Vibrant Ltd.

Study Protocol: V-240

Study number: NCT03031301

Protocol number: 240CLD
Protocol Date: December 6th, 2017, Rev. 03

A prospective, multicenter, randomized, double-blind, Sham-controlled study to assess the efficacy and safety of the Vibrant capsule administered 5 times per week

1. Sponsor Statement of compliance

The sponsor of this study, Vibrant Ltd., manufacturer of the investigational device, legally represented by Lior Ben-Tsur, Chief Executive Officer, states the following:

a. to assume responsibility related to the clinical investigation;
b. that the treatments used to perform the clinical study are adequate for the device under investigation;
c. that the clinical study, as for the responsibility of the manufacturer, will be conducted in conformance with:

The Federal Food, Drug, and Cosmetic Act, as amended, and regulations promulgated thereunder ("the Act") and the United States Food and Drug Administration ("FDA") regulations governing the protection of human subjects and regulations governing clinical investigators, The World Medical Association Declaration of Helsinki, titled "Ethical Principles for Medical Research Involving Human Subjects", ICH/GCP guidelines, Applicable relevant national legislation, HIPAA as defined in 45. C.F.R. section 164.501 or relevant national equivalent and following revisions or other analogous internationally recognized standards, to be specified, and only after the approval, by the competent Ethics Committee, of the investigational protocol, the informed consent and the documentation required by the above mentioned standards;

Print Name: Signature: Date:

[redacted] ---------- ----------

2. Investigator Agreement:

Prior to participation in this study, a written approval must be obtained from the Institutional Review Board, and copy should be provided to the Sponsor, Vibrant Ltd., or their authorized representatives, along with the Institutional Review Board approved Informed Consent Form.

The Principal Investigator must also:

- Conduct the study in accordance with the study protocol, the Investigator Agreement, Declaration of Helsinki, Good Clinical Practices, international harmonized standards for clinical investigation of medical devices (Title 21 of the Code of Federal Regulations (21 CFR), part 812 (Investigational Device Exemptions), the laws and regulations of the countries where the study will take place, indemnity/insurance requirements and any other applicable regulations.
- Agree to participate in an appropriate training program as part of the study initiation.
- Assure that informed consent is obtained from each subject prior to enrollment, using the Institutional Review Board approved form.
- Assure that the study is not commenced until Institutional Review Board approval has been obtained.
- Provide all required data and agree to source document verification of study data with subject's medical records.
- Allow staff of the Sponsor and its authorized representatives, as well as representatives from regulatory agencies, to review, inspect and copy any documents pertaining to this clinical investigation.

The Principal Investigator (PI) may delegate one or more of the above functions to an associate or sub-investigator. However, the PI retains overall responsibility for proper conduct of the study, including obtaining and documenting subject informed consent, compliance with the study protocol, and the collection of all required data.

Principal Investigator Statement:
I the undersigned, have reviewed this protocol and agree to conduct this study in adherence to the study protocol, GCP (Good Clinical Practice) compliance, Ethical principles set forth in the declaration of Helsinki and authority regulations for the protection of human subjects participating in clinical trials.

Print Name:	Signature:	Date:
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3. List of Abbreviations

%	Percent
AE	Adverse Event
ADE	Adverse Device Effect
AGA	American Gastroenterological Association
AR	Authorized Representative
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CSBM	Complete Spontaneous Bowel Movement
eCRF	Electronic Case Report Form
CI	Confidence Interval
CIC	Chronic Idiopathic Constipation
DSMB	Data and Safety Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
FA	Full Analysis Set
FC	Functional Constipation
GCP	Good Clinical Practice
FDA	Food and Drug Administration
IBS-C	Irritable Bowel Syndrome with Constipation
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFU	Instruction for Use
IRB	Institutional Review Board
ISF	Investigator Site Files
ITT	Intent To Treat
Mg	Milligram
µg	Microgram
Min	minute(s)
MFR	Manufacturer
NCAs	National Competent Authorities
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
mITT	Modified Intent to Treat
OTC	Over The Counter
PAC-QOL	Patient Assessment of Constipation Quality of Life questionnaire
PEG	Polyethylene glycol
PI	Principal Investigator
PP	Per Protocol
QOL	Quality of life
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SBM	Spontaneous Bowel Movement
TSQM	Treatment Satisfaction Questionnaire for Medication
US	United States
USADE	Unanticipated Serious Adverse Device Effect

4. Protocol Synopsis

Name	A prospective, multicenter, randomized, double-blind, Sham-controlled study to assess the efficacy and safety of the Vibrant capsule administered 5 times per week
Indication	The Vibrant Capsule is intended for the treatment of subjects with Functional Constipation.
Objectives	The objectives are to assess the efficacy and safety of the Vibrant capsule administered 5 times per week
Design	The study is a prospective, adaptive, multicenter, randomized, double-blind, Sham-controlled study, to evaluate the efficacy and safety of the Vibrant Capsule in relieving constipation in subjects with functional constipation. Two arms will be assessed: - Vibrant Capsule administered 5 times per week - Sham Capsule administered 5 times per week The study will be performed in up to 40 centers in the USA. One interim analysis will be performed after at least 120 evaluable subjects will complete the study. The following parameters will be assessed: primary endpoint, tolerability and main safety parameters. Depending on the results of the interim analyis: • The study will be stopped, • The study will continue as planned, • The sample size will be increased. Subjects will be followed continuously for an approximatively 2 week run-in period and then will be randomized to either Vibrant or Sham capsules for a treatment period of 8 weeks. Data reporting will be done on an electronic Case Report Form (eCRF) and an eDiary. Subjects will be asked to refrain from taking any medication or supplement to relieve their constipation, during the entire study period except as allowed under the protocol. After the run-in period, the subjects will return and eligibility will be re-assessed. Subjects will be trained on how to use the base unit and will swallow the first capsule on site the day of baseline visit. They will activate and ingest the rest of the capsules at home by themselves, using the base unit. Subjects will be instructed to complete a simple subject eDiary each day throughout the duration of the study. A final visit will take place at the end of the 8 week treatment period.

	Subjects will receive phone calls at least once a week and subject compliance will be monitored during the 8 weeks of the study. Subjects will stop using all medication or supplement to relieve constipation during the entire study period and comply to use constipation aid only for rescue. Subjects will be authorized to use rescue medication after 3 consecutive days without a bowel movement. Subjects will report their daily bowel movements and use of medication using the eDiary. Data about time of activation of the capsules will be automatically registered and transmitted by the base unit. Subjects will be requested to ingest the capsules at a specific time of the day.
Study duration	Study duration is 10 to 11 weeks - 2 to 3 weeks of run-in - 8 weeks of treatment
Endpoints	The two primary efficacy endpoints are the CSBM1 success rate, defined as an increase from the run-in period of at least one weekly Complete Spontaneous Bowel Movement (CSBM) during at least 6 of the 8 weeks of treatment, and CSBM2 success rate, defined as an increase from the run-in period of at least two weekly Complete Spontaneous Bowel Movement (CSBM) during at least 6 of the 8 weeks of treatment. Secondary efficacy endpoints include: - Change from baseline (run-in period) in average straining. - Change from baseline (run-in period) in average stool consistency, using the Bristol Stool Scale - Change from baseline (run-in period) in average bloating. - SBM success rate, defined as as an increase from the run-in period of at least one weekly Spontaneous Bowel Movement (SBM) during at least 6 of the 8 weeks of treatment. Additional efficacy endpoints - Change from baseline (run-in period) in weekly number of Spontaneous Bowel Movement (SBM). - Change from baseline (run-in period) in weekly number of Complete Spontaneous Bowel Movement (CSBM). - Change from baseline (run-in period) in average abdominal gas. - Change from baseline (run-in period) in average abdominal pain. - Change from baseline (run-in period) in abdominal discomfort. - Time to occurrence of spontaneous bowel movement after first capsule activation. - Treatment satisfaction score using the TSQM (Treatment Satisfaction Questionnaire for Medication)

	- Change from baseline (run-in period) in quality of life using the PAC-QOL (Patient Assessment of Constipation Quality of Life) questionnaire. - Ease of use of the device. Safety endpoints include all adverse events related and unrelated to the study treatment.
Subject Population	Subjects with Functional Constipation refractory to existing treatments.
No. of Subjects	The study is planned to enroll approximately 238 subjects.
Inclusion criteria	1. Subjects aged 22 years and older 2. Subjects with Chronic Idiopathic Constipation (CIC) according to Rome III criteria and who have not experienced relief of their symptoms from available therapies (osmotic and stimulant laxatives used for at least one month at recommended dose) 3. Subjects with an average of <3 Spontaneous Bowel Movements (SBM) per week and ≥1 SBM per week 4. Normal colonoscopy performed within 10 years prior to study participation, unless the subjects are <50 years old and without alarm signs and/or symptoms 5. Subject signed the Informed Consent Form (ICF) 6. Female subjects must have a negative blood pregnancy test during screening, confirmed by a negative urine pregnancy test during baseline and must not be lactating prior to receiving study medication. For females of child-bearing potential, a hormonal (i.e., oral, implantable, or injectable) and single-barrier method, or a double-barrier method of birth control must be used throughout the study. All other female subjects must have the reason for their inability to bear children documented in the medical record [i.e., tubal ligation, hysterectomy, or post-menopausal (defined as a minimum of one year since the last menstrual period)]; in these circumstances, a pregnancy test will not be necessary.
Exclusion criteria	1. History of complicated/obstructive diverticular disease 2. History of intestinal or colonic obstruction, or suspected intestinal obstruction. 3. History of significant gastrointestinal disorder, including any form of inflammatory bowel disease or gastrointestinal malignancy (celiac disease is accepted if the subject has been treated and is in remission) 4. History of gastroparesis 5. Use of any of the following medications:

	○ Medications that may affect intestinal motility, prokinetics, anti-depressants, anti-Parkinsonian medications, opiates, opioids, calcium-channel blockers, aluminum/magnesium hydroxide ○ With the exception of antidepressants, thyroid or hormonal replacement therapy, when the subject has been on a stable dose for at least 3 months prior to enrollment. 6. Clinical evidence of significant respiratory, cardiovascular, renal, hepatic, biliary, endocrine, psychiatric or neurologic disease. 7. Presence of cardiac pacemaker or gastric electrical stimulator. 8. History of, or current eating disorders, such as anorexia, bulimia, or compulsory overeating. 9. Diagnosis of mega-rectum or colon, congenital anorectal malformation, clinically significant rectocele, history of intestinal resection (with an exception for appendectomy, cholecystectomy and inguinal hernia repair), history of bariatric surgery or evidence of any structural abnormality of the gastrointestinal tract that might affect transit 10. History of Zenker's diverticulum, dysphagia, Barrett's esophagus, esophageal stricture or achalasia 11. Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs): chronic use is defined as taking full dose NSAIDs more than three times a week for at least six months. Subjects on cardiac doses of aspirin may be enrolled in the study 12. Subjects with pelvic floor dysfunction/defecatory disorder, based on subject history 13. Participation in another clinical study within one month prior to screening. 14. Women who are pregnant or lactating 15. Use of any medication for constipation relief during the study, except as rescue medication, as indicated by study rules 16. Inability to use an electronic daily Diary (on a computer, phone application, tablet or other electronic device) to report bowel movements, symptoms and medication usage 17. Subject participated in a previous Vibrant study 18. Any other condition which in the opinion of the investigator may adversely affect the safety of the subject or would limit the subject's ability to complete the study
Statistical analysis	Study Hypotheses: In this study, we will test the following hypotheses: • $H_0 : P_{a1}-P_{s1}=0$ • $H_1: P_{a1}-P_{s1}\neq 0$

Where P_{a1} is the CSBM1 success rate in the active arm, and P_{s1}, the CSBM1 success rate in the sham arm.
AND:

- $H_0 : P_{a2}-P_{s2}=0$
- $H_1: P_{a2}-P_{s2}\neq 0$

Where P_{a2} is the CSBM2 success rate in the active arm, and P_{s2}, the CSBM2 success rate in the sham arm

Sample size:
A sample size is calculated to test both null hypotheses. Calculations (using SAS® proc power) show that a sample size of a total of 214 subjects (107 in each arm), would provide 80% power at astudywise 5% level of significance, i.e. 2.5% for each one of the two primary endpoints) , to detect a difference of 20% in the success rate, assuming a success rate of 25% in the sham arm.
The sample size will be increased to at least 238 subjects (119 in each arm) to account for a potential 10% of drop-outs.

Major Efficacy Analyses:
The subject's CSBM1 success status (i.e. if the subjects achieve an increase from baseline of at least 1 weekly CSBM during at least 6 out of the 8 treatment weeks) will be modeled and compared between the study arm with a logistic regression model, with the baseline weekly number of CSBM and site as covariates. The adjusted success rate per study arm, and their difference between the groups will be presented along with their respective 95% Confidence Intervals (CI).
The CSBM2 success rate will be analyzed in the same manner.
The SBM success rate will be analyzed a similar manner.

5. INTRODUCTION

This document is a clinical research protocol and the described study will be conducted in compliance with the protocol, standards of Good Clinical Practices and associated regulations, and all applicable research requirements.

6. BACKGROUND

Chronic constipation is a common gastrointestinal disorder in the general population. It is estimated that chronic constipation affects between 2 and 27% of the population. A majority of chronic constipation sufferers are women, who represent three-fourths of those affected[1].

Constipation may be primary (Chronic Idiopathic Constipation (CIC), Irritable Bowel Syndrome with Constipation (IBS-C)) or secondary to other factors (such as drugs like opioids, colorectal cancer, diabetes, Parkinson's disease or spinal cord injury). It is estimated that 100 million adults in the United States (US) have chronic pain[2].

There is no widely accepted definition of chronic constipation. Although physicians often define constipation based on stool frequency, subjects experience constipation as a multi-symptom disorder that includes infrequent bowel movements, hard or lumpy stools, straining, bloating, a feeling of incomplete evacuation after a bowel movement and abdominal discomfort[3]. The Rome Foundation has created symptom-based diagnostic criteria for chronic constipation. To meet the definition of chronic constipation, the criteria must be fulfilled for the prior 3 months with symptom onset at least 6 months prior to diagnosis[4].

Chronic constipation impacts quality of life and is perceived by subjects as a severe disease[3]. Adding to the burden of disease, constipation is among the ten most expensive gastrointestinal diseases in terms of direct and indirect healthcare costs[5]. A recent systematic review of the disease burden of IBS and CIC found the attributable direct costs of IBS to range from approximately $1,600 to $7,500 per subject-year, whereas the attributable direct costs of CIC range from approximately $1,900 to $7,500 per subject-year[6].

Although a variety of treatment options are available for chronic constipation, subjects have reported low satisfaction with current treatment alternatives in multiple published studies. Thus, there is a need for additional therapeutic options that address subject symptoms and preferences.

Constipation Management

The American Gastroenterological Association (AGA) has established a treatment algorithm for constipation that provides multiple therapeutic steps depending on severity of symptoms. See http://www.gastrojournal.org/article/S0016-5085(12)01545-4/pdf. The first step in the treatment of constipation focuses on lifestyle modification with three main parameters: adequate fluid intake, a high fiber diet and regular physical activity.

Fiber absorbs water, increases stool bulk, and in doing so stimulates the bowel to decrease stool transit time and ease evacuation. Medicinal and dietary fiber supplements, such as psyllium, can be added to the high fiber diet or used as primary therapy.

If lifestyle modification does not produce satisfactory results, subjects have access to a number of FDA-approved products (Food and Drug Administration), available both over the counter (OTC) and by prescription. Stool softeners (docusate sodium, docusate calcium) act by decreasing surface tension to allow water to enter the bowel more readily, making the stool softer, which makes it easier and less painful to pass. However, there is currently limited data on the efficacy of stool softeners in subjects with constipation[1].

Osmotic laxatives are also available, including polyethylene glycol (PEG), lactulose, magnesium hydroxide, magnesium citrate, magnesium sulfate, and sodium phosphate. PEG and lactulose have been shown to improve stool frequency and stool consistency[1,6,7].

Osmotic laxatives contain poorly absorbed ions or molecules that retain water in the intestinal lumen. Although effective, they can cause bloating and cramping. In addition, due to their mechanism of action, they should be used with caution in older adults and in subjects with renal impairment because of the risk of dehydration and electrolyte disturbances.

Stimulant laxatives include senna, bisacodyl or sodium picosulphate. They induce fluid and electrolyte secretion by the colon or induce peristalsis in the colon, thereby producing a bowel movement.

Recent advances in research have resulted in new classes of medication for the treatment of constipation, available on prescription. For example, linaclotide is an agonist of guanylate cyclase-C receptors, and increases chloride, bicarbonate and fluid secretion into the intestinal lumen, lubricating the stool and accelerating gastrointestinal transit. Linaclotide was FDA-approved in 2012 for CIC and IBS-C. Adverse events include diarrhea, which leads to discontinuation of the medication in approximately 5% of subjects[8]. In total, 8% of subjects in linaclotide clinical trials discontinued due to adverse events, and 27% had their dose reduced or suspended secondary to adverse reactions, the majority of which were diarrhea or other gastrointestinal adverse reactions. See http://www.accessdata.fda.gov/drugsatfda_docs/label/ 2014/202811s004lbl.pdf

Lubiprostone is approved for use in women with IBS-C and in men and women with CIC, as well as opioid-induced constipation in subjects with non-cancer pain. It is a selective chloride channel activator, increasing ion and fluid secretion. The main adverse events associated with lubiprostone are mild to moderate nausea and diarrhea[2,9].

Approximately 29% of subjects who received lubiprostone 24 mcg twice daily in clinical trials experienced nausea; 4% of subjects had severe nausea while 9% of subjects discontinued treatment due to nausea. Approximately 12% of subjects who received lubiprostone 24 mcg twice daily experienced diarrhea; 2% had severe diarrhea while 2% discontinued treatment due to diarrhea. In addition, it has been reported to cause dyspnea, which was reported in 2.5% of the treated chronic idiopathic constipation population and 0.4% in the treated IBS-C population. Although not classified as serious adverse events, some subjects discontinued treatment because of this event. These events have usually been described as a sensation of chest tightness and difficulty taking in a breath, and generally have an acute onset within 30-60 minutes after taking the first dose. They generally resolve within a few hours after taking the dose, but recurrence has been frequently reported with subsequent doses. See http://www.accessdata.fda.gov/drugsatfda_docs/label/ 2008/021908s005lbl.pdf.

In subjects with severe chronic constipation, surgery may be considered; however, it is generally limited to use in the most severe cases after medical management has failed to provide adequate relief. In subjects with severe incapacitating slow transit constipation, colectomy with ileorectal anastomosis can improve constipation and related symptoms[10,11].

In summary, while there are a variety of treatments available for constipation, there is currently no satisfactory treatment for many constipated subjects: a US study showed that 47% of constipated subjects are not completely satisfied with their current constipation treatment[3], while a European study showed that only 27% of European subjects are satisfied with current treatment options[5]. Furthermore, many subjects become refractory to one or more OTC laxatives with chronic use, which may cause frustration for both the clinician and the subject, and ultimately leads many subjects to abandon therapy and remain dissatisfied with their condition[2]. Nearly 90% of subjects express interest in new therapies[12].

7. DEVICE NAME AND INTENDED USE

7.1 Device Name

Vibrant Capsule

7.2 Intended Use

The Vibrant Capsule is an orally administrated capsule intended for the treatment of Functional Constipation (FC) in subjects aged 22 years or older.

8. DEVICE DESCRIPTION

The Vibrant Capsule is designed to mechanically induce a peristaltic wave in the large intestine, thus aiding in relieving constipated subjects. Constipation relief is achieved by the capsule's vibrations impinging on the gastrointestinal wall, consequently inducing peristaltic activity which promotes transit and facilitates defecation.

The Vibrant Capsule has several important features:

- Small Dimensions.
- Easy to swallow (smooth shell).
- [redacted]

8.1 Capsule

T[redacted]

Figure 1. The capsule and components

[redacted]

Figure 2. The blister of 10 capsules

8.2 Accessory: activation base unit

A user friendly activation base was developed by the company for subject use ( ). The activation base (or base unit) is meant to be used at home by subjects. The base unit is easy to use and requires a simple training before taking it home. Subjects will activate the capsule themselves at home.

7)

Setting up the base unit

Activation of the Vibrant Capsule using the base unit

8.3 Mode of operation

[redacted]

9. RISKS & BENEFITS

The Vibrant Capsule is designed according to international standards for medical devices. Compliance with these standards ensures that the device can be used safely in human beings.
Biocompatible materials are used for the vibrating capsule components. The use of biocompatible materials should protect the subject of any hazardous from possible adverse events.

The device classification according to ISO10993-1 and FDA's guidance *Use of International Standard ISO-10993-1:2009, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" : Draft Guidance for Industry and Food and Drug Administration Staff* ("FDA Biocompatibility Guidance") is as follows:
Category: Surface device.
Contact duration: permanent contact (>30 days)
Contact: breached or compromised surfaces.

[redacted]

9.1 Risks

The Vibrant capsule has been designed to mechanically induce a normal peristaltic wave in the large intestine, thus aiding in relieving constipated subjects.

The capsule moves through the gastrointestinal system, without interacting with any other body system and does not deliver medication of any kind. The Vibrant capsule targets basic pathophysiological factors contributing to chronic constipation by inducing intrinsic contractile activity without using chemical supplements. The capsule operates without any biological interference.

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Device manufacturing and assembly is done in an ISO 13485:2003 facility.

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12. STUDY OBJECTIVE

The objectives are to assess the efficacy and safety of the Vibrant capsule administered 5 times per week.

13. STUDY ENDPOINTS

13.1 Primary endpoint

The two primary efficacy endpoints are the CSBM1 success rate, defined as an increase from the run-in period of at least one weekly Complete Spontaneous Bowel Movement (CSBM) during at least 6 of the 8 weeks of treatment, and CSBM2 success rate, defined as an increase from the run-in period of at least two weekly Complete Spontaneous Bowel Movement (CSBM) during at least 6 of the 8 weeks of treatment.

13.2 Secondary endpoints

Secondary efficacy endpoints include:

- Change from baseline (run-in period) in average straining
- Change from baseline (run-in period) in average stool consistency, using the Bristol Stool Scale
- Change from baseline (run-in period) in average bloating.
- SBM success rate, defined as as an increase from the run-in period of at least one weekly Spontaneous Bowel Movement (SBM) during at least 6 of the 8 weeks of treatment.

13.3 Additional secondary endpoints

Additional efficacy endpoints include:

- Change from baseline (run-in period) in weekly number of Spontaneous Bowel Movement (SBM).
- Change from baseline (run-in period) in weekly number of Complete Spontaneous Bowel Movement (CSBM).
- Change from baseline (run-in period) in average abdominal gas.
- Change from baseline (run-in period) in average abdominal pain.
- Change from baseline (run-in period) in abdominal discomfort.
- Time to occurrence of spontaneous bowel movement after capsule activation.

- Treatment satisfaction score using the TSQM (Treatment Satisfaction Questionnaire for Medication)
- Change from baseline (run-in period) in quality of life using the PAC-QOL (Patient Assessment of Constipation Quality of Life) questionnaire
- Ease of use of the device

13.4 Safety endpoints

Safety endpoints include all adverse events related and unrelated to the study treatment.

14. STUDY CONDUCT & POPULATION

This study will be performed in accordance with the design and specific provisions of this protocol , in accordance with the ethical principles that have their origin in the Declaration of Helsinki, that are consistent with Good Clinical Practice (GCP), Title 21 of the Code of Federal Regulations (21 CFR), part 812 (Investigational Device Exemptions), and the applicable regulatory requirements.

14.1 Inclusion Criteria

1. Subjects aged 22 years and older
2. Subjects with Chronic Idiopathic Constipation (CIC) according to Rome III criteria and who have not experienced relief of their symptoms from available therapies (osmotic and stimulant laxatives used for at least one month at recommended dose)
3. Subjects with an average of <3 Spontaneous Bowel Movements (SBM) per week and ≥1 SBM per week
4. Normal colonoscopy performed within 10 years prior to study participation, unless the subjects are <50 years old and without alarm signs and/or symptoms
5. Subject signed the Informed Consent Form (ICF)
6. Female subjects must have a negative blood pregnancy test during screening, confirmed by a negative urine pregnancy test during baseline and must not be lactating prior to receiving study medication. For females of child-bearing potential, a hormonal (i.e., oral, implantable, or injectable) and single-barrier method, or a double-barrier method of birth control must be used throughout the study. All other female subjects must have the reason for their inability to bear children documented in the medical record [i.e., tubal ligation, hysterectomy, or post-menopausal (defined as a minimum of one year since the last menstrual period)]; in these circumstances, a pregnancy test will not be necessary.

14.2 Exclusion Criteria

1. History of complicated/obstructive diverticular disease
2. History of intestinal or colonic obstruction, or suspected intestinal obstruction.
3. History of significant gastrointestinal disorder, including any form of inflammatory bowel disease or gastrointestinal malignancy (celiac disease is accepted if the subject has been treated and is in remission)
4. History of gastroparesis
5. Use of any of the following medications:
    - Medications that may affect intestinal motility, prokinetics, anti-depressants, anti-Parkinsonian medications, opiates, opioids, calcium-channel blockers, aluminum/magnesium hydroxide
    - With the exception of antidepressants, thyroid or hormonal replacement therapy, when the subject has been on a stable dose for at least 3 months prior to enrollment.
6. Clinical evidence of significant respiratory, cardiovascular, renal, hepatic, biliary, endocrine, psychiatric or neurologic disease.
7. Presence of cardiac pacemaker or gastric electrical stimulator.
8. History of, or current eating disorders, such as anorexia, bulimia, or compulsory overeating.
9. Diagnosis of mega-rectum or colon, congenital anorectal malformation, clinically significant rectocele, history of intestinal resection (with an exception for appendectomy, cholecystectomy and inguinal hernia repair), history of bariatric surgery or evidence of any structural abnormality of the gastrointestinal tract that might affect transit
10. History of Zenker's diverticulum, dysphagia, Barrett's esophagus, esophageal stricture or achalasia
11. Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs): chronic use is defined as taking full dose NSAIDs more than three times a week for at least six months. Subjects on cardiac doses of aspirin may be enrolled in the study
12. Subjects with pelvic floor dysfunction/defecatory disorder, based on subject history
13. Participation in another clinical study within one month prior to screening.
14. Women who are pregnant or lactating
15. Use of any medication for constipation relief during the study, except as rescue medication, as indicated by study rules
16. Inability to use an electronic daily Diary (on a computer, phone application, tablet or other electronic device) to report symptoms and medication usage
17. Subject participated in a previous Vibrant study
18. Any other condition which in the opinion of the investigator may adversely affect the safety of the subject or would limit the subject's ability to complete the study.

14.3 Duration of Study

Study duration includes 2-3 weeks of run-in , followed by 8 weeks of treatment - Total of 10-11 weeks.
The sample size is calculated for 238 subjects.

15. STUDY TREATMENT

Detailed study treatment herein:

15.1 Study Design

The study is a prospective, multicenter, adaptive, randomized, double-blind, sham-controlled study to evaluate the efficacy and safety of the Vibrant Capsule in aiding relieving constipation.

The objective is to assess the efficacy and sfaety of the Vibrant Capsule with a frequency of administration of 5 capsules per week.

The study will be performed in up to 40 centers in the USA.

One interim analysis will be performed after at least 120 evaluable subjects will complete the study. The following parameters will be assessed: primary endpoint, tolerability and main safety parameters.
Depending on the results of the interim analyis:

- The study will be stopped,
- The study will continue as planned,
- The sample size will be increased.

Data reporting will be done on an electronic Case Report Form (eCRF). In addition, subjects will fill in daily information about their bowel movements, clinical symptoms and medication usage on an electronic Diary (eDiary). The eDiary will be accessed via a computer, smartphone, tablet or other suitable device, through a designated website. Information about time of activation of the Vibrant Capsules will be recorded automatically by the base unit and automatically transferred to a designated website.

Subjects with Chronic Idiopathic Constipation (CIC) according to Rome III criteria who failed currently available therapy (defined as osmotic and stimulant laxatives used for at least one month at recommended dose) and meet the inclusion criteria will be offered participation in this study. The background of the proposed study and its risks and benefits will be explained to the subject and the informed consent form will be signed.

Subjects will be screened for study eligibility according to inclusion and exclusion criteria. The daily bowel movements frequency, history of constipation, etiology of constipation and medication use (including prescription medication) will be throroughly assessed. Subject demographic and medical information acquired from the subject or the subject's medical chart, including age, gender, previous medical history, risk factors etc. will be also recorded on the eCRF.
In addition, subjects will undergo a physical examination including digital rectal examination, vital sign measurements and blood tests.

Subjects will then fill in the the Rome III questionnaire to confirm the diagnosis of Chronic Idiopathic Constipation and fill out the Bristol Stool Scale and PAC-QOL questionnaire. Findings will be recorded on the eCRF.

Eligible subjects will then be asked to refrain from taking any medication or supplement they are using to relieve their constipation, and will perform a daily self-assessment of their normal spontaneous bowel movements for 14 consecutive days (run-in period), utilizing the eDiary. Subjects will also be asked to record clinical symptoms and usage of any medication or supplement on the eDiary during the run-in period.

After the run-in period the subjects will visit the medical center for the baseline visit. Eligibility will be re-assessed and confirmed based on the subject's completed eDiary and Rome III questionnaire. The subject will fill in the PAC-QOL questionnaire again and be trained in the medical center to use the base unit. He will activate himself the first capsule and will ingest it in front of the medical staff. All the other capsules will be ingested from the home of the subject. Only the first ingestion will take place in the medical center.
During the treatment period, subjects will ingest Vibrant Capsule 5 days per week: one capsule on Mondays, Tuesdays, Thursdays, Fridays, Saturdays. Subject will not ingest any capsule on Wednesdays and Sundays. The subject will ingest a total of 40 capsules in 8 weeks considering the sequence.
If the baseline visit falls on a Wednesday, the subject should ingest the first capsule on site. In order to compensate, a capsule will not be ingested the day after (Thursday), then the subject should follow the normal schedule.

Capsule intake will be performed during the evening, between 9 PM and 10 PM (except on days where a capsule is ingested on site).

The subjects will be asked to refrain from taking any medication or supplement they are using to relieve their constipation until they complete the study.
After 8 weeks, treatment will be ceased and subjects will visit the medical center one last time for evaluation and completion of Rome III questionnaire, PAC-QOL questionnaire and other assessments.

Subjects will be instructed to complete a simple subject eDiary throughout the duration of the study. This will include daily recordings of capsule intake, number and time of bowel

movements, clinical symptoms, satisfaction score and medication/supplements usage, including rescue medication.

Please refer to section 15.15 for a detailed study schedule.

Data collection will include physician identification, investigational device identification data and usage of the capsule. This data will be documented on the eCRF, together with the occurrence of any adverse events during the capsule usage.

All subject adverse events (whether device related or not) will be recorded during the course of the clinical study. All serious adverse events/complications will be reported immediately (within 24 hours) to the study sponsor/monitor and to the Institutional Review Board.

15.2 Medical History

Subject demographic and medical information acquired from the subject or the subject's medical chart, including age, gender, weight, height, body mass index (BMI), number of natural childbirth and previous medical history and medications will be recorded, including: a history of clinically significant abnormalities of all body systems; concurrent diseases; relevant past medical history.
The information will be recorded in the eCRF for all subjects participating in this study.

15.3 Constipation History

Full history of constipation will be recorded on the eCRF, including duration of constipation, full history and habits of medication (over the counter and prescription) and supplements use, frequency of spontaneous bowel, current medication/supplements use, description of current diet (with focus on water intake and fiber intake), physical activity (number of hours of physical activity per week), recent change in bowel movements.

15.4 Physical Examination

During the screening visit all subjects will undergo a conventional physical examination by an authorized physician. The physical examination will include diagnosis and documentation of any significant abnormalities or diseases. The physical examination will include a digital rectal examination.

15.5 Assessment of pelvic floor dysfunction (defecatory disorder)

Assessment of pelvic floor dysfunction will be based on subject history. Subjects with suspicion of pelvic floor dysfunction will be excluded.
If subjects have been previously diagnosed with pelvic floor dysfunction following anorectal manometry, a balloon expulsion test, or other examinations, documented results from these tests can be used to exclude subjects.

15.6 Blood and urine tests

During the screening visit all subjects will undergo the following blood tests: blood count, calcium, creatinine, Blood Urea Nitrogen (BUN), sodium, potassium and TSH. Blood pregnancy test will be performed during the screening visit. A pregnancy urine test will be performed during the baseline visit.

15.7 Screening visit (day -21 to -14)

At the screening visit, subjects will be evaluated for eligibility and undergo physical examination, digital rectal examination, vital sign measurements and blood tests. They will undergo a thorough interview about their constipation and the Rome III questionnaire (see appendix C) will be completed. The Bristol Stool Scale (see Appendix A) and PAC-QOL Questionnaire (see Appendix D) will also be completed by the subject.

The investigator will confirm their eligibility and their physical and mental suitability to participate in this study.
Subjects exiting the trial at this stage will be considered screening failure subjects and be replaced with new subjects.

The subject will be trained by the study coordinator to access and use the eDiary.
The eDiary contains questions about bowel movements and their associated clinical symptoms (straining, abdominal pain, abdominal discomfort, abdominal gas, bloating, need for digital maneuver, sensation of complete evacuation), usage of rescue medication and usage of other medication or supplements (name of drug, dosage, number of takes per day, reason for medication).
The information will be transferred to the eCRF every day.

The subject will define his/her preferred device to use the eDiary. The subject and study coordinator will define together the time of the day during which the subject will fill in the eDiary and a daily alert will be set up on the phone of the subject. The daily diary can be found in Appendix H.

15.8 Run-in period (day -21 to -14, to -1)

Eligible subjects will be observed and monitored for the first 2 weeks, in which they will be asked to refrain from taking any medication or supplement to relieve their constipation.
The run-in period may be extended by a few days in case of technical issue (difficulty to access eDiary), to allow for a wash-out period, or other. The run-in period may be extended by up to 7 days.
Subjects will complete the eDiary every day and there should be a period of at least 14 consecutive days between the first day the subject fills in the diary and the last day of

run-in period. 14 consecutive days of the eDiary will be monitored to determine eligibility of the subjects.
On the day of screening, the coordinator should determine with the subject the last day of intake of constipation medication/aid and ensure that the last intake of constipation medication/aid has been taken more than 24 hours before the first diary entry.

The subjects will receive at least 1 short phone call/week from the study coordinator, more if needed.
The phone calls will be about 5-10 minutes long and will ask check subject compliance with the eDiary, occurrence of adverse events, use of rescue medication, subject understanding of what he needs to do in the context of the study and discuss any issue or difficulty that the subject might have. Confirmation of date and time of the phone call will be reported on the eCRF.

If a subject does not fill in his/her eDiary, the sponsor/investigator will be alerted and the subject will be contacted by phone call in order to receive more information and gather the missing information. Compliance of the subject will be closely monitored.
Subjects who fail to fill in their diary 3 times or more (not due to technical issues) during the run-in period will be considered as screening failures due to lack of compliance.

15.9 Treatment

On day 0 (baseline visit), the subject will arrive to the clinic. Eligibility will be re-assessed and confirmed based on the Rome III questionnaire and on the subject's completed diary. Subjects need to have an average of at least 1 SBM per week but less than 3 SBM per week during the two weeks of run-in. They must have at least 1 SBM per week for each of the 2 weeks of run-in.

The PAC-QOL questionnaire will be completed.

Eligible subjects will be randomized to:

- Vibrant arm, with a frequency of administration of 5 capsules per week, OR
- Sham arm, with a frequency of administration of 5 capsules per week.

Treatment duration is 8 weeks.
The subject will be trained by the study coordinator to use the base unit and activate the capsules. After an oral explanation, the subject will read the base unit user manual, and the study coordinator will make sure the subject fully understands how to use the base unit. The subject will then activate the first capsule, in front of the study coordinator, and swallow it. The subject will answer a short questionnaire which will test the subject's understanding about key elements in the training. The questionnaire can be found in Appendix E.
The subject will then be released home with the base unit and capsules for the first two weeks of treatment. The subject will be asked to continue with the daily completion of the eDiary.
Actual point of enrollment for the subject is considered the day of first capsule intake.

Subjects will be asked to refrain from any medication or supplement they are using to relieve their constipation, throughout the treatment period. A rescue treatment will be authorized upon need (refer to section 15.10 for details).

Capsule intake should take place during the evening between 9 PM and 10 PM, on Mondays, Tuesdays, Thursdays, Fridays and Saturdays.
The first intake, which will take place in the medical center during the day, will not follow these rules.

Capsule distribution for the subject will be in 3 time points:

- Day 0 (baseline visit): capsules for 2 weeks of treatment will be provided
- Day 14 ± 2 days (treatment visit 1): capsules for 3 weeks of treatment will be provided
- Day 35 ± 2 days (treatment visit 2): capsules for 3 weeks of treatment will be provided.

The subjects will receive at least one phone call per week from the study coordinator. The phone calls will be about 5-10 minutes long and will check subject compliance with capsule ingestion and the eDiary, occurrence of adverse events, use of rescue medication, subject understanding of what he/she needs to do in the context of the study and discuss any issue or difficulty that the subject might have. Confirmation of date and time of the phone call will be reported on the eCRF.
Compliance of the subject will be closely monitored.

Overall the subject will visit the site twice during the treatment period: a first time 2 weeks after the baseline visit, and a second time 3 weeks after that. The last visit will be the termination visit. The subject will receive the capsules in 3 separate visits:

- Baseline visit: capsules for 2 weeks of treatment
- Visit 1 during treatment period: capsules for 3 weeks of treatment
- Visit 2 during treatment period: capsules for 3 weeks of treatment.

The subject will receive spare capsules and must bring back to the site all remaining capsules in his/her possession for each visit. The capsules must be counted and accounted for.
During each visit, an interview will be conducted, where the following topics will be discussed: occurrence of adverse events, compliance to filling in the daily information on the eDiary and to the treatment, concomitant medication/rescue taken, evolution of constipation symptoms, subject's perceptions about the treatment, motivation of the subject, or any other topic relevant.

15.10 Rescue Treatment

Subjects will stop using all medication or supplement to relieve constipation during the entire study period and comply to use constipation aid only for rescue.
Using one rescue medication is authorized only after 3 consecutive days without a bowel movement and under the rules described below. The subjects will not be required to contact the investigator prior to taking any medication/supplement but they will be required to declare all the rescue medication on their eDiary. The following treatment is recommended (not by order):

1. Dulcolax® suppository/bisacodyl suppository
2. Fleet Enema®
3. Dulcolax®/bisacodyl tablet (1x5mg)

The subject is allowed to take a rescue medication/supplement that is not in the above list, without contacting the investigator. The subject must declare all rescue intake in the eDiary.
In a situation where the investigator prescribes a rescue medication/supplement that is not in the above list, the investigator will need to mention it and give the reason in a note to file or appropriate form.

Subjects who take rescue medication three times or more during the run-in period will be considered as screening failures.

A spontaneous bowel movement is defined as a bowel movement that occurs at least 48h after laxative/rescue intake and without digital maneuver.
A complete spontaneous bowel movement is defined as a spontaneous bowel movement associated with a feeling of complete evacuation by the subject.

15.11 Termination visit

After 8 weeks, treatment will be ceased. Subjects will visit again the medical center for evaluation and completion of the PAC-QOL questionnaire, the TSQM (Treatment Satisfaction Questionnaire for Medication)[16], an ease of use questionnaire, the termination form and end of study form. The subject will be evaluated for occurrence of adverse events, concomitant medication/rescue and compliance to the eDiary and treatment.
The subjects will bring back all remaining capsules in their possession as well as the base unit. The capsules must be counted and accounted for.

The TSQM and ease of use questionnaires can be found in Appendix F and G respectively.

15.12 Concomitant medication

All medication taken by the subject in addition to the investigational device is termed concomitant medication. All concomitant medication taken during the study must be documented in the case report form (name of drug, date of intake, dosage, number of

takes per day, reason for medication). The subject will fill in all the information daily on the eDiary.

15.13 Prohibited medication

The medications listed below will be prohibited during the entire study:

- Medications that may affect intestinal motility
- Prokinetics
- Antidepressants
- Anti-Parkinsonian medications
- Opiates
- Opioids
- Calcium-channel blockers
- Aluminum/magnesium hydroxide.

Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) is also prohibited. Chronic use is defined as taking full dose NSAIDs on a regular basis (i.e. more than three times a week) for at least six months.
Subjects on cardiac doses of aspirin may be enrolled in the study.

The following medications are equally prohibited, but with an exception when the subject has been on a stable dose of the medication for at least 3 months:

- Antidepressants
- Thyroid or hormonal replacement therapy.

15.14 Recording

All tests will be performed prior to procedure in case where not already done per routine hospital protocol. Device handling and function will be recorded.
The standard treatment and care provided to all subjects, alongside the Vibrant capsule and other treatments will be performed and recorded on the appropriate study eCRF.
The subject will be questioned on his clinical status, the presence of any medical intervention performed since the last visit and any adverse events or discomforts. When necessary, the subject will be asked to arrive for a follow-up visit at the clinic.

15.15 Study Schedule

Table 11 summarizes the required data collection from assessments and tests performed during the study.

Procedures	Screening	Baseline	Treatment visit 1	Treatment visit 2	Termination visit

Visit No.	1	2	3	4	5
Day	-21 to -14	0	14 (±2 days)	35 (±2 days)	56 (±2 days)
IC	+				
Eligibility Criteria	+	+			
Physical Exam	+				
Digital Rectal Exam	+				
Vital Signs	+				
Lab Data	+				
Urine Pregnancy test (if applicable)		+			
Administration of capsule		+			
Evaluation of training		+			
Rome III	+	+			
PAC-QOL	+	+			+
Bristol Stool	+				
TSQM & ease of use					+
Subject eDiary	+	+	+	+	+
Adverse Events	+	+	+	+	+
Concomitant Medication	+	+	+	+	+

Table 11 – Study Schedule of Assessments

15.16 Deviations from study protocol

Any deviation from the study protocol should be notified to the sponsor, documented on study deviation forms and reported to the Ethics Committee as required.

Protocol deviations related to treatment compliance (e.g. missed capsule, capsule taken on a Wednesday or Sunday, etc.) will not be declared on the protocol deviation form accessible via the EDC (Electronic Data Capture). Protocol deviations related to treatment compliance will be monitored and declared by the Sponsor, CRO and sites using a platform external to the EDC. This external platform will use the information transmitted from the base units about activations (base unit serial number, date and time of activation, success/failure) as a basis to monitor treatment compliance.
Additional information transmitted by the subject from the eDiary about number of capsules taken out of the blister and swallowed for each day, as well as direct information given by the subject to the study coordinator by phone, email or SMS, will be used by the

Sponsor and CRO to make a final decision about treatment compliance, for each day of treatment, for all subjects.
A final list of protocol deviations related to treatment compliance will be issued at the end of the study, from the external platform, and signed. This list will be considered equivalent as protocol deviations forms. The site will not manually enter these protocol deviations in the EDC.

15.17 Investigative Center Selection Criteria

The investigative site will meet the following selection criteria prior to inclusion in this study:

- Clinical research study experience and resources that demonstrate good compliance with study requirements and timely, complete documentation of subject follow-up.
- Sufficient subject volume to meet enrollment timeframe.

16. ADVERSE EVENTS RECORDING

At each evaluation, the investigator will determine whether any adverse events (AE's) have occurred. All adverse events occurring during the study will be recorded on the appropriate case report form page by the investigator. The nature, severity and relation of the adverse event to the study device will be documented.

16.1 Reporting Requirements

Timely and complete reporting of Adverse Events (AE) and safety assessment allows:

- Protection of safety and study subjects.
- Greater understanding of the overall safety profile of the study treatment.
- Appropriate modification of study protocols and improvement in study design and procedures.
- Adherence to regulatory requirements.

The definitions and reporting requirements adopted in this study are derived from the current International standard on clinical investigations: Title 21 of the Code of Federal Regulations (21 CFR), part 312 (Investigational New Drug Application), Section 32 (IND Safety Reporting) and part 812 (Investigational Device Exemptions), Section 150 (Reports).

16.2 Definitions

Adverse Events (AE)
AE is defined as any untoward medical occurrence in a subject. This definition does not imply that there is a relationship between the adverse event and the device under investigation. An AE can therefore be any unintended sign, symptom, disease or injury or any untoward clinical signs (including an abnormal laboratory findings) in subjects,

users or other persons whether or not related to the investigational medical device. The following should be reported as AE:

- Untoward medical conditions or signs or symptoms that were absent before starting study treatment.
- Untoward medical conditions or signs or symptoms present before starting study treatment and worsen (increase severity or frequency) after starting study treatment.
- Abnormal laboratory findings.
- Clinical signs or symptoms that require therapy.

Device Deficiency
Device Deficiency is defined as Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

Adverse Device Effect (ADE)
ADE is adverse event, related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device, the operation, or any malfunction of the investigational medical device, device failure or misuse, and any event that is a result of a user error.

Device failures, Malfunctions and Misuse
Investigators are instructed to report all possible device failures or misuse observed during the course of the trial. These incidents will be documented in the case report form provided as follows:

- **Device Failure** - A device failure has occurred when the device is used in compliance with the Instructions for Use, but does not perform as described in the Instructions for Use. A device failure occurs when
  - A capsule fails to activate.
  - The transmission about the first capsule activation cannot be performed (during the baseline visit) by the base unit. This event must lead to the replacement of the base unit.
  - The base unit loses its ability to transmit information permanently. This event must lead to the replacement of the base unit.

  Device Misuse - Any use of the investigational device by an investigator or subject that is contradictory to the application described in the Instructions for Use will be categorized as device misuse.

Serious Adverse Events (SAE)
A SAE is an adverse event that:
1. Led to a death,
2. Led to a serious deterioration in the health of the subject that:

a. Resulted in a life-threatening illness or injury
b. Resulted in a permanent impairment of a body structure or a body function
c. Required in-subject hospitalization or prolongation of existing hospitalization
d. Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.

3. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Device deficiencies that might have led to a SAE if a suitable action had not been taken or intervention had not been made or if circumstances had been less opportune are also handled under the SAE reporting system.
However, planned hospitalization for pre-existing condition and/or procedure required by the clinical trial protocol, without serious deterioration in health, is not considered to be a SAE.

Serious Adverse Device Effect (SADE)
A Serious Adverse Device Effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)
USADE is defined as serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report or other study related documents.

16.3 Anticipated Adverse Events

The Vibrant Capsule targets pathophysiological parameters of chronic constipation by inducing natural bowel activity without using chemical supplements.
Anticipated Adverse Events include those that are reasonably expected to occur in association with a clinical investigation assessing a treatment for functional constipation. Events can occur as a result of the disease or as a result of the treatment (including usage of the home base unit). They may include but are not limited to the following (in alphabetical order):

- Abdominal pain/discomfort/cramping
- Blood in the stool may develop or increase
- Bloating/Flatulence
- Diarrhea
- Nausea may develop or increase
- Rectal pain may develop or increase
- Sensation of vibration in the abdomen
- Uncontrolled leakage of stool may occur
- Vomiting may develop

All events listed above, and additional events that the investigator will evaluate will fit the definition of ‘anticipated event’, will be categorized as such in the study.

16.4 Adverse Event Reporting

All adverse events and adverse device effects occurring during the clinical trial must be recorded by the investigator on the appropriate AE form in the eCRF, within a reasonable time (up to 5 calendar days from investigator's awareness of the event). All AEs will be characterized by the following criteria:

- Intensity or Severity
- Relatedness
- Outcome
- Treatment or Action Taken.

16.4.1 Intensity or Severity

The following categories of the intensity of an adverse event are to be used:
Mild – Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no sequelae.
Moderate – Interferes with the subject's usual activity and/or requires symptomatic treatment.
Severe – Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

16.4.2 Relatedness

The investigator will use the following definitions to assess the relationship of the AE to the investigational medical device:
Not related - The cause of the AE is known and the event is not related to the investigational medical device.
Possibly related - There is a reasonable possibility that the event may have been caused by the investigational medical device.
The AE has a timely relationship to the study procedure(s); however, follows no known pattern of response, and an alternative cause seems more likely or there is significant uncertainty about the cause of the event.
Probably related - It is likely that the event was caused by the investigational medical device.
The AE has a timely relationship to the study procedure(s) and follows a known pattern of response; a potential alternative cause, however, may explain the event.
Related - A related event has a strong temporal relationship and an alternative cause is unlikely.

16.4.3 Outcome

The clinical outcome of the AE or SAE will be characterized as follows:
Death - The SAE CRF must be completed for this outcome (see 16.5 Expedited Reporting of Serious Adverse Events).
Recovered without sequelae - The subject returned to baseline status

Ongoing - Subject did not recover and symptoms continue
Recovered with sequelae - The subject has recovered but with clinical sequelae from the event
Unknown - The subject outcome is unknown

16.4.4 Treatment or Action taken

The treatment or action taken after the occurrence of an AE or SAE will be reported as:
Interventional Treatment - Surgical, percutaneous or other procedure
Medical Treatment - Medication frequency of administration reduction/interruption or discontinuation, or medication initiated for event
None - No action is taken

16.5 Expedited Reporting of Serious Adverse Events

Any Serious Adverse Event, and device deficiencies should be reported to Vibrant Ltd. within 24 hours of investigators' knowledge of the event. Investigator should report these events on the appropriate SAE form / Device Deficiencies Form in the eCRF and send the form by fax or e-mail, to the following safety contact person:

If applicable, the investigator should also inform the representative of the appropriate local Ethics Committee, within 24 hours of investigator's awareness of the event. A copy of the report cover letter should be filed within the study file.

The sponsor is responsible for the ongoing safety evaluation of the investigational medical device. The sponsor will promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the Medical Ethics Committee approval/favorable opinion to continue the trial.

The sponsor will expedite the reporting to all concerned investigator(s)/institutions(s), to the EC(s), where required, and to the regulatory authority(ies) of the occurrence of Unanticipated Serious Adverse Device Effects.

16.6 Follow- Up of Unresolved Events

All adverse events should be followed until they are resolved or the subject's participation in the study ends.

17. STATISTICAL CONSIDERATIONS

17.1 Study Design and Objectives

The study is planned as a **prospective, multicenter, adaptive, randomized, double-blind, sham-controlled study,** designed to assess the safety and efficacy of active Vibrant capsules compared with sham capsules when administered 5 times per week in patients with Functional Constipation.
After a run-in period of approximatively 14 days, subjects will be randomized with a ratio of 1:1 to either active capsule or sham capsule. The subjects will then be treated with the active Vibrant or sham capsule for 8 weeks.
An adaptive design is planned with one interim analysis.

17.2 Study Endpoints

17.2.1 Primary Efficacy Endpoint

The primary efficacy endpoints are:

- the CSBM1 success rate, defined as an increase from the run-in period of at least one weekly Complete Spontaneous Bowel Movement (CSBM) during at least 6 of the 8 weeks of treatment.
- the CSBM2 success rate, defined as an increase from the run-in period of at least two weekly Complete Spontaneous Bowel Movement (CSBM) during at least 6 of the 8 weeks of treatment.

The study will be deemed successful if either the CSBM1 or the CSBM2 success rate is statistically significantly higher in the active arm than in the sham arm.

17.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

1. Change from baseline (run-in period) in average straining
2. Change from baseline (run-in period) in average stool consistency, using the Bristol Stool Scale
3. Change from baseline (run-in period) in average bloating.
4. SBM success rate, defined as an increase from run-in perdion at least one weekly spontanuous Bowel Movement (SBM) during at lease 6 out of 8 weeks of treatment

17.2.3 Additional Efficacy Endpoints

-
- Additional efficacy end points
- Change from baseline (run-in period) in weekly number of Spontaneous Bowel Movement (SBM).
- Change from baseline (run-in period) in weekly number of Complete Spontaneous Bowel Movement (CSBM).
- Change from baseline (run-in period) in average abdominal gas.
- Change from baseline (run-in period) in average abdominal pain.
- Change from baseline (run-in period) in abdominal discomfort.
- Time to occurrence of spontaneous bowel movement after first capsule activation.
- Treatment satisfaction score using the TSQM (Treatment Satisfaction Questionnaire for Medication)
- Change from baseline (run-in period) in quality of life using the PAC-QOL (Patient Assessment of Constipation Quality of Life) questionnaire.
- Ease of use of the device.

17.2.4 Safety Endpoints

Safety endpoints include all adverse events related and unrelated to the study treatment.

17.3 Study Hypotheses

In this study, we will test the following hypotheses:

- $H_0 : P_{a1}-P_{s1}=0$
- $H_1: P_{a1}-P_{s1}\neq 0$

Where P_{a1} is the CSBM1 success rate in the active arm, and P_{s1}, the CSBM1 success rate in the sham arm.

AND:

- $H_0 : P_{a2}-P_{s2}=0$
- $H_1: P_{a2}-P_{s2}\neq 0$

Where P_{a2} is the CSBM2 success rate in the active arm, and P_{s2}, the CSBM2 success rate in the sham arm.

17.4 Interim Analyses

One interim analysis is planned, after at least 120 evaluable subjects complete the 8 weeks treatment. Planning an interim analysis that permits an increase in the sample size as described below does not additionally inflate the type I error according to references [1-2-3]. In addition, the final analysis is performed using the conventional test as appropriate for the statistical hypothesis

17.4.1 Procedure

After all the relevant data will be entered into the database, and the database cleaned, a soft lock to the database will be performed. An independent un-blinded statistician (not the study statistician) will perform the assessments described below. A designated Data Monitoring Committee will recommend whether to stop the study once the interim results are available.
At the interim analysis, the data of the evaluable subjects will be analyzed .

17.4.2 Blinding

ONLY the un-blinded statistician and members of the interim decision committee will be exposed to the interim report. The members of the DSMB (Data and Safety Monitoring Committee) may also have access to the unmasked information of the interim analysis. Investigators and company directors will only be informed of a decision to continue or to discontinue the trial, or to implement modifications in trial procedure. The un-blinded statistician who is responsible for conducting the interim analyses should ensure that the unmasked data is not available to any unauthorized person within or outside the company.

17.4.3 Decision Rules

An Interim Analysis will be done after at least 120 subjects completed the study for sample size adaptation, with the highest sample size of 476 subjects including drop outs (section 17.5).

17.4.4 Controlling the Alpha level for the primary endpoint

The overall alpha level for this study is 5%. According to [1-2-3], planning an interim analysis that permits an increase in the sample size as described above does not inflate the type I error.

17.5 Sample size

A sample size is calculated to test the null hypothesis. Calculations (using SAS® proc power) show that a sample size of 214 subjects (107 in each study arm), would provide 80% power at an overall 5% (2.5% for each one of the two primary endpoints) level of

significance (two-sided) to detect a difference of 20% in the success rate, assuming a success rate of 25% in the sham arm.
The sample size will be increased to at least 238 subjects (119 in each arm) to account for a potential 10% of drop-outs.

17.6 Randomization

After a subject meets the eligibility criteria, he/she will be equally allocated (with a 1:1 ratio) to one of the following 2 treatment groups based on a randomization scheme with randomized blocks stratified by center:

- Active capsule
- Sham capsule

The randomization scheme will be prepared by BioStats using the SAS® (version 9.4.) random number generating procedure.

17.7 Blinding

This is a double blind study, the subjects, the investigators and the evaluators will be blinded to the treatment allocated to each subject.

17.8 Data Analysis Sets

17.8.1 Intent to Treat (ITT)

The ITT analysis set will consist of all subjects randomized. In accordance with the ITT principle, all subjects randomized will be kept in their originally assigned treatment group.

17.8.2 Modified Intent to Treat (mITT)

The mITT analysis set will consist of all randomized subjects who met the inclusion criteria of the protocol and successfully completed Visit 1. In accordance with the ITT principle, all subjects randomized will be kept in their originally assigned treatment group. Subjects with no valid post baseline assessment will not be part of the relevant analysis.

17.8.3 Per-Protocol (PP)

The per-protocol analysis set will consist of all subjects from the mITT analysis set without major protocol violations and successfully completed the study.
Major protocol deviations include:

- o Subject who received, by mistake, both treatments (sham capsule and Vibrant capsule).
- o More than 25% of the capsules missed or swallowed without activation during the treatment period (calculated according to device accountability CRFs).
- o Subjects with less than 2 weeks (with at least 5 days each week) of valid diary data.
- o Use of at least one prohibited drug like opioids, Ca+ channel blockers, etc. for more than a week.

17.8.4 Statistical Analysis of Analysis Sets

The ITT analysis set will serve as the main set for safety and efficacy assessments. The primary and secondary efficacy assessment will also be performed on the PP and mITT analysis sets.

17.9 Statistical Analysis

17.9.1 General Considerations

Statistical analyses will be performed using SAS® v9.4 or higher (SAS Institute, Cary NC, USA).
Baseline demographic and other baseline characteristics, together with safety analyses will be performed on all enrolled subjects. Baseline values are defined as the last valid value prior to treatment.
All statistical tests will be two-sided. If statistical tests are performed nominal p-values will be presented. Where confidence limits are appropriate, a two-sided 95% confidence interval will be constructed.
For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test will be used as appropriate. For comparison of proportions (categorical variables), the Chi-squared test or Fisher's exact test will be used as appropriate.

17.9.2 Significance levels and handling of type I error

17.9.2.1 Type I Error

The overall significance level for this study is 5% using two-tailed tests. According to [1-2-3], planning an interim analysis that permits an increase in the sample size as described in section 17.4 does not inflate the type I error. The treatment by site interaction will be tested at a significance level of 15%.

17.9.2.2 Primary Endpoints

The Benjamini and Hochberg technique for controlling the false discovery rate will be implanted for the two primary endpoints for adjusting the level of significance as well as the confidence intervals.

17.9.2.3 Hierarchy Approach for Secondary Endpoints Analysis

The hierarchy approach will be adopted for the primary and secondary endpoints to control type I error due to multiple endpoints testing. Thus, the primary endpoints will first be analyzed and only if one of them will be found statistically significant (see the method described in section 17.9.2.2 above), will the secondary endpoints be analyzed.
The first secondary endpoint will be tested, first, for statistical significance and only if found significant (versus an alpha level of 5%), the next in line will be tested. Only if the

first and second secondary endpoints are found statistically significant, then the third one will be tested, and so on.
The order of the secondary endpoints is as listed in paragraph 17.2.2.

17.9.3 Demographic and Other Baseline Variables

Demographic and baseline condition related characteristics will be tabulated. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum, and categorical variables by a count and percentage.

17.9.4 Disposition of Subjects

Treatment tolerability will compare between the treatment groups, the number and percent of subjects who fail to complete the study and the number and percent of subjects who fail to complete the study because of Adverse Events will be presented. Time to withdrawal will also be assessed and presented by Kaplan-Meier curves and will be compared using the Log-Rank test if relevant.

17.9.5 Efficacy Analysis

The subject's CSBM1 success status (i.e. if the subjects achieve an increase from baseline of at least 1 weekly CSBM during at least 6 out of the 8 treatment weeks) will be modeled and compared between the study arm with a logistic regression model, with the baseline weekly number of CSBM and site as covariates. The adjusted success rate per study arm, and their difference between the groups will be presented along with their respective 95% Confidence Intervals (CI).

The CSBM2 success rate will be analyzed in the same manner.

The SBM success rate will be analyzed in the same manner.

The change from baseline in number of weekly CSBM will be modeled with an Analysis of Covariance (ANCOVA) model, with baseline weekly number of CSBM and site as covariates. The adjusted means of the change from baseline per study arm, and their difference between the groups will be presented along with their respective 95% CI.

The change from baseline in count of weekly SBM, in symptoms, and in quality of life will be analyzed with similar ANCOVA models, with their respective baseline values as covariate.

Time to occurrence of SBM after intake of the first Vibrant capsule (either active or sham) will be assessed and presented by Kaplan-Meier curves and will be compared between the study arms using the Log-Rank test if relevant.

Treatment satisfaction, and ease of use will be presented in tabular form.

17.9.6 Treatment by Center Interaction

Treatment by site interaction will be tested in the primary analysis at a significance level of 5%. Poolability across centers, for the primary end-point, will be assessed using logistic regression, study arm, baseline number of weekly CSBM, center along with the study arm by center interaction term will be entered into the models. Centers with less than 10 subjects will be grouped together. If the interaction term is found significant, the reason for this interaction will be further explored and rationalized. This evaluation may include demographic features, symptoms at presentation, clinical and treatment history, and site comparability in the features found to be associated with the primary efficacy variables.

17.9.7 Safety Analysis

Safety assessments will be performed on the ITT data analysis set.
The MedDRA dictionary will be used to standardize the terms used by investigators to describe the Adverse Events (AEs). The AE dictionary, will be provided.
Tables displaying the frequency and incidence of AEs with post baseline onset date until (including) Termination/Early Termination visit will be presented by treatment group, System Organ Class (SOC), and Preferred Term (PT) according to the MedDRA dictionary. Incidence will be calculated as the percent of subject's reporting a specific AE at least once, out of the total number of subjects in that group. Frequency refers to the number of distinct reports of the same AE.
Frequency and incidence tables of AEs by treatment group, severity, relationship to study device and outcome will be generated.
Incidence and frequency tables of serious AEs (SAEs) will be presented by treatment group. Individual subject narratives will be provided.
Individual data listings of all AEs, SAEs and discontinuations due to AEs and their attributes will be generated.
Every AE from a certain start date, even if reported across several visits, will appear in the listings only once - with stop date (if available)..

17.9.8 Handling of Missing Data

Subjects with less than 6 weeks of diary data will be considered as failures for the CSBM1, the CSBM2 and SBM success rates.
For the time to first SBM analysis, subjects with no known SBM will be considered left censored.
For the analyses of the other endpoints, no imputation for missing values will be performed.

Multiple imputation for binary data will be used as the primary imputation method in the case of missing data for the primary performance end-points, baseline variable to be used in the analysis: BMI, sex, Age, duration of historical symptoms, straining and Bristol

stool scale at baseline. Once the data is finalized if this method is deemed inappropriate a more appropriate analysis may be performed.
Additional sensitivity analysis of the primary end-point will be performed to assess the impact of missing data on the study outcome using possible imputation methods for binary data:

- Tipping point analysis.
- Observed Data: Use only subjects with 8 weeks of non-missing diary data and who did not withdraw early from study.
- Best Case Scenario: Assume all subjects with missing data in study group are successes; Assume all subjects in the sham group with missing data are failures.
- Worst Case Scenario: Assume all subjects with missing data in study group are failures; Assume all subjects in the sham group with missing data are successes.

In addition, for missing diary day, the number of bowel movement will be imputed to "0", and the intake of rescue medicine to "No".

18. DATA MONITORING PLAN

The Principal Investigator and his study staff will monitor all data accrual. In addition a data monitor will visit the study site during the study and review the progress of the clinical trial including safety data and ensure as possible that it is conducted, recorded, and reported in accordance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirement(s). A written report form will be issued after each monitoring visit (including initiation and close out visits). The monitoring visit report will include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance. The investigator/institution should provide direct access to source data/documents for trial-related monitoring and auditing, IRB/IEC review and inspection by the appropriate regulatory authority/ies.

Verification during monitoring visit will include:

1. That the investigator has adequate qualifications and resources and remains adequate throughout the trial period, that facility, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.
2. Verifying for the investigational product(s):
    a. That storage conditions are acceptable.
    b. That the investigational product(s) are supplied only to subjects who are eligible to receive it according to protocol and no other use is being done with the Vibrant devices.

c. That the receipt, use, and return of the investigational product(s) at site are controlled and documented adequately and that supplies delivery notes are confirmed upon reception throughout the trial.
d. That the unused investigational product(s) at sites will be returned.

3. Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.
4. Verifying that written informed consent was obtained before each subject's participation in the trial.
5. Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).
6. Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.
7. Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreements, and have not delegated these functions to unauthorized individuals.
8. Verifying that the investigator is enrolling only eligible subjects and at sufficient recruitment rate.
9. Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.
10. Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.
11. Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other.
12. The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
13. Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.
14. Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
15. All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.
16. Verifying that the investigator had answered all of the queries that came up from inspection of the CRFs or other trial material.
17. That the investigator is maintaining the essential documents.
18. Verifying that deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements are reported by the investigator to the IRB/IEC and that appropriate actions were taken to prevent recurrence of the detected deviations.

Should there be an unexpected number of device failures or related complications that increase the risks to the participants, or critical efficacy endpoints at intervals that are not satisfying, the study will be halted and analysis performed to determine whether to continue, modify the protocol, or close the study.

19. DATA CONFIDENTIALITY

Each subject will be identified by his/ her initials and a unique subject identification number. Source data will be stored with source documents. The Investigator Site Files (ISF) will be held in a secure area. The subject's name and personal data will remain confidential and will not be published in any way. However, the sponsor's monitor or representative and regulatory representatives, auditors and inspectors may have access to medical files in order to verify authenticity of data collected.

20. FUNDING

The study is funded by Vibrant Ltd.

21. ETHICS

Prior to study initiation the site shall obtain EC or IRB approval of the study. A copy of the written EC approval must be provided to the sponsor prior to the start of the study. Any changes in the study protocol, informed consent forms, or investigator must be re-approved by the EC or IRB and the approval documented. All subjects enrolled in the study will provide their consent prior to entering the study. An informed consent form shall be signed and dated by the subject. The investigator will retain the forms as part of the study records.
This study will be executed in accordance with the Declaration of Helsinki, in agreement with the guidelines for conducting a clinical investigation in accordance with the principles of ICH GCP outlined in the E6 document. By signing the present protocol, the investigator commits to carry it out in accordance with local legal requirements.

Other investigator responsibilities relative to the EC include the following:

1. During the conduct of the study, the investigator will submit progress reports to the EC as required, and request re-review and approval of the study at least once a year;
2. The investigator will report immediately to the EC of any unexpected serious adverse events that occur during the study, and provide the sponsor with a copy of the correspondence;
3. If the sponsor notifies about serious adverse events reported in other studies using this device, the investigator must report that information to the EC;
4. As required, the investigator must obtain approval from the EC for protocol amendments and for revisions to the consent form or subject recruitment advertisements;
5. The investigator should provide the EC with any other information it requests before or during conduct the study;
6. The investigator must maintain a file of study-related information that includes all correspondence with the EC;

7. The investigator must notify EC when study is completed (i.e. after the last study visit of the final study subject);
8. After study completion (within 12 months is recommended) the investigator should provide the EC with a final report on the study. The recommended components of a final report are as follows; dates of study start and completion, number of subjects enrolled/treated, number of subjects who discontinued participation early and reason why, itemization and discussion of any serious adverse event.

22. INFORMED CONSENT

Written informed consent must be obtained from each study subject. The subject will be asked to read the informed consent form and to sign the form to indicate consent to participate in the study.
The investigator will explain carefully to the subject the research nature of the study. The scope and aims of the research will be described together with known or foreseeable benefits, risks and discomforts that subjects may experience. Appropriate alternative treatments will be discussed so that the subject may determine whether or not he or she wishes to participate in the study. The subject must understand that throughout the study his or her participation remains voluntary and protected by the Declaration of Helsinki.
The investigator is responsible for obtaining written (or witnessed) informed consent from potential subjects prior to study entry. Subjects will be given time to read the informed consent and ask any questions before being asked to sign the form. The informed consent (approved by the sponsor and the Ethics Committee) must be signed and dated by the subject and the investigator. One copy of the signed consent will be given to the subject, a second copy will be sent to the referral investigator and the original will be retained by the investigator.
Subjects may withdraw their consent to participate in the study at any time without prejudice. The investigator may withdraw a subject if, in his clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol. Attempts should be made to complete any examinations and the sponsor must be notified of all withdrawals.
Should a protocol amendment be made, the subject's consent form may be revised to reflect the changes of the protocol. It is the responsibility of the investigator to ensure that an amended informed consent is approved or reviewed by the EC, and that it is signed by all subjects subsequently entered in the study and those currently in the study, if affected by the amendment.

23. REGULATORY AND HEALTH AUTHORITY AUDITS

The European Union's authorities and/or the Food and Drug Administration (FDA) and/or the local state health authorities may request access to all study records, including source documents for inspection. The investigator and hospital staff are requested to cooperate with these audits. The investigator must notify the sponsor of any health

authority audit as soon as notification of such audit is made. A representative or designee of the sponsor may also conduct similar audits and may be present during health authority audit.

24. ELECTRONIC REPORTING OF DATA

All medical data in this trial are to be recorded directly in the EDC (Electronic Data Capture) system. Documentation on paper will be restricted to exceptional circumstances only.
The investigator must ensure the accuracy, completeness and timeliness (and legibility in case of documentation on paper) of data.

Sites will get trained on how to access and use the EDC and will be foreseen with a personal user login and password.
Subjects will access and complete their diaries online via a website specifically created for the purposes of the study. Subjects will be trained on how to access and use this website and will be foreseen with a personal user login and password.

25. RECORD RETENTION

It is required that a copy of all records (e.g., informed consent documents, source documents, safety reports, study device dispensing record, etc.) which support case report forms for this study, be retained in the files of the responsible investigator for a minimum of fifteen (15) years following notification by the sponsor that all investigations (not merely the investigator's portion) are completed, terminated and/or discontinued. If the principal investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Vibrant Ltd. must be notified in writing of the name and address of the new custodian.

26. PROTOCOL MODIFICATIONS

An amendment to the protocol may be proposed by an investigator. The amendment will be prepared and approved by the sponsor according to the sponsor's relevant SOP. The amendment must be submitted to the IRB. When applicable, the amendment's implementation will take place only once approved by the IRB.
If for any unexpected reasons, there is any requirement to deviate from the treatments stated above, the protocol deviation should be discussed with a Vibrant Ltd. representative.

27. PUBLICATION POLICY

All information concerning this study that was not previously published is considered confidential information. This confidential information shall remain the sole property of Vibrant Ltd.; it shall not be disclosed to others without written consent of Vibrant Ltd. and shall not be used except in the performance of this study.
Any investigator involved with this study is obligated to provide the Sponsor with complete test results and all data derived from the study.

28. SUBJECT / STUDY DISCONTINUATION

Subjects should be removed from the study whenever considered necessary for their welfare or when the subject expresses a desire to withdraw from the study. Non-compliance with the protocol, the occurrence of a Serious Adverse Event or any medical condition that, in the opinion of the investigator, warrants discontinuation from the study for the safety of the subject, may necessitate discontinuing a subject. If a subject is discontinued, the reason must be entered on the case report form and signed by the investigator. In case of any questionable situation, the study monitor or Vibrant Ltd. personnel should be consulted. When a subject is removed from the study as a result of Serious Adverse Event, a final physical examination must be performed. Subjects removed from the study because of an adverse event will be followed-up until the adverse event has been resolved.

In the case that the occurrence of adverse events is greater than anticipated, the clinical investigation will be suspended; in such a case, a safety committee will be arranged to decide if the study could be continued. The Ethics Committee will be notified and the results of the safety committee discussions will be brought for the EC review and decision.

Early termination could be a result of:

1. Withdrawal of informed consent by the subject.
2. Subjects who after inclusion develop medical diseases which may affect the function and interpretation of study results.
3. Serious protocol deviation.
4. Non-compliance with medical device administration or study procedures as determined by the sponsor.
5. Change in subject's condition.
6. Subject is Lost to follow-up.
7. Confirmed pregnancy.
8. Regulatory authorities stop the trial.

During the study, subjects exiting the trial will be replaced with new subjects, in order to have approximately 238 subjects at the end of the trial.

Vibrant Ltd., reserves the right to discontinue any study for administrative reasons at any time, such as, but not limited to a decision to discontinue further clinical investigation with the device, improper conduct of the study by the investigator, inability to obtain the number of subjects required by the protocol, etc. Reimbursements for reasonable expenses will be made if such an action is necessary.

29. DEVICE ACCOUNTABILITY

Complete traceability records will be kept of all devices during the study. Vibrant devices and relevant accessories will be provided by Vibrant Ltd., bearing required labeling. Device identification and accessory identification will be documented in subject medical records, CRF and in center log.

Each clinical investigator will be responsible for the safe storage with restricted access of the investigational materials in their possession, thereby preventing use of any materials by any persons not participating in the study.
All base units and remaining capsules (untouched or taken out of the blister package) must be brought back by the subjects to the site by the time they exit the study. The number of remaining capsules must match the information transmitted by the base unit about capsule activations and the information gathered about the subject's treatment compliance throughout the study. In order to perform this task, the Sponsor, CRO and study coordinator will rely on the same platform used to monitor protocol deviations related to treatment compliance. A final account, and the whereabouts of each capsule provided to the subject will be documented in the EDC by the study coordinator. Capsule failures will not be documented in the EDC but on the external platform, using the base unit information.

After completion of the study, all unused or remaining devices must be returned in their original package to Vibrant Ltd. Hakochav, Yokneam 2069206 P.O.Box 516, Israel.
All investigators will be responsible for using the products according to the IFU and protocol and maintaining product inventory and records.

30. APPENDICES

A. Appendix A – Bristol Stool Scale
B. Appendix B – Full list of Adverse Events – Phase 3 clinical investigation
C. Appendix C - Rome III questionnaire and instructions for completion
D. Appendix D – PAC-QOL questionnaire
E. Appendix E – Baseline training questionnaire
F. Appendix F – TSQM questionnaire
G. Appendix G – Ease of use questionnaire
H. Appendix E - Subject daily diary

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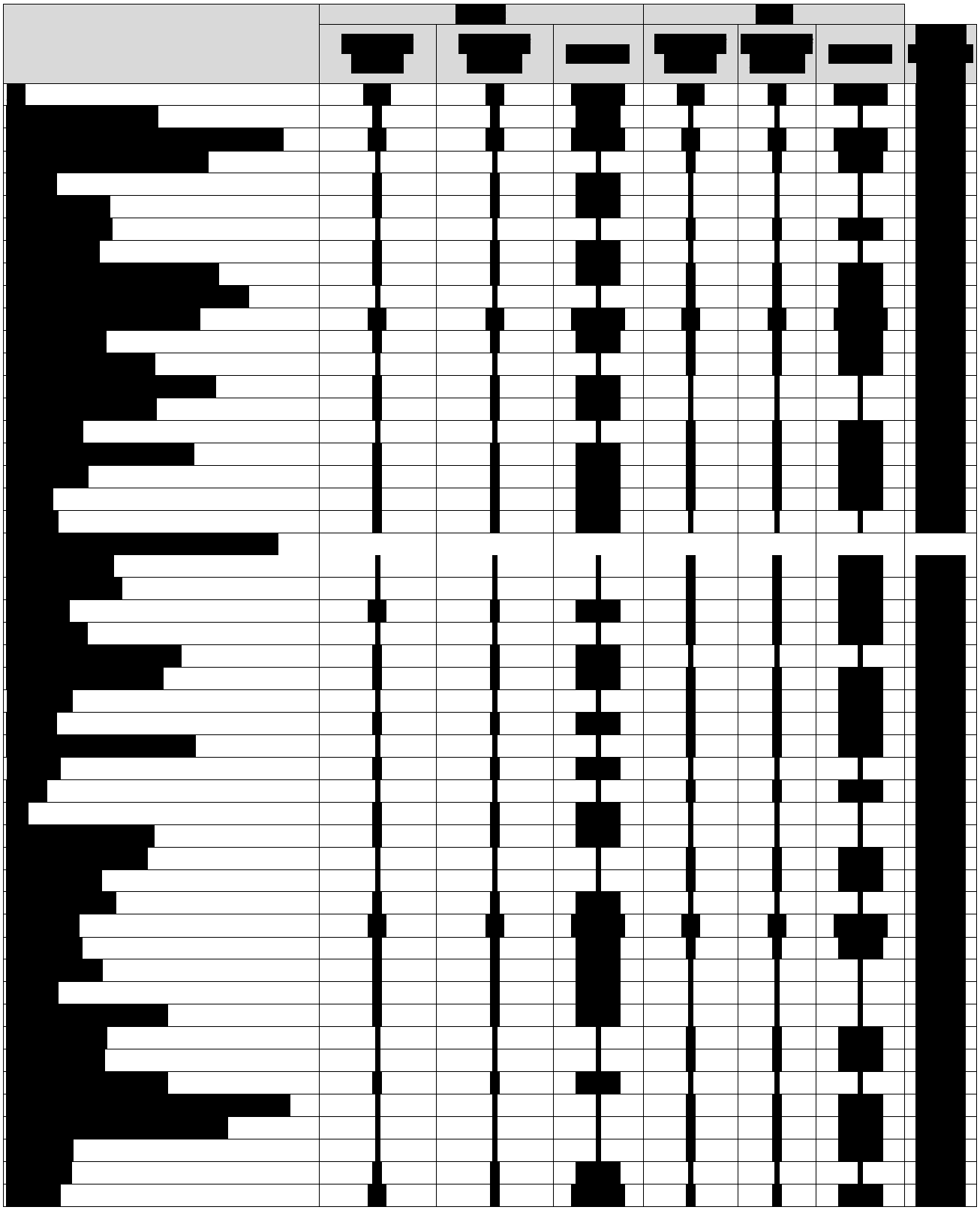
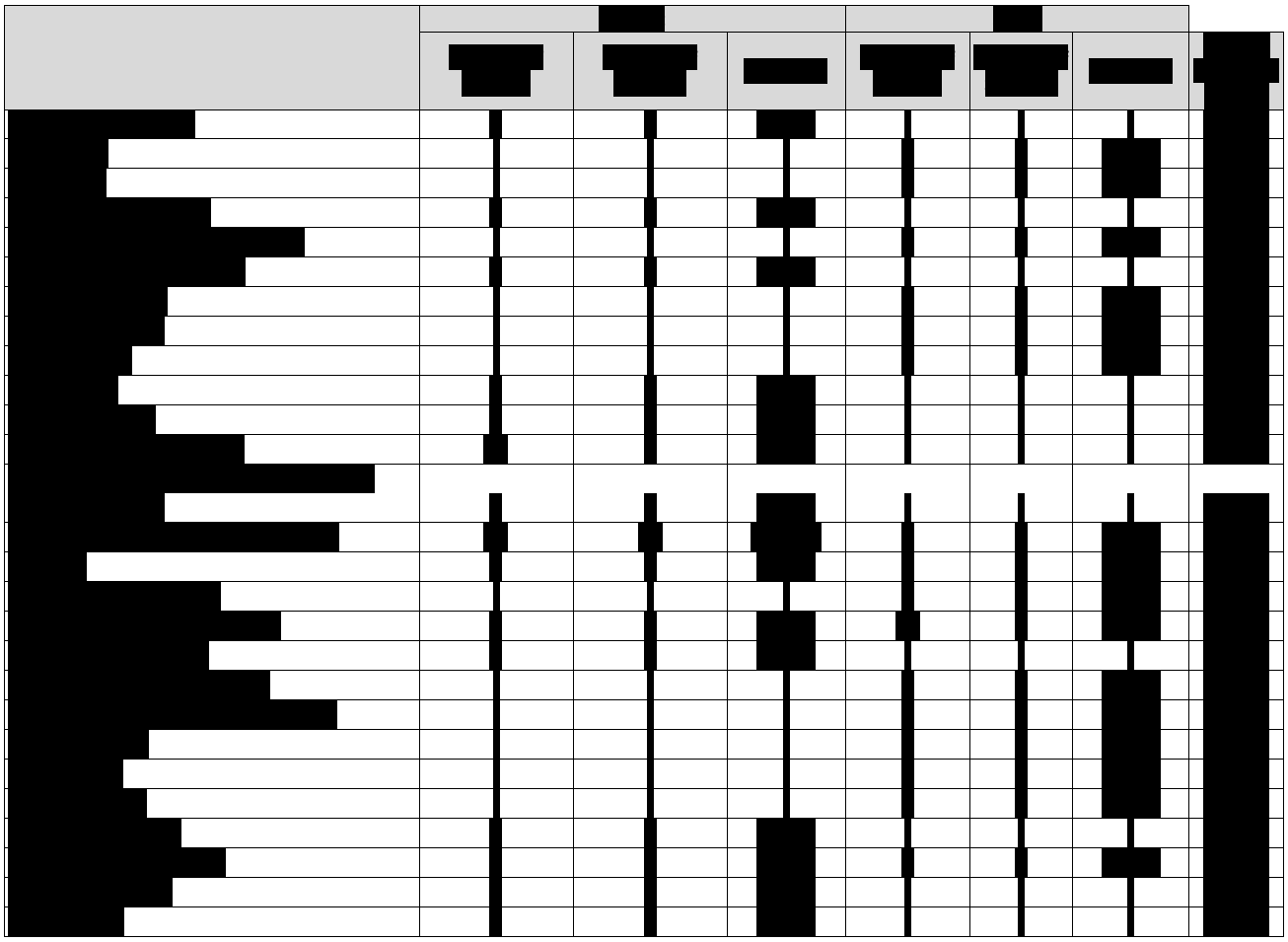
APPENDIX A – Bristol Stool Scale

The Bristol Stool Scale:

How to analyze stools:

Appendix B - Full list of Adverse Events – Phase 3 clinical investigation

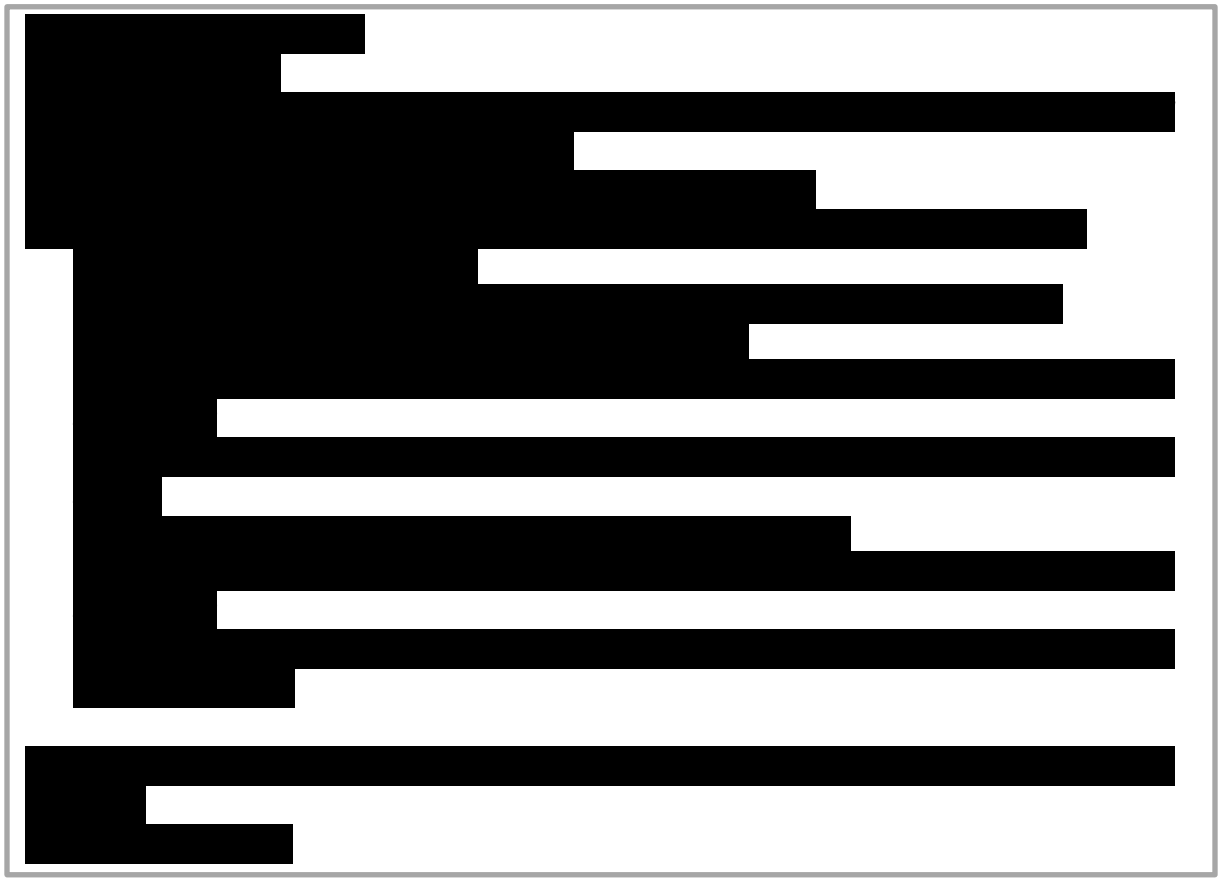




APPENDIX C – ROME III (Questionnaire and Instructions for Completion)

Instructions for completion:
Complete questions 41 to 67 only.

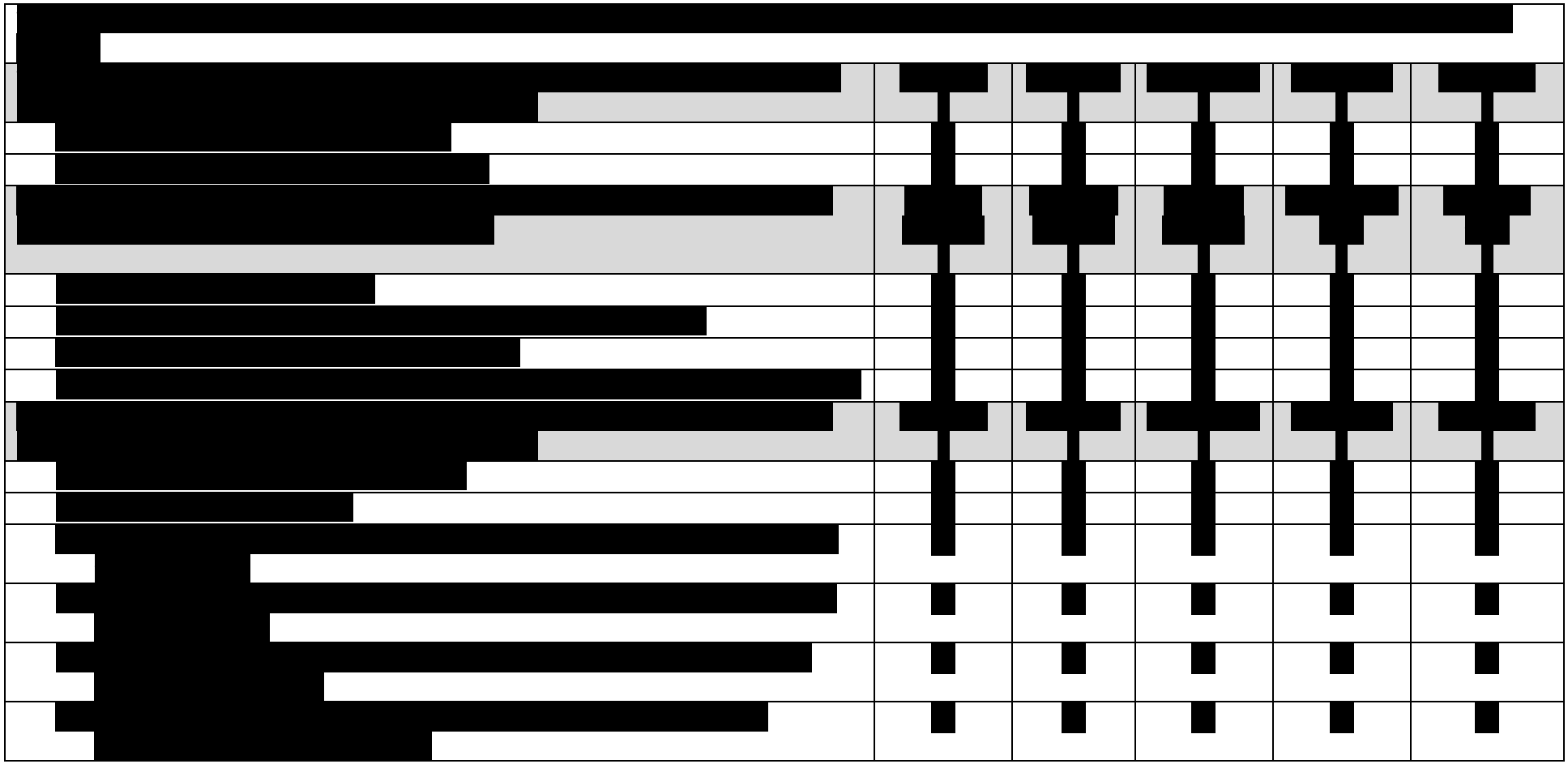
S[redacted]



ROME III ADULT QUESTIONNAIRE

Question	*Answer*

APPENDIX D – Patient Assessment of Constipation Quality of Life (PAC-QOL) Questionnaire



APPENDIX E – Baseline training questionnaire

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APPENDIX F – TSQM Questionnaire

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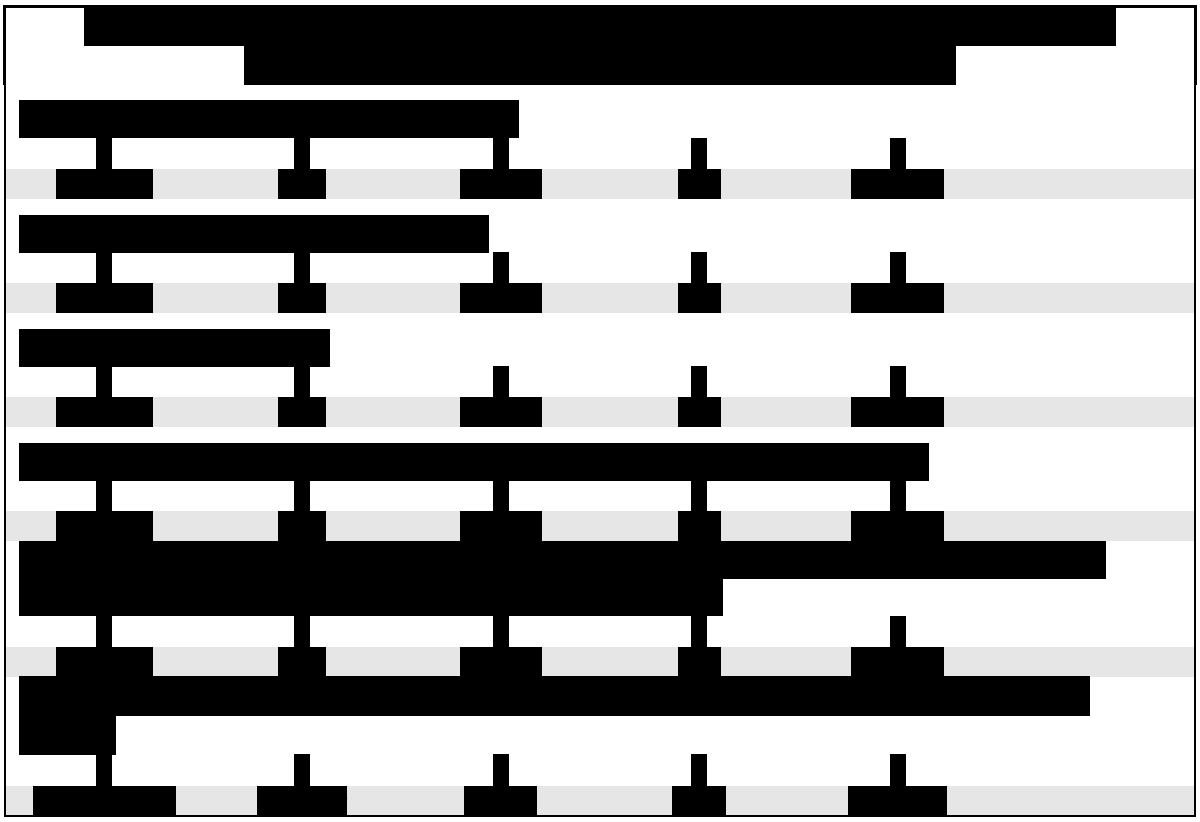
[redacted]

APPENDIX G – Ease of use questionnaire



APPENDIX H – Subject Diaries

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