately 5 minutes of video data in the colon missing or unevaluable, within the first 24 hours of capsule operation.
7. Subjects with missing colon image data due to filling of available data memory within 12 hours of operation and prior to excretion.
8. Subjects who undergo colonoscopy on Day 1 and the colonoscope reaches the capsule while it is still in the colon and recording video, as determined from review of the capsule video, prior to a timestamp of 24 hours.
9. Inability to measure polyps in structured light setting in CapsoView

The bowel cleanliness will be rated adequate or inadequate for each subject using the CC-CLEAR method.[18] The colon is divided into three segments: right (cecum and ascending colon), transverse, and left (descending/sigmoid and rectum). In each read, the reader assigns points for each segment based on the fraction of the mucosa visualized (Table 1). If only a portion of a segment is visualized because the capsule stopped recording, the score for the segment is based on the percentage of mucosa visualized *in the portion visualized*. In [18] the overall score for a read is considered adequate if all segment scores are at least 2. However, for this study, the cleanliness is considered adequate if all segment scores are at least 1. Otherwise, it is inadequate. Segments not included in the video because the camera stopped recording are not counted in the adequacy determination.

Table 1 CC-CLEAR Bowel cleanliness rating per segment

Points per segment	Percentage of mucosa visualized
0	Less than 50%
1	Between 50% and 74%
2	Between 75% and 89%

3	At least 90%

For the exclusion criteria numbered 2, 3, 5, 6, 7, 8, or 9, the subject is excluded from the evaluable population if the criterion is met based on either read. For calculating capsule transit for each subject, the first cecal time and excretion time will be the average of the two reads and the last cecal timestamp is the larger of the two.

Safety Population. This population will consist of all subjects who attempted to ingest the capsule, whether successful or not.

4.2 Study Endpoint Analyses

All polyps identified and resected during colonoscopy will be confirmed as polyps on the histopathology report to be considered polyps in the analysis. If a histopathology report is not available, those findings classified as polyps by the colonoscopist will be considered polyps in the analysis. Details of the endpoint analyses will be described in the Statistical Analysis Plan.

Coprimary Effectiveness Endpoints. The coprimary effectiveness endpoints involve the PPA and NPA for detecting polyps ≥ 6 mm.

PPA will be defined, based on all patients for whom OC's largest (reference) polyp ≥ 6 mm, as follows:

- True Positive (TP) if a polyp identified by CapsoCam is in same or adjacent colon segment and matches in size, per matching rules in section 4.3.

- False Negative (FN) if not

$$\text{Then PPA} = \frac{\text{TP}}{\text{TP} + \text{FN}}$$

NPA will be defined, based on all patients for whom OC's largest polyp < 6 mm, as follows:

- False Positive (FP) if CapsoCam identifies a polyp ≥ 6 mm

- True Negative (TN) if not

$$\text{Then NPA} = \frac{\text{TN}}{\text{TN} + \text{FP}}$$

Point estimates and 95% confidence intervals for PPA and NPA using exact Clopper-Pearson methodology will be computed.[17] The null and alternative hypotheses to be tested are defined in Section 4.6.

Secondary effectiveness endpoints involving polyp matching. All the secondary endpoints involving polyp matching will be analyzed in a manner analogous to the corresponding primary effectiveness endpoint, with endpoint-specific definitions of TP, FN, TN, and FP.

Multi-reader multi-case analysis. A multi-reader multi-case (MRMC) analysis will be applied to the secondary endpoints comparing the PPA and NPA with and without CADe. The MRMC is a case-nested-within-reader split-plot structure with one reader per case,[18, 19] using sufficient readers to generalize the results to a population of random readers. The possibly unequal number of positive and negative cases for each reader will be considered when calculating the cross-reader variances.

Sensitivity for advanced neoplasia. Advanced neoplasia comprises cancer or an advanced precancerous lesion, where an advanced precancerous lesion has at least one of the following characteristics:

- Adenoma of size ≥ 10mm
- Villous growth (tubulovillous or villous adenoma).
- High-grade dysplasia (HGD).

The histopathology report determines if a polyp is an adenoma, where SSPs are considered adenomas, and if it has villous growth or HGD.

Additional Analyses. In addition, we will cross-tabulate the size of the largest polyp detected with OC by the size of the largest polyp detected with CapsoCam® using the categories of 0 mm, > 0 to < 6 mm, 6 to <10 mm, and ≥ 10 mm.

4.3 Polyp Matching Rules

Many of the study endpoints involve polyp matching. This section defines the rules for such matching. The matching rules are applied to polyp sizes and polyp-size thresholds expressed in millimeters to one decimal place. So, for example, a polyp measured to be 5.8 mm in colonoscopy or by the capsule is *not* rounded to 6 mm before comparison to the 6.0 mm threshold and is thus not included in the ≥ 6 mm category.

For each subject with at least one polyp ≥ 6 mm detected by OC, the largest polyp will be the reference (index) polyp to which CapsoCam® detected polyps will be compared. The colon segment location of the polyp will be recorded as the cecum, ascending colon, transverse colon, descending/sigmoid colon, or rectum. If two or more OC polyps ≥ 6 mm in different colon segments are of equivalent size (all within 1.0 mm of the largest) and they are the largest in their segment, each will be a reference polyp for a separate CapsoCam® to-OC-polyp matching analysis, and the final matching result for this subject will be the one signifying the best CapsoCam® accuracy.

A polyp detected by CapsoCam® will be a match to the reference polyp if (1) its size is within ± 50% of the reference polyp, and (2) its location is in the same segment as the reference polyp or it is in an adjacent colon segment. The calculated upper and lower limits of the size matching range are rounded to one decimal place before determining if a capsule polyp is in the range. Very large polyps (≥ 20 mm) typically are not completely visualized by CapsoCam® in a single or even two frames, making accurate measurement difficult. Accurate measurement of very large polyps can be difficult in colonoscopy as well. Thus, for purposes of size matching, both study device and reference polyps measured larger than 20mm will be considered 20 mm for size matching. While polyp matching on size will primarily be based on the ±50% rule just described, sensitivity analyses will also be conducted in which the size matching will be based on a rule of –50% or larger.

4.4 Safety Assessment

Safety will be assessed based on analysis of adverse events (AEs). The frequency and capsule relatedness of AEs will be reported and reviewed with CEC and tabulated for reporting purposes.

4.5 Sample Sizes

Assumptions for sample size calculations:

- True PPA for detecting polyps ≥ 6 mm without CADe is 69%
- True PPA for detecting polyps ≥ 6 mm with CADe is 80%
- True NPA for detecting polyps ≥ 6 mm without CADe is 90%
- True NPA for detecting polyps ≥ 6 mm with CADe is 86%
- True sensitivity for detecting advanced neoplasia is 85%
- One-sided alpha = 0.025
- Non-inferiority margin of 0.1
- Within-reader between-test correlation of accuracy measurement errors, r1 = 0.6
- Error variances assume a binomial distribution
- PPA test-by-reader variance = 0.00033.
- NPA test-by-reader variance = 0.00015.
- Number of readers = 9.
- Readers read an equal number of positive cases and an equal number of negative cases.
- More readers increase the study power for demonstrating superior PPA and noninferior NPA with random readers. The number of readers is likely to exceed the conservatively assumed value of 9. On the other hand, the number of cases read by each reader may not be exactly equal, reducing the effective number of readers. For the sample size calculations, these affects are considered counteracting and thus ignored.

Calculated sample sizes for each statistically-powered endpoint:

- Observed PPA for detecting polyps ≥ 6 mm with CADe ≥ 65%, with 99% probability of success: 40 evaluable positive subjects.
- Observed NPA for detecting polyps ≥ 6 mm with CADe ≥ 75%, with 99% probability of success: 56 evaluable negative subjects.

- The PPA for detecting polyps ≥ 6 mm with CADe is superior to that without CADe with power 90%: 162 evaluable positive subjects.
- The NPA for detecting polyps ≥ 6 mm with CADe is non-inferior to that without CADe with power 90%: 432 evaluable negative subjects.
- The sensitivity for detecting advanced neoplasia is at least 65%: 52 evaluable positive subjects.

Enrollment Plan

It is desired to have at least as many cases with polyps ≥ 6 mm as were obtained in the pivotal study for the predicate device (PillCam)[12] and to have at least as many evaluable subjects. The PillCam study had 700 evaluable subjects and 192 subjects with at least one polyp ≥ 6 mm, which exceeds the calculated positive sample size of 40. Thus, this CapsoCam study will enroll subjects until there are at least 192 subjects with at least one polyp ≥ 6 mm and 432 without, with the total equaling at least 700.

4.6 Hypotheses

1. Secondary Endpoint #1 – The null hypothesis is that "true" difference in PPA for detecting polyps ≥ 6 mm with CADe versus without CADe (PPA with CADe – PPA without CADe) is ≤ 0. The alternative hypothesis is that this difference is > 0.
2. Secondary Endpoint #2 – The null hypothesis is that "true" difference in NPA for detecting polyps ≥ 6 mm with CADe versus without CADe (NPA with CADe – NPA without CADe) is ≤ -10%. The alternative hypothesis is that this difference is > -10%.
3. Secondary Endpoint #3 – The null hypothesis is that the sensitivity for detecting advanced neoplasia with CADe is < 65%. The alternative hypothesis is that it is ≥ 65%.

4.7 Multiple Comparisons

A hierarchical testing procedure will be utilized to control the overall study-wise type I error rate at the pre-specified one-sided alpha=0.025 level. Hypothesis testing will be conducted in the order listed. Formal hypothesis testing will stop following the first non-statistically significant result (p-value ≥0.05), and nominal p-values will be displayed for subsequent endpoints.

Full details of this approach will be described in the SAP.

4.8 Masking Procedures

The study design and clinical practice for this study prohibit the use of strict blinding methodology during the conduct of the study. However, the colonoscopist will not have access to the results of the CapsoCam results until after the colonoscopy has been completed.

5. PERSONNEL RESPONSIBILITIES

5.1 Principal Investigator Responsibilities

- Permit monitor inspection of facilities and records.

- Permit FDA and other government health authority's inspection of facilities and records.
- Submit protocol and informed consent to IRB and receive approval prior to enrolling first subject.
- Submit proposed amendments to protocol and informed consent to IRB and await approval, unless the change reduces the risk to subjects.
- Obtain informed consent of subjects.
- Implement study in accordance with protocol.
- Complete case report forms.
- Record and explain deviations from protocol and report to monitor.
- Submit annual progress reports, final reports, and adverse effect reports to IRB and Sponsor.
- Record the receipt, disposition, and return of study devices.
- Refrain from promoting study or study articles in such a way that the potential participant will be biased in his/her responses.
- Maintain medical histories of subjects.
- Retain records for two years following FDA approval of marketing application.

5.2 Sponsor Responsibilities

- Assure IRB approval of protocol and informed consent is obtained prior to enrollment of study subjects.
- Select and train monitors.
- Select Investigators.
- Train Investigators in study device use.
- Obtain Agreement Letter and curriculum vitae and proof of appropriate licensure of Investigator and other study staff.
- Control shipment of study devices.
- Conduct day-to-day administration of study.
- Investigate unanticipated, device related adverse effects.
- Document protocol deviations and violations.
- Obtain statement of financial disclosure.

6. RISK/BENEFIT ANALYSIS

The investigational study was designed to assure that the benefits and knowledge gained about the use of the CapsoCam® outweigh the potential risks to the study subjects. CapsoVision has submitted a previous version of this study protocol to the U.S. Food and Drug Administration (FDA). After review of the submission, FDA issued a decision letter on June 25, 2018 stating that the study would be a non-significant risk (NSR) device study.

6.1 Potential Risks to Study Subjects

The following are the possible risks associated with the Capsule Endoscope; some may be rarer than others:

- Abdominal discomfort while the capsule is passing through the subject's gastrointestinal tract

- Injury of the mucosa
- Bleeding of the mucosa
- Retention of the capsule (rarely) possibly resulting in obstruction; if this happens, the subject may need a procedure or surgery to remove the capsule. Often the capsule will pass with time or after administration of medication.
- Aspiration

Capsule endoscope retention poses the greatest potential risk. However, all subjects being enrolled in the study will meet all the eligibility criteria and therefore this study has been designed to minimize this risk to the study subject.

Retention of the capsule is highly unlikely, but has been reported in subjects with unknown and undiagnosed abdominal strictures. Exclusion criteria have been developed to minimize the possibility of a subject being enrolled in the study who has signs and symptoms of gastrointestinal strictures. In the event that a subject experiences retention of the capsule, the capsule may subsequently be excreted by itself over time or medical therapy may be administered to encourage capsule excretion. In some cases of capsule retention, endoscopic retrieval or other surgical intervention might be needed.

In the event that a subject fails to successfully retrieve and return a capsule within 7-14 days following ingestion of the study device, or it is suspected by the Principal Investigator that the capsule may be retained in the subject's gastrointestinal system, an abdominal x-ray will be performed to determine the location of the capsule. If the x-ray is negative, it will be assumed that the subject failed to notice the passage of the capsule during defecation, and that it was successfully excreted. If retention of the capsule is determined, appropriate treatment will be decided and provided by the Principal Investigator. Depending on the location of the retention, the subject's medical status and potential risks to the subject, removal may be done via endoscopic retrieval or via other surgical methods at the discretion of the Principal Investigator.

Additional Risks

The additional risks to study subjects are the risks posed from using the bowel preparation and post-capsule ingestion drugs in this study: NuLYTELY (or generic version), SuPrep, bisacodyl, simethicone and prucalopride (Motegrity). This increased risk has been mitigated by excluding subjects from the study who might be at increased risk by using these drugs. Risks of consuming NuLYTELY and SuPrep and similar sulfate-based prep as capsule boosters are low and are expected to be limited to subject discomfort and mild side effects which are listed below. The risk associated with prucalopride is low and is expected to be limited to subject discomfort and mild side effects which are listed below.

NuLYTELY is an osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults 18 years of age or older.

NuLYTELY is provided for use in this study. (contains polyethylene glycol 3350, sodium chloride, sodium bicarbonate, and potassium chloride) is a prescription medicine used by adults to clean the colon before a colonoscopy or barium enema X-ray examination. NuLYTELY and other osmotic bowel preparations can cause serious side effects, including: Serious loss of body

fluid (dehydration) and changes in blood salts (electrolytes) in your blood. These changes can cause: abnormal heartbeats that can cause death, seizures (can happen even if you have never had a seizure), or kidney problems. Your chance of having fluid loss and changes in body salts with NuLYTELY is higher if you: have heart problems, kidney problems, or take water pills or non-steroidal anti-inflammatory drugs (NSAIDS). The most common side effects of NuLYTELY include nausea, stomach (abdominal) fullness, bloating, stomach (abdominal) cramps, vomiting, and anal irritation.

The use of commercially available, oral solution SUPREP as a booster used in this study. SUPREP (sodium sulfate, potassium sulfate and magnesium sulfate) is an osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults. Nausea, vomiting abdominal discomfort/cramping and bloating are the most common side effects reported (occurring in up to 54% of subjects). Serious but rare side effects include fluid and electrolyte abnormalities, seizures, cardiac arrhythmias, renal impairment, and mucosal aphthous ulcerations.

The use of commercially available prucalopride, which is indicated for the treatment of chronic idiopathic constipation (CIC) in adults is also used in this study. Prucalopride induces a stimulation of contractile activity in the proximal colon and has been shown to stimulate and amplify giant migratory contraction, which is the high-amplitude type of contraction that initiates the urge to defecate. Thus, prucalopride not only accelerates the colonic transit but also accelerates gastric emptying and small bowel transit. In clinical trials, prucalopride was shown to significantly increase the spontaneous bowel movements when compared with the placebo group. In these studies, as well, it was observed a numerical improvement in mean colonic transit time and a significant increase in spontaneous complete bowel movement without marked changes in the anorectal function. For purposes of this study, a 2 mg dose is given prior to capsule ingestion. Common adverse reactions reported in clinical trials are headache, abdominal pain, nausea, diarrhea, abdominal distension, dizziness, vomiting, flatulence and fatigue, while less common adverse reactions occurring in < 2% of subjects receiving prucalopride 2 mg once daily include: abnormal gastrointestinal sounds, decreased appetite, migraine, and pollakiuria.

Adverse reactions of special interest were evaluated in a pool of 28 completed clinical trials (19 double-blind and 9 open-label) for prucalopride at doses including 0.5 mg, 1 mg, 2 mg, or 4 mg per day in adult subjects with CIC (the recommended dosage of prucalopride for CIC is 2 mg once daily). The total exposure in the double-blind trials was 565 subject-years in the prucalopride group, 384 subject-years in the placebo group, and 2769 subject-years in the double-blind and open-label clinical trials.

In an evaluation of prucalopride by an independent adjudication committee of all potential major adverse cardiovascular events (MACE), defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, the standardized incidence rate (IR) per 1000 subject-years for MACE for prucalopride was compared with the IR for placebo. In the double-blind trials, the IR for MACE was 3.5 (2 subjects out of 3366; 1 subject on 2 mg and 1 subject on 4 mg) in the prucalopride group and 5.2 (2 subjects out of 2019) in the placebo group.

In the double-blind trials, the IR for MACE was 3.5 (2 subjects out of 3366; 1 subject on 2 mg and 1 subject on 4 mg) in the prucalopride group and 5.2 (2 subjects out of 2019) in the placebo group. When combining the double-blind and open-label trials, the IR for MACE was 3.3 (9 subjects out of 4472, doses ranging between 0.5 to 4 mg) for prucalopride.

In population with CIC the recommended oral dose regimen for adults is 2 mg once daily, and for subjects with severe renal impairment 1 mg once daily (creatinine clearance (CrCL) less than 30 mL/min) common adverse reactions to prucalopride (2 mg Once Daily; N=1,279) and placebo (N=1251): Headache 19% vs. 9%, Abdominal pain 16% vs. 11%, Nausea 14% vs. 7%, Diarrhea 13% vs. 5%, Abdominal distension 5% vs. 4%, Dizziness 4% vs. 2%, Vomiting 3% vs. 2% Flatulence 3% vs. 2%, Fatigue 2% vs. 1%.

Additional side effects or adverse events are also possible as a result of the subject taking bisacodyl (10 mg/daily). However, side effects caused by bisacodyl when used infrequently and at this limited dose are fairly minor and serious effects are rare.

Bisacodyl is used to relieve occasional constipation and to clean out the intestines before bowel examinations. Bisacodyl belongs to a class of drugs known as stimulant laxatives. It works by increasing the amount of fluids that enter the bowels, causing bowel movements within 6 to 12 hours. Short-term usage of bisacodyl at normally- prescribed dosages may result in abdominal pain or cramps and rarely nausea or vomiting can occur. Rare side effects and adverse events usually associated with higher doses or longer-term use include: rectal bleeding, persistent diarrhea, dizziness, decreased urination, muscle cramps and/or weakness, or irregular heart rhythms. A very serious allergic reaction to this drug is rare, but possible. Subjects should be instructed to seek immediate medical attention if they notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, or trouble breathing, or any of the unusual side effects noted above.

Simethicone is an over-the-counter medication used to reduce bloating, discomfort or pain caused by excessive gas. There are no reports of side effects of this medication and allergic reaction is very rare. For this study, simethicone is used the night before and the morning of capsule ingestion at 80 mg/dose.

Subjects may experience identification of otherwise unnoticed abnormality(ies) in the colon by swallowing the CapsoCam® prior to having a colonoscopy. It is also possible that subjects may not experience a clinical benefit from study participation, however there may be a beneficial addition to the body of knowledge for this type of diagnostic tool.

7. MONITORING PROCEDURES

CapsoVision, Inc. is the Sponsor of this clinical study. Study monitoring will be performed in accordance with CapsoVision, Inc. procedures, or those approved by CapsoVision, Inc. CapsoVision, Inc. will have overall management responsibility for this study. In addition, CapsoVision, Inc. will direct regional monitoring staff who may serve as clinical study monitors, study administrators, and/or have oversight responsibility for data review and data integrity.

7.1 Clinical Study Monitors

CapsoVision Inc. will engage the services of one or more qualified organizations or individuals to perform monitoring functions, and provide participating sites with relevant contact information, as necessary. Study monitors may change periodically over the course of this study. All monitors will be qualified to perform their assigned responsibilities, and participating Investigators/site personnel will be notified of any changes as they occur.

Due to COVID-19 pandemic, monitoring will occur remotely until limitations of travel and mandates for mask use have been lifted at all participating sites. Monitoring will be frequent

enough to assure continued acceptability of the data by assessing site compliance with the study protocol, adherence to data collection procedures, and maintenance of study records. Scheduled monitoring visits will include, but are not limited to, the following:

- Site initiation visit: prior to enrolling subjects, an initiation visit will be conducted by clinical study personnel to review this study protocol and associated study operational procedures.
- Interim monitoring site visit: monitoring visits will be conducted at all sites to assess the progress of the study and identify any concerns that result from review of the study records, study management documents, or subject informed consent documents. To assure the integrity of the data, a representative number of individual subject records and other supporting documents will be compared to CRFs completed at the site to determine that:
    - The study protocol is being followed, and only eligible subjects are being enrolled; variances, if they occur, are recorded and reported as appropriate.
    - Informed consent is properly documented.
    - Adverse events are being reported appropriately.
    - Information recorded on CRFs is complete, accurate and legible.
    - Subjects failing to complete the clinical study and the reason for failure are properly recorded.
- Final monitoring/Close-out site visit: a close-out visit to participating sites may be made by the study monitor, if necessary. Any ongoing responsibilities will be discussed with the Investigator and/or site personnel as appropriate. At the close of the study at an investigational site, appropriately trained personnel appointed by the Sponsor will perform a close-out process remotely or on-site. The purpose of this visit is to collect all outstanding study data documents, ensure that the Investigator's files are accurate and complete, review record retention requirements, ensure final accounting of all study devices shipped to the Investigator, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study. The observations and actions made during the visit will be documented and communicated to the Investigator

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9. Appendix A

APPENDIX A

Summary of Prior Clinical Investigations

CapsoCam® SV-1 Capsule Endoscope Clinical Study

The CapsoCam® SV-1 capsule endoscope has been evaluated in a non-significant risk clinical study in the United States and Canada for obtaining 510k clearance from the US FDA per protocol # SV-1.

The CapsoCam® SV-1 Study was a prospective, randomized, comparative multi-center, non-significant risk study which enrolled 121 subjects with suspected small bowel disease who were referred for capsule endoscopy. All subjects signed the IRB approved informed consent prior to participation. The study began on January 3, 2012 and the last subject was enrolled on March 10, 2014. Of these 121 subjects, 120 (99%) subjects continued in the study as part of the Intent-to-Treat (ITT) cohort. One hundred fourteen (114, (94%)) subjects made up the Per Protocol (PP) cohort defined as subjects who: 1) were part of the ITT cohort; 2) met inclusion and exclusion criteria (or received a waiver that allowed enrollment); 3) ingested and retrieved both study capsules; 4) whose ingested capsules reached the small bowel; 5) had a primary diagnosis recorded by the video Readers for the study; and 6) were without major study protocol violations.

The Intent-to-Treat (ITT) cohort in the study consisted of 51 (42.5%) males and 69 (57.5%) females with a mean age of 55.2 years (SD=15.42), median age of 56 years (range 19-85). One hundred four (104 (86.7%)) self-identified their race as White. The Per Protocol (PP) cohort subset in the study consisted of forty-seven (47, 41.2%) males and sixty-seven (67, 58.8 %) females with a mean age of 55.7 years (SD=15.40), median age of 56.3 years (range 19-85). One hundred (100, 87.7%) self-identified their race as White.

Thirteen (13(11%)) of all enrolled subjects experienced fifteen (15) adverse events as reported by the clinical investigational site Investigators. Twelve (12) of these thirteen (13) subjects were included in the ITT analysis cohort.

One subject was not included in the ITT analysis cohort because the subject gagged when attempting to ingest the capsule endoscopes and, although enrolled, did not continue in the study.

Two (2) subjects reported experiencing two (2) adverse events each with the remaining ten (10) subjects only reported experiencing one (1) adverse event each.

Two (2) of the fifteen (15) adverse events were classified as Serious Adverse Events (SAEs). In both subjects from the same investigational site, previously undiagnosed bowel obstructions were present. In both subjects, retained ingested capsules were retrieved when surgical procedures to correct the bowel obstructions were performed. After the surgeries, the Investigator for the site reported no further adverse sequelae for either subject.

The remaining adverse events were largely attributed by the site clinical Investigators as due to discomfort associated with the administration of the small bowel prep drugs and agents

FDA 510(k) clearance of the CapsoCam SV-1 capsule endoscope (K151635) in February 2016.

CapsoCam® SV-2 Capsule Endoscope Clinical Validation

The CapsoCam® SV-2 capsule endoscope was evaluated in a clinical validation study per the protocol CVN-CVI-005 for the purpose of validating the safety profile of the SV-2 device and its ability to capture and download small bowel images in a manner consistent with the predicate CapsoCam® SV-1 Capsule Endoscopy System. The SV-2 Clinical Validation Study was a single center non-significant risk study which enrolled subjects with no known or suspected gastrointestinal diseases: "Normal Healthy Volunteers". The SV-2 Clinical Validation Study began on June 11, 2014 and the last subject was enrolled on July 9, 2014. Eleven (11) normal healthy volunteers with no known or suspected gastrointestinal disease, seven (7) and four (4) females, were enrolled in the study. The mean age of the enrolled subjects was 40 years (range 18 to 71). There were no reported adverse events (AEs) in the study.

Subsequent to the clinical validation study, the CapsoCam® SV-2 capsule endoscope has been commercially released outside the US since August 2014. Based upon information received to date, the product has performed as designed with a safe product performance profile.

The CapsoCam® Plus SV-3 capsule endoscope Clinical Validation

The CapsoVision CapsoCam® Plus (SV-3) capsule endoscope was evaluated in a clinical validation study per protocol CVN-CVI-006 for the purpose of validating the safety profile of the CapsoVision CapsoCam® Plus (SV-3) capsule device and its ability to capture and download small bowel images in a manner consistent with and comparable to the predicate CapsoCam® SV-2 Capsule Endoscopy System. The SV-3 Clinical Validation Study was a single center non-significant risk study which enrolled subjects with no known or suspected gastrointestinal diseases: "Normal Healthy Volunteers". The SV-3 Clinical Validation Study was initiated on October 1, 2015 and the fourth phase of enrollment was completed on April 11, 2016.

A total of 49 Subjects, twenty-eight (28) males twenty-one (21) females, were enrolled in the study. The mean age of the enrolled subjects was 37 years (range 19 to 63), were enrolled (Intention to Treat (ITT) population), having met the inclusion/exclusion criteria and signed the Informed consent.7 patients were withdrawn from the study: 1 subject did not return his capsule to the Sponsor/Investigator, and was believed to have inadvertently flushed it down the toilet; 1 subject attempted but could not swallow the CE/gagged after attempting to do so over a period of 1 hour, and 5 subjects experienced prolonged gastric retention of the CE such that no small bowel images were captured by the CE before it was excreted after the subjects resumed eating post procedure.There were no reported adverse events (AEs) in the study.

An analysis of the results on the remaining 47/49 (Per Protocol (PP) population) subjects was presented to the FDA to obtain 510(k) clearance of the CapsoCam® Plus (SV-3) capsule endoscope (K161773). Overall, the CapsoCam® Plus (SV-3) Validation Study CVN-CVI-006 study results demonstrated that the SV-3 Capsule Endoscope, as compared to the earlier generation CapsoCam® SV-1 Capsule Endoscope had comparable results. We have concluded from the study that the quality and clinical utility of the CapsoVision CapsoCam® Plus (SV-3) CE device is equivalent to that of the predicate device, SV-1 (K151635).

Prior Clinical Validation of CapsoVision Colon Capsule

Two previous early pilot studies with the objective to assess the visualization and imaging capability of the colon, using an earlier version of the CapsoVision Video Capsule diagnostic system, were performed by Professor Jacques Van Dam at Stanford (Protocol CV-001); and by Dr. Michael Draelos located in Highpoint, NC and Dr. John Canio located in Roseville, CA (Protocol CVI-002).

The study design used with Protocol CV-001 included two cohorts of subjects. Cohort 1 involved cecum drop and Cohort 2 involved oral ingestion. A total of 11 patients were enrolled in this study between April 1 and November 12, 2009. Eight subjects were enrolled in Cohort 1 and three subjects were enrolled in Cohort 2. Evaluation of the capsules returned for assessment for ten subjects (one capsule was lost at Stanford receiving department) revealed that bowel cleanliness was not adequate to allow visualization. Additionally, the desired transit time for the capsule of ≤12 hours was not achieved. The inadequate bowel cleanliness and resulting prolonged capsule transit time were attributable to the absence of commercially available products indicated for this purpose in the U.S. The study was discontinued since the effectiveness target defined as identification of 95% of polyps with diameter ≥ 10mm, comparable to standard colonoscopy, could not be met. No complications, adverse events or unanticipated adverse device effects were reported during this trial.

The other study (Protocol CVI-002) was initiated to assess the capsule's safety and visualization and imaging capabilities of the colon and the effectiveness of standard bowel preparation. The study was designed to enroll up to 50 subjects who swallowed the capsule following bowel preparation. A total of 21 patients were enrolled in Highpoint, NC between November 30, 2009 and October 14, 2010 and 22 patients were enrolled in Roseville, CA between January 8, 2010 and October 1, 2010. Evaluation of the capsules returned for assessment for the 41 subjects (two subjects lost the capsule) revealed that bowel cleanliness was not adequate to allow visualization. The effectiveness target defined as sufficient visualization of the colon to enable identification of 95% of polyps with diameter ≥ 10mm, comparable to standard colonoscopy, could not be achieved. Therefore, the study was discontinued for failure to generate meaningful clinical findings. No complications, adverse events or unanticipated adverse device effects were reported during this trial.

The CapsoCam® Colon capsule endoscope Clinical Validation

Provided below is a summary of prior clinical performance data regarding an earlier iteration of the subject device - the CapsoCam® Colon (CV-3). This information is being submitted since the CapsoCam® Colon (CV-3) is the same capsule as the CapsoCam® Colon (CV-2) version E (CV-2E), with the only exception that the CV-3 version also comprises the structured light size measurement technology.

The clinical feasibility evaluations, which are detailed below, were performed using two different clinical protocols: CLN-CVI-007 and CLN-CVI-4047. The various iterations of the CapsoCam® Colon (CV-2) device were developed with the intention of improving the visualization ability, user friendliness, and manufacturability of the device. The iterations primarily consisted of altering the balloon or outer shell design, the enteric coating formulation, and/or varying the center of gravity of the capsule.

Clinical protocol CLN-CVI-007

A clinical study was performed based on Clinical protocol CLN-CVI-007. The clinical study evaluated the performance of the CapsoVision CapsoCam® Colon capsule in 59 of 79 total enrolled subjects at one (1) Investigational Site. The investigational site obtained the necessary IRB approval prior to enrollment of any study subject. The majority of screened subjects were considered eligible for the study. After pre-procedure preparation, capsules were ingested and retrieved using the CapsoRetreive® system. Following retrieval of the CapsoCam® capsule endoscope, the capsule images were downloaded using the Capsule Data Access System (CDAS3) and read by the study Investigator using the CapsoView® Software (CVV).

Of the 59 subjects who ingested versions A, B, C, or D of the CapsoCam® Colon Capsule during the study, thirty-five (35) are defined as CapsoCam® Colon Capsule Study Completers who: 1) ingested the version D of the CapsoCam® Colon Capsule during the study and 2) had complete and interpretable small bowel imaging and imaging of the colonic mucosa. Four (4) subjects not classified as Completers experienced temporary gastric or small bowel retention resulting in incomplete or no images of the small bowel and/or of the colonic mucosa. One (1) subject not classified as a Completer had uninterpretable images due to technical difficulties with image recording. The remaining nineteen (19) not classified as Completers ingested the version A, B, or C of the CapsoCam® Colon (CV- 2) Capsule.

The CapsoCam® Colon Capsule Study outcomes and conclusions are based upon analysis of data from the 35 subjects in the CapsoCam® Colon Capsule Study Completer Cohort defined as subjects who: 1) ingested the CV-2 version D of the CapsoCam® Colon Capsule during the study and 2) had complete and interpretable small bowel imaging and imaging of the colonic mucosa. The CapsoCam® Colon Capsule version D is the version of the capsule for which CE mark is being pursued.
The conclusions reached through the analysis of the CapsoCam® Colon Capsule Study Completer Cohort are as follows:

Based upon the results of the clinical evaluation in the CapsoCam® Colon Capsule Endoscope Completer Cohort (n =35 subjects), the CapsoCam® Colon Capsule Endoscope has been proven to be safe and effective.

Safety of clinical prescription of the CapsoCam® Colon Capsule Endoscope has been demonstrated by the absence of Serious or Unanticipated Adverse Events. There were no capsule retentions defined as subjects retaining the capsule after resuming post procedural food ingestion. All capsules in this cohort, and the overall per protocol study cohort who ingested (swallowed) study capsules, were excreted. In all cases of capsule ingestions and excretions, the deflated balloons remained securely attached to the capsules.

The subjects experienced few adverse events overall with the exception of a small number of anticipated bowel preparation and booster regimen adverse events, for example, nausea, limited episodic vomiting, and modest abdominal discomfort. These bowel-preparation related adverse events are known to be possible whenever bowel preparations are administered and are well characterized in their manufacturers' prescription information. All bowel preparation and boosters used in the study and possible adverse events were described in the protocol and to the subjects during the screening and enrollment phases of the study. Virtually all research subjects found the bowel preparation and boosters regimens tolerable and stated that they would be willing to undergo colon capsule endoscopy again if prescribed by their physicians.

Efficacy of the device has been demonstrated by the CapsoCam® Colon Capsule Endoscope meeting the objectives of the study as outlined in the protocol defined information to be gained from the study:

The CapsoCam® Colon Capsule Endoscope captures diagnostic quality images throughout the small bowel and colon, provided the subject (patient) follows the bowel preparation and booster regimen instructions defined for optimal use of the capsule. The capsule operational time has been demonstrated to be adequate for the capsule to capture both small bowel and colon images during the diagnostic evaluation. And, finally, recorded images are successfully downloaded using the Capsule Data Access System (CDAS3) utilizing the current versions of the CapsoView® Software (CVV) in both Mac and PC formats and thus available for physicians to review and interpretation of clinical results.

Clinical protocol CLN-CVI-4047

The CapsoCam® Colon (CV-2) study is currently being conducted based on clinical protocol CLN-CVI-4047 at one (1) investigational site, with the intended use of visualizing the colon mucosa. The clinical feasibility study, with anticipated completion Q4-2020, evaluates the performance of the CapsoCam® Colon (CV-2) (versions D-G). The investigational site obtained the necessary IRB approval prior to enrollment of study subjects. The majority of screened subjects have been eligible for study participation. After pre-procedure preparation, capsules were ingested and retrieved using the CapsoRetreive® system. Following retrieval of the CapsoCam® Colon (CV-2), the capsule images were downloaded using the Capsule Data Access System (CDAS) and read by the study Investigator using the CapsoView® Software (CVV).

As of 4/23/2023, the clinical study has evaluated the performance of the CapsoCam® Colon (CV-2) in three hundred ninety-seven (397) subjects, defined as subjects who were initially screened and signed the study consent form. Of these 397 consented subjects, three hundred sixty-nine (369) subjects ingested the CapsoCam® Colon (CV-2) during the study. Two hundred forty-four (244) of the 369 subjects (66.1%) excreted within the targeted time of 24 hours and had interpretable imaging of the colonic mucosa.

There were no capsule retentions after resuming post procedural food ingestion and all capsules were excreted with the balloons still securely attached. The subjects experienced few adverse events overall with the exception of a small number of anticipated bowel preparation and booster regimen adverse events; for example, nausea, limited episodic vomiting, and modest abdominal discomfort. These bowel-preparation related adverse events are known to be possible whenever bowel preparations are administered and are well characterized in their manufacturer's prescription information. In addition, one subject had an allergic reaction to the bowel preparation (MoviPrep). The patient was administered Benadryl in the emergency room and withdrew from the study before ingesting the capsule. Virtually all other research subjects found the bowel preparation and boosters regimens tolerable and stated that they would be willing to undergo colon capsule endoscopy again, if prescribed by their physicians.

The recorded images from all capsules were successfully downloaded using the Capsule Data Access System (CDAS) utilizing the current versions of the CapsoView® Software (CVV) and thus available for the independent readers to review and evaluate the imaging quality. Based on the independent reader reports, who rated each region of the colon with a segment score from 0-3 (where anything above 2 is considered adequate), the CapsoCam® Colon (CV-2) captures diagnostic quality images throughout the colon (and the small bowel), provided the study subject follows the bowel preparation and booster regimen instructions defined for optimal use of the capsule.

In addition, the capsules target operational life (as outlined in the Device Description, Section 3) exceeded the total transit times for the one-hundred-forty-nine (149) of the 190 subjects (78.4%) in the CapsoCam® Colon (CV-2) Study Completer Cohort.

Based upon the interim results of the clinical evaluation of the CapsoCam® Colon (CV-2) Completer Cohort (n =149 subjects), outlined above, the outcome demonstrates preliminary safety of clinical administration of the CapsoCam® Colon (CV-2) versions, as shown by the absence of serious or unanticipated adverse events, and effectiveness.

Finally, out of the 190 subjects who ingested CapsoCam® Colon (CV-2), fifty-seven (57) subjects ingested CapsoCam® Colon (CV-2) version E, which as discussed above, is exactly the same capsule as CapsoCam® Colon (CV-3), with the only exception that the CV-3 version also comprises the structured light size measurement technology. The remaining one-hundred-thirty-three (133) subjects ingested one of the other CapsoCam® Colon (CV-2) versions (D, F, or G).

Clinical protocol CLN-CVI-5248

This pilot study was undertaken to assess the safety and performance of the CapsoCam® Colon capsule and inform the larger planned, Pivotal study. One hundred-twelve subjects (112) were enrolled (ingested the capsule) at five (5) investigational sites including locations in California, Florida, Michigan and Ohio. More site details are located in Table 1. One hundred-ten capsules (110) were returned after ingestion. Two (2) capsules were lost in the study (1 by mail courier, 1 subject failed to use the retrieval kit), two (2) subjects did not complete colonoscopy after capsule swallow (1 withdrawal, 1 anesthesia contraindicated arrhythmia). Two (2) capsule videos contained images that were too dim to be of diagnostic quality due to capsule malfunction and were deemed technical failures. One site failed to capture any colonoscopy images or video or provide usable polyp size estimates in one (1) subject leading to exclusion. Intent-to-treat analysis includes all 112 subjects, per protocol analysis includes 105 subjects.

The largest polyps (which are $\geq$6 mm) on colonoscopy were compared to capsule findings according to size and location. A match for a subject was considered to have occurred if the largest (reference) polyp $\geq$ 6 mm identified on colonoscopy was matched by size ($\pm$ 50%) and location (same or adjacent colon segment) with a polyp identified on capsule video. Positive Percent Agreement (sensitivity) and Negative Percent Agreement (specificity) were calculated for each reader. The overall PPA/NPA for polyps $\geq$6 mm for 105 subjects were 84.8% and 92.7% respectively with a prevalence of 21.9%. Overall PPA/NPA for polyps $\geq$10 mm were 87.5% and 99.0% respectively with a prevalence of 7.6%. Detection of sessile serrated polyps $\geq$ 6mm was also analyzed and PPA was 87.5% for both readers with a prevalence of 3.8% in the study. The 95% confidence interval (CI) for PPA for polyps $\geq$ 6 mm was 71.1 - 98.5%.

Complete examination was considered to have occurred when readers were able to visualize excretion. Complete examination was assessed for all returned capsules (110) and was shown to occur in 76% of study participants. In two instances the capsules were removed during next day colonoscopy, while still recording and thus were not considered to be complete examinations.

Capsule safety was confirmed with no reports of device related adverse events, serious adverse events or unanticipated adverse device effects. All events and observations reported in the study were not related to the study or related to medications for bowel preparation or to the prokinetic boosters. There were no serious adverse events reported for bowel preparation or booster consumption.

Based on the results of the study, the safety profile remains the same CapsoCam Colon capsule.