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Medtronic

Statistical Analysis Plan

Clinical Investigation Plan Title	A prospective single-center pilot study evaluating the technical feasibility of mucosal staining during Colon Capsule Endoscopy (CCE) procedure in Colorectal Cancer (CRC) high risk population, when using MB-MMX (SPICE study)
Clinical Investigation Plan Identifier	MDT20062
Clinical Investigation Plan Version	Ver.4.0
Statistical Analysis Plan Version Date	Ver.1.0, 23-Jun-2022
Sponsor/Local Sponsor	Given Imaging Ltd., an indirect wholly owned subsidiary of Medtronic plc. ("Medtronic") 2 Hacarmel St. New Industrial Park, P.O. Box 258 Yokneam 2066724, Phone: +972 (4) 909-7700 Local Sponsor (EU legal representative) Covidien Services Europe Ltd, an indirect wholly owned subsidiary of Medtronic plc. Block 3090-3094, Lake Drive Citywest Business Campus, Dublin D24 Xn47 Ireland

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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Naama Schwartz, PhD, Senior biostatistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
CCE	Colon Capsule Endoscopy
CIP	Clinical Investigation Plan
CRC	Colorectal Cancer
FAS	Full Analysis Set
MB-MMX	Per-oral Methylene Blue Formulation
PPAS	Per Protocol Analysis Set
SAP	Statistical Analysis Plan
95%CI	95% Confidence Interval

3. Introduction

Given Imaging Ltd. (an indirect wholly owned subsidiary of Medtronic plc.) is sponsoring the SPICE study, a prospective single-center open-label pilot clinical study. The purpose of this study is to evaluate the technical feasibility of mucosal staining during capsule endoscopy (PillCam™ COLON2) procedure when using MB-MMX as mucosal enhancement technique. The study will be conducted in population with high risk for CRC. The MDT20062 SPICE Study Clinical Investigation Plan (CIP) Ver.4.0 16-Jun-2022 document was used to formulate this SAP.

4. Study Objectives

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

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

5. Investigation Plan

This is a single-center, prospective, non-randomized, open label pre-market clinical trial, designed to evaluate the technical feasibility during CCE procedure, when using MB-MMX as a contrast- enhancement technique of mucosal staining in CRC high risk population. Up to 15 subjects, 45-75 years old, classified as being at high risk for CRC, will be enrolled in 1 site in Spain. Subjects will undergo a standard bowel preparation (4L PEG), including 200 mg Methylthioninium chloride, corresponding to 8 tablets of 25 mg MB-MMX (per product's instructions for use) and will undergo a CCE procedure. An experienced

Gastroenterologist will read the CCE procedure and complete a subjective questionnaire, to evaluate mucosal enhancement during a CCE procedure, when using MB-MMX as a contrast-enhancement technique.

This is an initial pilot study with descriptive endpoints.

6. Determination of Sample Size

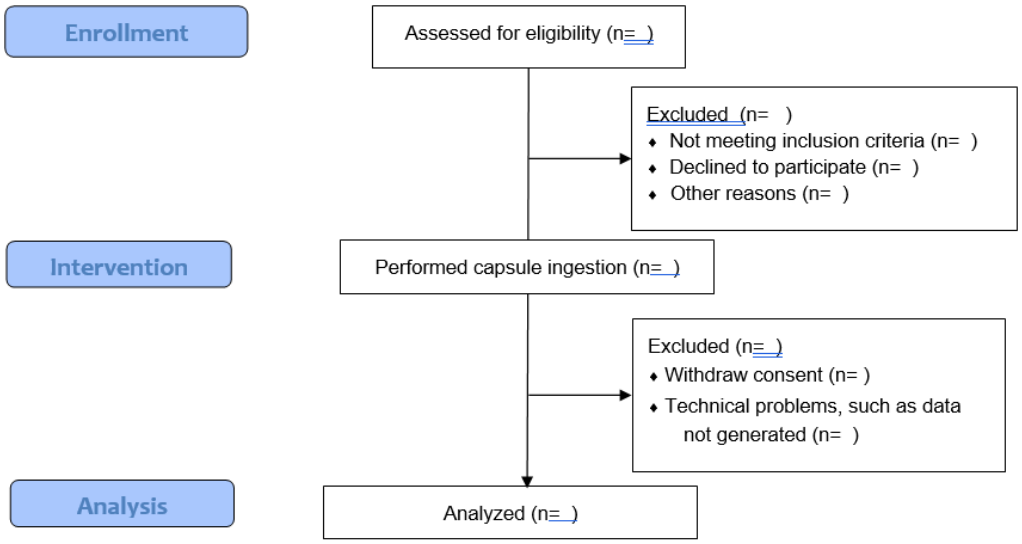
This is a single-center, prospective, non-randomized clinical trial aimed to evaluate technical feasibility with descriptive endpoint(s), thus, no formal sample size was calculated and up to 15 patients are planned to be enrolled to this study. No interim analysis is planned.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

The following flow diagram will be presented



7.1.2 Clinical Investigation Plan (CIP) Deviations

Except from the eligibility criteria and informed consent deviations, bowel preparation related deviations and MB-MMX intake deviations will be reported.

The deviations will be presented with a designated table (for more than 1 deviation for the entire trial), stating the relevant information (subject#, deviation date, deviation description, result of the deviation {excluded from the per-protocol analysis set for example}.

7.1.3 Analysis Sets

Full Analysis Set (FAS) - includes all enrolled subjects who:

- Signed the informed consent **and**
- Satisfied the eligibility criteria **and**
- Ingested the PillCam™ COLON2 capsule

Full analysis set (FAS) will include all of the subjects the ingested the capsule and will be used for subject disposition, population and procedures description, for performance and for Safety analyses.

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

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

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

In addition, as there was an amendment to the CIP, and as a result, the 5 first subjects received a split dose PEG regimen and the rest received a single dose of PEG regimen, a sub-group analysis will be performed as well according to the prep regimen.

7.2 General Methodology

This is a single-center, prospective, non-randomized clinical trial designed to evaluate the technical feasibility (descriptive) of mucosal staining during CCE procedure, using MB-MMX, in CRC high risk population. As a result, the methods for analysis will be descriptive in nature (frequency and percent as well as distribution measures such as: mean, standard deviation, median and range). 95% confidence intervals (95%CI) will be presented as well.

In any case of post hoc analysis which will include statistical testing, P-value<0.05 will be considered significant.

7.3 Center Pooling

Not applicable, single center study

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

All available data will be included in the data listings and tabulations.

7.5 Adjustments for Multiple Comparisons

Not applicable.

7.6 Demographic and Other Baseline Characteristics

Demographic and other characteristics will be provided. Summary statistics (arithmetic mean, standard deviation, and range for quantitative variables) will be presented for the total study population. Frequency tables for qualitative data will be provided.

7.7 Treatment Characteristics

The procedure stages will be presented as well. For example, the compliance rate for the preparation and the MB-MMX tablets intake will be reported as frequency and rate. Concomitant medications will be listed and summarized by indication.

7.8 Interim Analyses

No interim analyses are planned.

7.9 Evaluation of Objectives

Primary objectives/endpoints analysis

Polyp enhancement

For each subject, the images with polyps that were detected from the COLON2 Capsule Endoscopy procedure will be considered, i.e. the final sample size for this analysis is the number of images with polyps (one image per polyp) - the analyzed unit is the polyp image. For each polyp the reader will indicate if there was a contrast between the polyp and the healthy mucosa (yes/no). Out of the entire polyp images (from all of the subjects together), the percent of colonic polyps which have a visible contrast to the healthy colonic mucosa will be presented along 95%CI.

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

Detrimental effect

For each subject, each of the colonic segments (5 segments per subject) will be evaluated for the interference level of detrimental effects, i.e. the final sample size for this analysis will be up to 75 colonic segments - the analyzed unit is the colonic segment. For each segment the reader will indicate the level of interference according to a 5-point scale (1 =no interference to 5= high interference).

The level of interference refers to the detrimental effects on the visualization of the colonic mucosa during CCE, due to use of MB-MMX (detrimental effect will be considered as any observation, such as an excessive blue dye deposit, dark and dim appearance of the tissue, interfering with tissue visualization). Analysis of this endpoint will include summary statistics (arithmetic mean, standard deviation, median and range) as well as frequency and percent of each scale level.

The rate of colonic segments with high level of interference (i.e. 4-5 levels) out of the entire sample of segments will be presented along 95%CI.

Secondary objectives/endpoints analysis

All AEs will be reported by number, type, relatedness (device/procedure), seriousness, severity and duration. All AEs will be captured, regardless of severity. The percent of cases with at least one AE out of the total cases, will be presented with 95%CI. All of the available information will be analyzed according to the CIP criteria (inclusion, exclusion, deviations etc.).

7.10 Safety Evaluation

Explained in section 7.9, as the safety is the secondary objective of this study. In addition, any device deficiencies that could led to a serious AE will be described. In case of deaths, a list of deaths with reasons will be provided as well.

8. Validation Requirements

A level III validation will be required for the study, due to its nature (small scale descriptive study).