Study number: NCT02829047

Protocol number: 220CLD
Protocol Date: August 26, 2016 Rev. 03

A prospective, multicenter, open-label, single-arm study to assess the tolerability, safety and efficacy of a new frequency of Vibrant Capsule administration

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] ---------- Date: August 26, 2016

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
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
Mg	Milligram
µg	Microgram
Min	minute(s)
MFR	Manufacturer
NCAs	National Competent Authorities
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over The Counter
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
US	United States
USADE	Unanticipated Serious Adverse Device Effect

4. Protocol Synopsis

Name	A prospective, multicenter, open-label, single-arm study to assess the tolerability, safety and efficacy of a new frequency of Vibrant Capsule administration
Indication	The Vibrant Capsule is intended for the treatment of patients with Functional Constipation, with an average of ≥1 and <2.5 spontaneous bowel movements (SBMs) per week
Objectives	The objectives are to assess the tolerability, safety and efficacy of a new frequency of Vibrant Capsule administration: one per day for 2 days, followed by one day without
Design	The study is a prospective, multicenter, open-label, single-arm study, to evaluate the tolerability, safety and efficacy of the Vibrant Capsule in relieving constipation. One arm will be assessed: Vibrant Capsule administered with a sequence of one per day for 2 days, followed by one day without, one per day for 2 days followed by one day without, etc. (14 capsules in 3 weeks). The study will be performed in up to 15 centers in the USA. The study will have one interim analysis. The interim analysis will be performed after 20 patients complete the study and are evaluable. The following parameters will be assessed: ease of use of the home base unit, tolerability and safe use of the new frequency of Vibrant Capsule administration. Patients will follow a 2 weeks baseline period and then take the Vibrant Capsule for a treatment period of 6 weeks. Data reporting will be done on an electronic Case Report Form (eCRF) and an eDiary. During the 2 weeks of baseline, patients will be asked to refrain from taking any medication or supplement to relieve their constipation. After 14 days the patients will return and eligibility will be re-assessed. Patients will be trained on how to use the base unit. They will activate and ingest the capsules at home by themselves, using the base unit. Patients will be instructed to complete a simple patient eDiary each day throughout the duration of the study. After 3 weeks of treatment, the patient will attend for evaluation and to receive new capsules. A final visit will take place at the end of the 6 week treatment period. Patients will receive phone calls up to twice per week and patient compliance will be monitored during the 8 weeks of the study.

	Patients will be authorized to use rescue medication after 3 consecutive days without a spontaneous bowel movement. Patients 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. Patients will be requested to ingest the capsules at a specific time of the day.
Study duration	Study duration is 8 weeks - 2 weeks of baseline - 6 weeks of treatment
Endpoints	The primary efficacy endpoint is the SBM success rate, defined as an increase from the run-in period of at least one weekly Spontaneous Bowel Movement (SBM) during at least 3 of the 6 weeks of treatment. Subjects with less than 2 weeks (with at least 5 days per week) of valid diary during the treatment period will be considered as non-evaluable. Secondary efficacy endpoints include: [redacted] Safety endpoints include all adverse events related and unrelated to the study treatment.
Patient Population	Patients with Functional Constipation refractory to existing treatments.

No. of Subjects	Approximately 134 subjects
Inclusion criteria	1. Patients aged 22 years and older 2. Patients 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. Patients 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 patients are <50 years old and without alarm signs and/or symptoms 5. Patient signed the Informed Consent Form (ICF) 6. Female subjects must have a negative urine pregnancy test 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 urine 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: o Medications that may affect intestinal motility, prokinetics, anti-depressants, anti-Parkinsonian medications, opiates, opioids, calcium-channel blockers, aluminum/magnesium hydroxide o 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. Patients on cardiac doses of aspirin may be enrolled in the study 12. Patients with pelvic floor dysfunction/defecatory disorder, based on patient 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. Any other condition which in the opinion of the investigator may adversely affect the safety of the patient or would limit the patient's ability to complete the study
Sample size	134 subjects. No formal sample size calculations were performed. A sample size of approximately 134 subjects is considered sufficient to fulfill the study goals.
Statistical analysis	Statistical analyses will be performed using SAS® v9.4 (SAS Institute, Cary NC, USA). Statistical analyses of safety and efficacy measures will be mainly descriptive in nature. Continuous variables will be summarized by a mean, standard deviation, minimum, median, and maximum range and categorical variables by a count and percentage. Confidence intervals will be provided where relevant. *Major Efficacy Analyses:* The subject's success status (i.e. if the subjects achieve an increase from baseline of at least 1 weekly SBM during at least 3 out of the 6 treatment weeks) will be calculated. The success rate will be presented along with its exact binomial two sided 95% Confidence Intervals (CI).

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, patients 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 patients 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 patient-year, whereas the attributable direct costs of CIC range from approximately $1,900 to $7,500 per patient-year[6].

Although a variety of treatment options are available for chronic constipation, patients have reported low satisfaction with current treatment alternatives in multiple published studies. Thus, there is a need for additional therapeutic options that address patient 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, patients 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 patients 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 patients 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 patients[8]. In total, 8% of patients 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 patients 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 patients who received lubiprostone 24 mcg twice daily in clinical trials experienced nausea; 4% of patients had severe nausea while 9% of patients

discontinued treatment due to nausea. Approximately 12% of patients 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 patients 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 patients 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 patients 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 patients: a US study showed that 47% of constipated patients are not completely satisfied with their current constipation treatment[3], while a European study showed that only 27% of European patients are satisfied with current treatment options[5]. Furthermore, many patients become refractory to one or more OTC laxatives with chronic use, which may cause frustration for both the clinician and the patient, and ultimately leads many patients to abandon therapy and remain dissatisfied with their condition[2]. Nearly 90% of patients 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 intended t[redacted] for the relief of patients with Functional Constipation (FC), with an average of at least 1 and less than 2.5 spontaneous bowel movements (SBMs) per week.

8. DEVICE DESCRIPTION

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Figure 1. The capsule and components

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8.2 Accessory: activation base unit

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8.3 Mode of operation

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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 patient 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.

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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 patients.

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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12. STUDY OBJECTIVE

The objectives are to assess the ease of use, tolerability, safety and efficacy of a new frequency of Vibrant Capsule administration: one per day for 2 days, followed by one day without (14 capsules in 3 weeks).

13. STUDY ENDPOINTS

13.1 Primary endpoint

The primary efficacy endpoint is the SBM success rate, defined as an increase from the run-in period of at least one weekly Spontaneous Bowel Movement (SBM) during at least 3 of the 6 weeks of treatment. Subjects with less than 2 weeks (with at least 5 days per week) of valid diary during the treatment period will be considered as non-evaluable.

13.2 Secondary endpoints

[redacted]

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. Patients aged 22 years and older
2. Patients 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. Patients 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 patients are <50 years old and without alarm signs and/or symptoms
5. Patient signed the Informed Consent Form (ICF)
6. Female subjects must have a negative urine pregnancy test 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 urine 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. Patients on cardiac doses of aspirin may be enrolled in the study

12. Patients with pelvic floor dysfunction/defecatory disorder, based on patient 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. Any other condition which in the opinion of the investigator may adversely affect the safety of the patient or would limit the patient's ability to complete the study.

14.3 Duration of Study

Study duration includes 2 weeks of run-in, followed by 6 weeks of treatment - Total of 8 weeks.

Overall duration of the study is expected to be up to 10 months: up to 8 months of patient enrollment, eight weeks of run-in and treatment period.
The goal is to enroll up to 134 subjects.

15. STUDY TREATMENT

Detailed study treatment herein:

15.1 Study Design

The study is a prospective, multicenter, open-label, single-arm pilot study to evaluate the tolerability, efficacy and safety of the Vibrant Capsule in aiding relieving constipation.

The objective is to assess the tolerability, safety and efficacy of the Vibrant Capsule with a frequency of administration of one per day for 2 days, followed by 1 day without.
The study is a single-arm study.

The study will be performed in up to 15 centers in the USA.

The study will have one interim analysis.
The interim analysis will be performed after 20 patients complete the study and are evaluable. The following parameters will be assessed: ease of use of the home base unit and the safe use of the new frequency of Vibrant capsule administration.
Depending on the results of the interim analyis:
- The study will be modified to adapt changes for the ease of use or tolerability.
- The study will continue as planned.

Data reporting will be done on an electronic Case Report Form (eCRF). In addition, patients 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. On smartphone and tablet, the website will be accessed via an application.
Information about time of activation of the Vibrant Capsules will be recorded automatically by the base unit and automatically transferred to the eCRF.

Patients 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 patient and the informed consent form will be signed.

Patients 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. Patient demographic and medical information acquired from the patient or the patient's medical chart, including age, gender, previous medical history, risk factors etc. will be also recorded on the eCRF.
In addition, patients will undergo a physical examination including digital rectal examination, vital sign measurements and blood tests.

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

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

After 14 days the patients will visit the medical center for the baseline visit. Eligibility will be re-assessed and confirmed based on the patient's completed eDiary and Rome III questionnaire. The patient will 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 patient. Only the first ingestion will take place in the medical center.
During the treatment period, patients will ingest Vibrant Capsule using the following sequence: one per day for 2 days, 1 day without, one per day for 2 days, 1 day without, etc. The patient will ingest a total of 28 capsules in 6 weeks considering the sequence.

Capsule intake will always be performed at the same time: during the evening, between 9 PM and 10 PM.

After 6 weeks, treatment will be ceased and patients will visit the medical center one last time for evaluation and completion of Rome III questionnaire, Bristol Stool Scale and other assessments.

Patients will be instructed to complete a simple patient eDiary throughout the duration of the study. This will include daily recordings of number and time of bowel movements, clinical symptoms 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 patient 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

Patient demographic and medical information acquired from the patient or the patient'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 patients 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, usage of rescue medication, 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 patients will undergo a conventional physical examination by an authorized physician. The physical examination will include diagnosis and documentation of any significant abnormalities or diseases.

15.5 Assessment of pelvic floor dysfunction (defecatory disorder)

Assessment of pelvic floor dysfunction will be based on patient history. Patients with suspicion of pelvic floor dysfunction will be excluded.
If patients 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 patients.

15.6 Blood and urine tests

During the screening visit all patients 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 -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) will also be completed by the patient.

The investigator will confirm their eligibility and their physical and mental suitability to participate in this study.
Patients exiting the trial at this stage will be considered screening failure patients and be replaced with new patients to reach the goal of 120 patients.

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

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

Eligible patients 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.
Patients will complete the eDiary every day.
The patients will receive 2 short phone calls/week from the study coordinator.
The phone calls will be about 5-10 minutes long and will ask check patient compliance with the eDiary, occurrence of adverse events, use of rescue medication, patient understanding of what he needs to do in the context of the study and discuss any issue or difficulty that the patient might have. The phone calls will be made more than 1 day apart. Confirmation of date and time of the phone call will be reported on the eCRF.

If a patient does not fill in his/her eDiary, the sponsor/investigator will be alerted and the patient will be contacted by phone call the next day in order to receive more information and gather the missing information. Compliance of the patient will be closely monitored.

15.9 Treatment

On day 0 (baseline visit), the patient will arrive to the clinic. Eligibility will be re-assessed and confirmed based on the Rome III questionnaire and on the patient's completed diary. Based on the Vibrant Capsule's intended use, patients 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.

The Bristol Stool Scale will be completed.

Eligible patients will take the Vibrant Capsules. The study is open-label.

Treatment duration is 6 weeks.
The patient will be trained by the study coordinator to activate the Vibrant Capsules using the base unit. After an oral explanation, the patient will read the label, and the study coordinator will make sure the patient fully understands how to use the base unit. The patient will then activate his/her first capsule, in front of the study coordinator, and swallow it.
The patient will be released home with the base unit and capsules for the first three weeks of treatment. He/She will be asked to continue with the daily completion of the eDiary.
Actual point of enrollment for the patient is considered the day of first capsule intake.

Patients 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 will be performed during the evening between 9 PM and 10 PM.
Only the first intake, which is in the medical center, will not take place at such a time.

Half of the capsules the patient is scheduled to take will be provided at the baseline visit. The patient will be provided with the second half of the capsules during a mid-treatment visit to the medical center (day 21).

The first week of treatment, the patient will receive two short phone calls from the study coordinator. Starting the second week of treatment, he will receive one phone call per week.
The phone calls will be about 5-10 minutes long and will check patient compliance with capsule ingestion and the eDiary, occurrence of adverse events, use of rescue medication, patient understanding of what he/she needs to do in the context of the study and discuss any issue or difficulty that the patient might have. During the week when two phone calls are needed, the phone calls will be made more than 1 day apart. Confirmation of date and time of the phone call will be reported on the eCRF.
If a patient does not fill in his eDiary, the investigator will be alerted and the patient will be contacted by phone call the next day in order to receive more information and gather the missing information. Compliance of the patient will be closely monitored.

After three weeks of treatment, the patient will come back to the medical center. 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, concomitant medication/rescue taken, evolution of constipation symptoms, patient's perceptions about the treatment, motivation of the patient, or any other topic relevant. The patient will bring back all remaining capsules (spare not activated and defective) from the first 3 weeks of treatment.
The patient will receive capsules for the last three weeks of the treatment period and will be released home.

15.10 Rescue Treatment

Patients with no spontaneous bowel movement for 3 consecutive days will be authorized to use rescue, if they wish to. The patients will not be required to contact the investigator prior to taking any medication/supplement but they will be required to declare 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)

If the patient takes a rescue medication/supplement that is not in the above list, the patient will need to give a reason for it in his eDiary.
If 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.

Patients 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 24h 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 patient.

15.11 Termination visit

After 6 weeks, treatment will be ceased. Patients will visit again the medical center for evaluation and completion of the Rome III questionnaire, Bristol Stool Scale and study end form. The patient will be evaluated for occurrence of adverse events, concomitant medication/rescue and compliance to the eDiary.
The patients will bring back all remaining capsules in their possession as well as the base unit.

15.12 Concomitant medication

All medication taken by the patient 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 patient 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.
Patients 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 patients, alongside the Vibrant capsule and other treatments will be performed and recorded on the appropriate study eCRF.
The patient 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 patient 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	Mid-treatment visit	Termination visit
Visit No.	1	2	3	4
Day	-14	0 (+1-2 days)	21 (±1-2 days)	42 (±1-2 days)
IC	+			
Eligibility Criteria	+	+		
Physical Exam	+			
Digital Rectal Exam	+			
Vital Signs	+			
Lab Data	+	+		
Administration of capsule		+		
Rome III	+	+		+
Bristol Stool	+	+	+	+
Patient 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.

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, malfunctions 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 and also negatively impacts treatment of the study subject.
- **Device Malfunction** - A device malfunction occurs when an unexpected change to the device that is contradictory to the Instructions for Use is observed, which may or may not affect device performance.
- **Device Misuse** - Any use of the investigational device by an investigator 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-patient 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 patient's usual activity or is transient, resolved without treatment and with no sequelae.
Moderate – Interferes with the patient's usual activity and/or requires symptomatic treatment.
Severe – Symptom(s) causing severe discomfort and significant impact of the patient'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 patient returned to baseline status
Ongoing - Patient did not recover and symptoms continue
Recovered with sequelae - The patient has recovered but with clinical sequelae from the event
Unknown - The patient 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 Sponsor's Reporting to National Competent Authorities (NCA)

The sponsor of the clinical investigation (which could be the manufacturer (MFR), or his authorized representative (AR)) have to report at the same time to all NCAs where the clinical investigation has commenced, the following reportable events:

1. Any SAE

2. Any Investigational Medical Device Deficiency that might have led to a SAE if
    a) suitable action had not been taken OR
    b) intervention had not been made OR
    c) if circumstances had been less fortunate
3. New findings/updates in relation to already reported events.

- A SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it, should be reported immediately, but not later than 2 calendar days after awareness by sponsor.
- Any other reportable events or a new finding/update to it should be reported immediately, but not later than 7 calendar days following the date of awareness by the sponsor.

Reporting should be made using the SAE reporting guidelines in 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).
Sponsor will also submit to the NCAs all safety updates and periodic reports, as required by applicable regulatory requirements.

16.7 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, open-label, single-arm study, designed to assess the tolerability, safety, ease of use and efficacy of active Vibrant capsule when administered 14 times every 3 weeks in patients with Functional Constipation.
After a run-in period of 14 days, subjects will be treated with the active Vibrant capsule for 6 weeks.
An adaptive design with 1 interim analysis is planned.

17.2 Study Endpoints

17.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the SBM success rate, defined as an increase from the run-in period of at least one weekly Spontaneous Bowel Movement (SBM) during at least 3 of the 6 weeks of treatment. Subjects with less than 2 weeks (with at least 5 days per week) of valid diary during the treatment period will be considered as non-evaluable.

17.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Ease of use
- CSBM success rate, defined as as an increase from the run-in period of at least one weekly Complete Spontaneous Bowel Movement (CSBM) during at least 3 of the 6 weeks of treatment. Subjects with less than 2 weeks (with at least 5 days per week) of valid diary during the treatment period will be considered as non-evaluable.
- Change from baseline in weekly number of Spontaneous Bowel Movement (SBM).
- Change from baseline in weekly number of Complete Spontaneous Bowel Movement (CSBM).
- Change from baseline in average stool consistency, using the Bristol Stool Scale
- Change from baseline in average bloating.
- Change from baseline in average abdominal gas.
- Change from baseline in average abdominal pain.
- Change from baseline in average straining.
- Change from baseline in abdominal discomfort.
- Change from baseline in average abdominal pain during defecation.
- Time to occurrence of spontaneous bowel movement after capsule.

17.2.3 Safety Endpoints

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

17.3 Interim Analyses

One (1) interim analysis is planned, after approximately 20 subjects will complete the 6 weeks of treatment with the Vibrant capsule.

17.3.1 Procedure

At the interim analysis, after all the relevant data will be entered into the database, and the database cleaned, a soft lock to the database will be performed. The ease of use, tolerability and safety will be assessed.

17.3.2 Decision Rules

The following decision upon the interim analysis report are planned:

- Stop the study in case of severe safety concern
- Continue the study as planned.
- Modify the frequency of use and/or the device's usability

17.3.3 Controlling the Alpha level for the primary endpoint

As the interim analyses is planned, only for futility or to modify the frequency of use and/or the device's usability, and that the primary endpoint is not based upon any statistical inference, not at the interim (only point estimate will be calculated) and not end the final analyses, no procedure is requested to control the overall alpha level.

17.4 Sample size

The chosen sample size is 120 subjects who will be enrolled and complete the 6 treatment weeks.
The final sample size will be determined following the completion of the interim analysis, based on the efficacy of the new frequency of vibration capsule.

The sample size account for a potential 10% of drop-outs.
The sample size will be increased to at least 134 to account for a potential 10% of drop-outs, as needed.

17.5 Randomization

This is an open-label, single-arm study.

17.6 Blinding

Not Relevant.

17.7 Data Analysis Sets

17.7.1 Full Analysis Set (FA)

The FA analysis set will consist of all subjects who were treated with at least one Vibrant capsule. Subjects with no valid post baseline assessment will not be part of the relevant analyses.

17.7.2 Per-Protocol (PP)

The per-protocol analysis set will consist of all subjects from the FA analysis set without major protocol violations.

17.7.3 Statistical Analysis of Analysis Sets

The FA analysis set will serve as the main set for safety assessments.
The PP analysis set will serve as the main set for efficacy assessments.
The primary efficacy assessment will also be performed on the FA analysis set.

17.8 Statistical Analysis

17.8.1 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.

17.8.2 Significance levels and handling of type I error

17.8.2.1 Type I Error

The overall significance level for this study is 5% using two-tailed tests and two sided Confidence Intervals (CI).
The analyses of this study are mainly descriptive in nature.

17.8.3 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.

17.8.4 Disposition of Subjects

Treatment tolerability will be presented, 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.

17.8.5 Efficacy Analysis

The subject's success status (i.e. if the subjects achieve an increase from baseline of at least 1 weekly SBM during at least 3 out of the 6 treatment weeks) will be calculated. The success rate will be presented along with its exact binomial two sided 95% Confidence Intervals (CI).

Ease of Use will be presented in a tabular form.

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

The change from baseline in number of weekly SBM will be modeled with an Analysis of Covariance (ANCOVA) model, with baseline weekly number of SBM and site as covariates. The adjusted means of the change from baseline will be presented along with its 95% CI.

The change from baseline in count of weekly CSBM, and in symptoms, 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 will be assessed and presented by Kaplan-Meier curves.

17.8.6 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, baseline number of weekly SBM, and center will be entered into the models. Centers with less than 10 subjects will be grouped together by geographical area. If the center term is found significant, the reason for this 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.

17.8.7 Safety Analysis

Adverse events (AE) will be presented by seriousness, severity and relation to treatment by treatment group. The number of reports, the number of subjects, and the incidence (percent of subjects) will be tabulated by study arm.

17.8.8 Handling of Missing Data

Missing value will not be imputed and will be left “as-is”.
For the time to first SBM analysis, subjects with no known SBM will be considered left censored.

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 patient will be identified by his/ her initials and a unique patient 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 patients enrolled in the study will provide their consent prior to entering the study. An informed consent form shall be signed and dated by the patient. 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.

Patients will also have access to this EDC to complete their diaries online.

Both sites and patients will get trained on how to access and use the EDC 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 EC. When applicable, the amendment's implementation will take place only once approved by the EC.
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. Patients 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. Patient is Lost to follow-up.
7. Confirmed pregnancy.
8. Regulatory authorities stop the trial.

During the study, patients exiting the trial will be replaced with new patients, in order to have 120 patients 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 number will be documented in patient 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.
After completion of the study, all unused 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 - Patient daily diary

31. REFERENCES

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APPENDIX A – Bristol Stool Scale

The Bristol Stool Scale:

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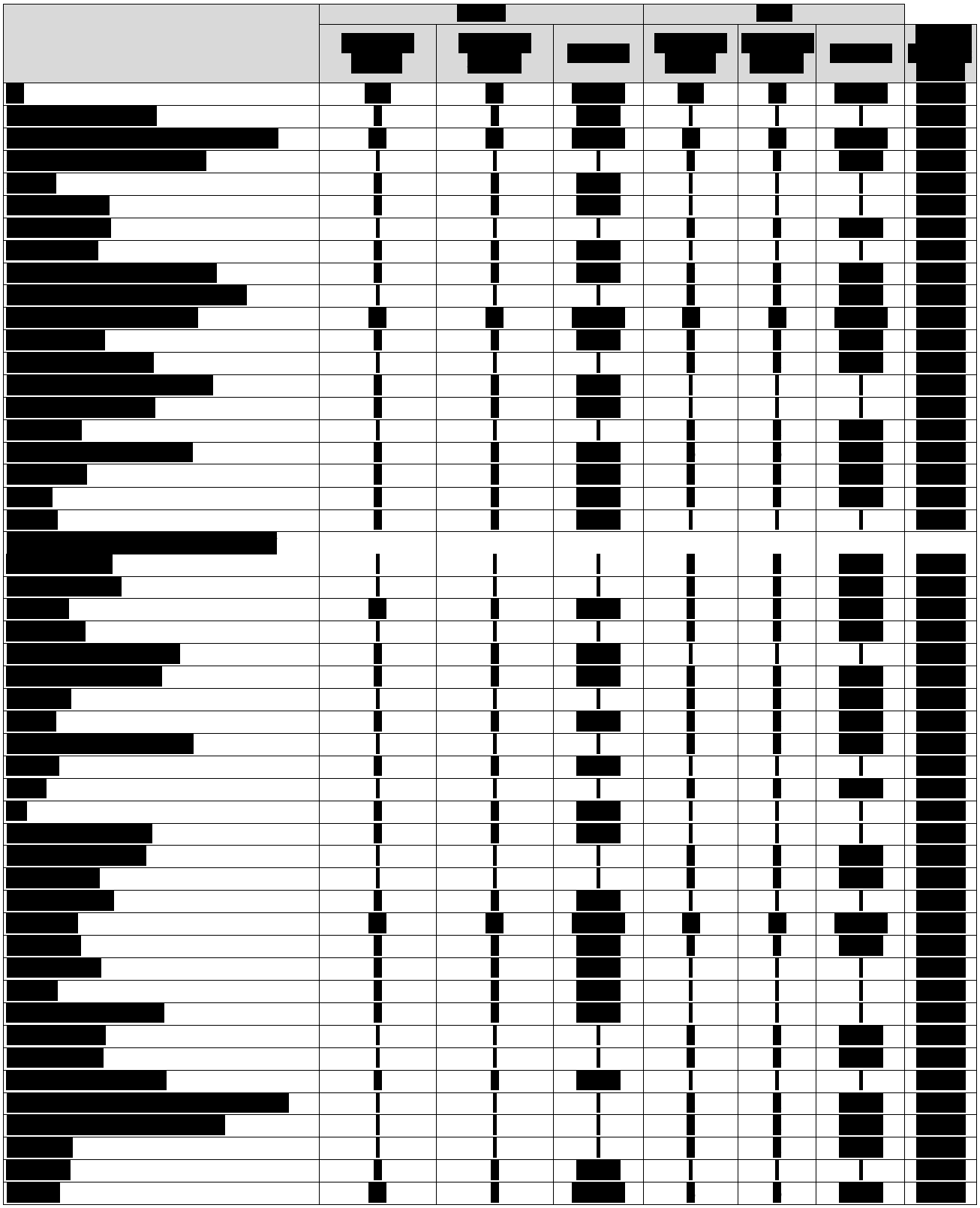
Appendix B - Full list of Adverse Events – Phase 3 clinical investigation



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

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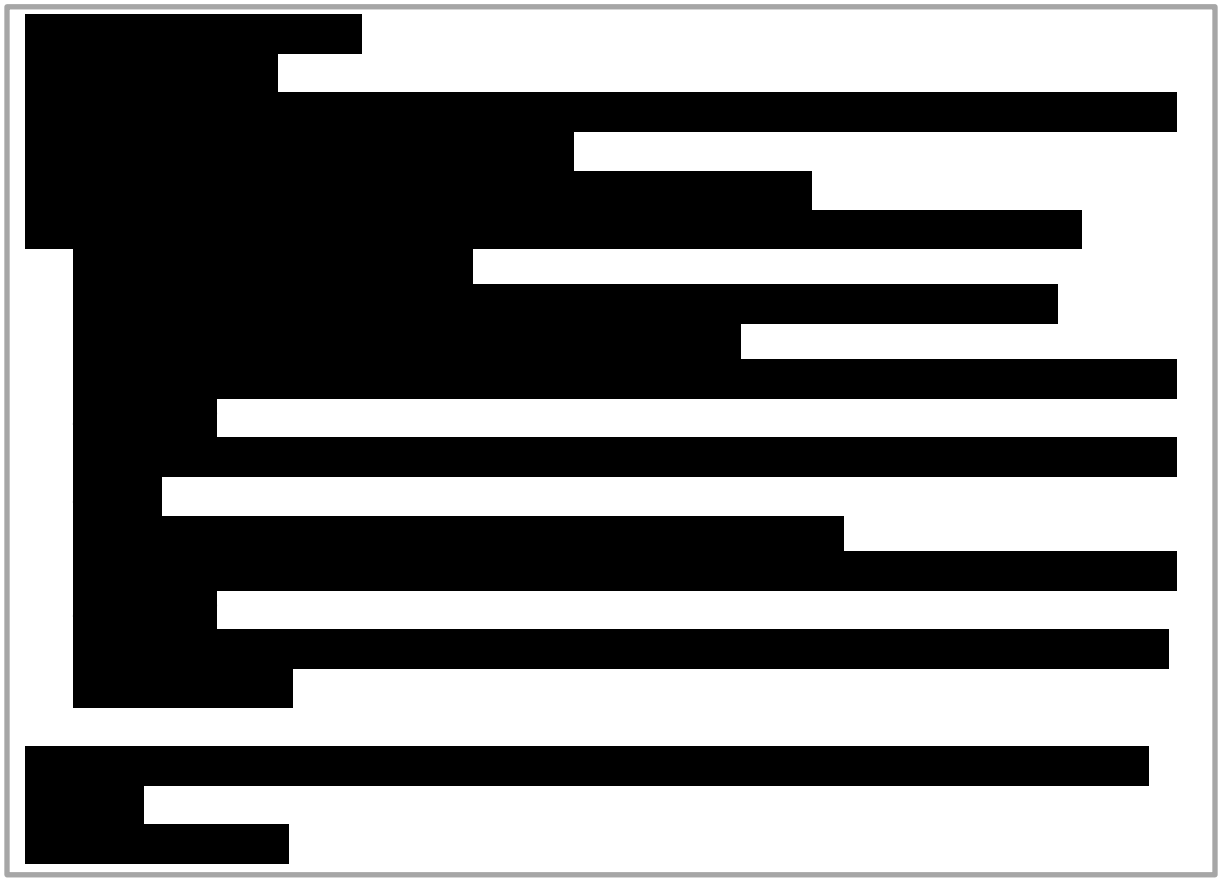

APPENDIX D – Patient Diaries

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PART 2A

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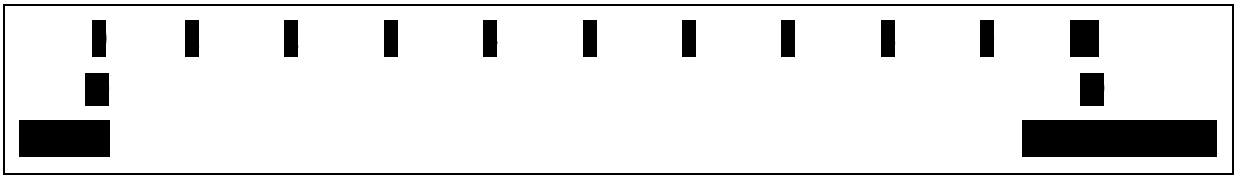

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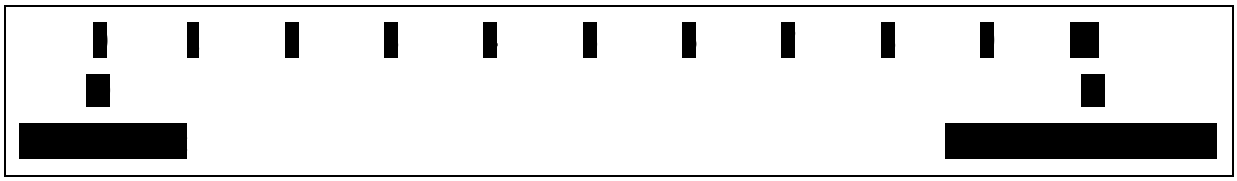

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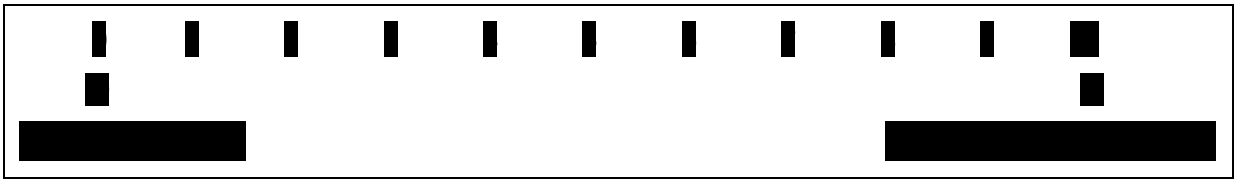

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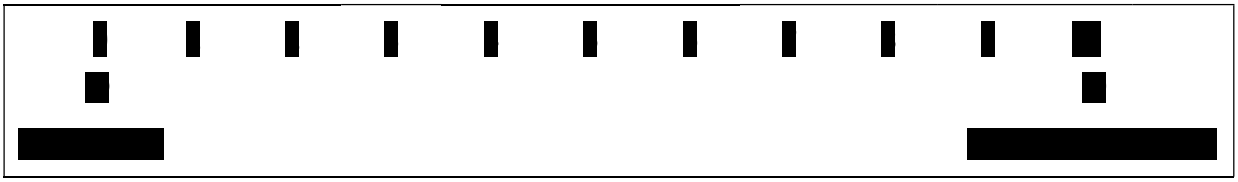

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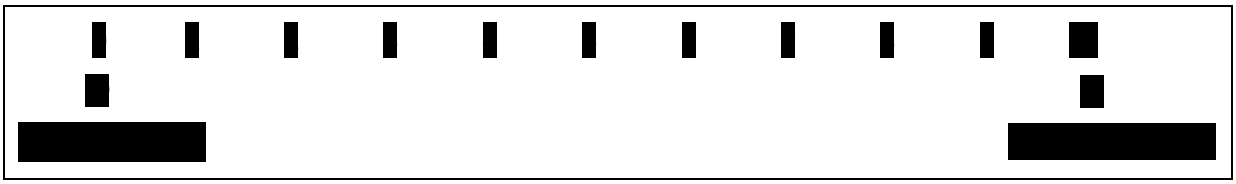

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