

The Vibrating Capsule: Safety and Tolerability in Patients with Chronic Idiopathic Constipation

Short Running Title: Vibrating Capsule is Safe and Tolerable in CIC

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Key Points:

1. The Vibrating Capsule treatment for Chronic Idiopathic Constipation was associated with a low adverse event rate across 6 trials in this post-hoc analysis
2. There were no severe adverse events or recorded capsule retentions across all 6 trials
3. The Vibrating Capsule was well tolerated with no patient stopping treatment early during any of the 6 trials.

Declarations:

Consent for publication: No individual data was used in this study

Availability of Data and Materials: The analyzed data from the current study are not publicly available due to the novelty of the treatment but are available from the corresponding author upon reasonable request.

Competing Interests:

Bryan F Curtin, William D. Chey, Brennan M.R. Spiegel, Darren Brenner, Anthony Lembo: Served on a scientific advisory board for Vibrant Gastro

Satish SC Rao and Eamonn M M Quigley: Served on Vibrant advisory board and received research grant support for Vibrant clinical trials

Authors Contributions:

Bryan F Curtin: Concept, preparation of the article and revision.

Satish SC Rao: Concept, manuscript writing and revision.

Eamonn MM Quigley: manuscript writing and revision. William D. Chey: manuscript writing and revision. Darren M. Brenner: manuscript writing and critical revision

Abstract:

BACKGROUND: Chronic Idiopathic Constipation (CIC) remains a significant problem globally with increasing estimates for disease burden. In a Phase 3 placebo-controlled trial, a novel treatment using the Vibrating Capsule was recently shown to be effective in treating patients with CIC. However, its safety and tolerability has not been described in detail.

METHODS: We analyzed safety data from six trials encompassing the development of the Vibrating Capsule, including, dose-ranging and pivotal studies. The incidence of adverse events, treatment discontinuation, tolerability and satisfaction were assessed.

KEY RESULTS: A total of 800 patients who took either an active vibrating capsule or a sham / placebo (non-vibrating) but similar capsule from 6 studies were included in this post-hoc analysis. The most common adverse gastrointestinal events were bloating (2.9%), abdominal pain (2.9%), nausea (2.3%) and diarrhea (1.9%). A sensation of vibration was reported by 11.7% of patients. The adverse events rates were low, and investigators categorized most of them as unrelated to treatment. There were no serious adverse events such as retention of therapeutic capsules and no patient stopped therapy or withdrew due to adverse effects. The majority of patients (83%) found the system convenient, with an overall treatment satisfaction rate of 71%.

CONCLUSIONS AND INFERENCES: The Vibrating Capsule, a first in class treatment for CIC was found to be safe and well tolerated by patients in clinical trials. No patient discontinued treatment due to adverse events.

Introduction:

Chronic Idiopathic Constipation (CIC) is a global problem. Recent studies suggest that the global prevalence of CIC is approximately 11.7% ⁽¹⁾. This significant disease burden leads to loss of productivity and decreased quality of life for sufferers ⁽²⁻⁵⁾. There are currently more therapeutic options for CIC than ever before, yet patients report significant dissatisfaction with these options due to either lack of efficacy or side effects such as nausea, diarrhea and abdominal discomfort ^(6, 7). For these reasons, many patients express interest in non-pharmacologic options for their constipation ⁽⁸⁾. This underscores the unmet need for novel treatment modalities for patients with CIC.

More recently there has been interest in utilizing non-pharmacologic, mechanical stimulation devices that would treat CIC via a different mechanism. These devices offer the potential for improving CIC symptoms while avoiding many of the side effects associated with pharmacological treatments ⁽⁹⁾. The novel Vibrating Capsule is an orally ingested device that was recently proven to significantly improve constipation symptoms in CIC patients in a placebo-controlled phase 3 trial ⁽¹⁰⁾. This trial showed a greater percentage of patients receiving the vibrating capsule achieved its primary efficacy end point of an increase in 1 Complete Spontaneous Bowel Movement (CSBM) per week with the Vibrating Capsule compared to sham / placebo capsules. The proposed mechanism of action is augmentation of peristalsis in sync with the circadian rhythm of colonic motility ⁽¹¹⁾.

Despite previously demonstrated efficacy, concerns remain about the safety and tolerability of this novel intervention. Capsule devices have been utilized in the GI tract for some time, with video capsule endoscopy established as a vital component of the evaluation of occult bleeding from the gastrointestinal tract or in the diagnosis of tumors of the small intestine. Over several decades of use in clinical practice the retention rate of the video capsule has been approximately 2% ⁽¹²⁾. The novel Vibrating Capsule requires patients to take a similar sized non-dissolvable capsule five times per week so

concerns regarding retention or other side effects require an assessment. Here, we conducted an extended post-hoc analysis of the safety and tolerability data of the use of vibrating capsule in the treatment of patients with CIC across multiple clinical trials.

Methods

Study Design

From 2011-2021, six studies were performed to assess the safety and efficacy of the Vibrating Capsule (Figure 1), and all were included in this analysis (V111, V179, V240, V250, V300, V270). Studies were conducted for 8 weeks at multiple sites in the United States and Israel. Participants were assessed 4 times throughout the trial period including initial screening, a baseline visit after 14 days of run-in, week 4, and a close out visit at week 8. Depending on the specific trial, an in-person questionnaire or an app-based diary was used to track factors such as frequency of bowel movements, stool consistency via the Bristol Stool Form Scale, Patient Assessment of Constipation Quality of Life (PAC-QOL), treatment satisfaction scores, and ease-of-use questionnaires. Adverse events and side effects were also recorded at these visits as well as throughout the clinical trials. All participants signed an informed consent document that was approved by a central or local institutional review board, as appropriate. All patients, study evaluators, treating clinicians, and sponsors were blinded to the treatment allocations (excluding the single-arm safety study (V111)). Participants were recruited from clinics and through local advertisement at each site.

Participants

Participants included in this analysis were aged 22 years or older, met Rome III criteria for CIC and had failed to experience relief of their symptoms following at least one month of treatment with osmotic or stimulant laxatives (¹³). Patients with an average of ≥ 1 spontaneous bowel movements (SBMs) per week and ≤ 2.5 SBMs per week, during screening were eligible. All patients were required to have had a colonoscopy within the previous 5 years unless they were < 50 years old and had no alarm features (¹⁴). Patients with a history of complicated/obstructing diverticular disease, intestinal

obstruction, inflammatory bowel disease, gastrointestinal malignancy, gastroparesis, Zenker's diverticulum, dysphagia, esophageal stricture, pelvic floor dysfunction, megarectum, history of bariatric surgery, significant systemic illnesses, pregnancy/lactation, or with a pacemaker were excluded from the study. Patients with constipation secondary to drugs including opiates or who satisfied criteria for IBS-C (Rome III) were excluded (¹³).

Treatment Description

The Vibrating Capsule (Vibrant®, Vibrant Ltd, Hakochav Yokneam, Israel) requires an activation pod that programs the capsule to time the onset of the treatment protocol. Details of capsule activation and treatment paradigms have been previously described (¹⁰). The capsule measures 24.2 mm x 11.3 mm and contains a vibrating trigger, a medical grade energy source, a computer activation chip, and a latex-free biocompatible shell. Activation protocols varied across trials with 2-5 capsules ingested per week during the treatment periods. Vibration protocols led to activation for approximately 1-2 hours at 3 oscillation cycles per minute with periods of rest in between. The capsule was designed to be expelled in stool.

All the trials included in this analysis used an inactive sham / placebo capsule (Excluding the single-arm safety study (V111)). It is important to note that the sham / placebo capsule looked identical to the active vibrating capsule, and had similar dimensions. Given the similar constitution of the capsules and the primary purpose here was to address safety (rather than efficacy), we felt that it would be appropriate to include patients from multiple clinical trials in the total analysis, similar to other previous safety studies in CIC patients (¹⁵).

Results

Demographics:

A total of 800 patients were treated with a Vibrating Capsule or a sham / placebo control capsule in the six trials and were included in the analysis (Table 1). Four hundred and twenty-nine (53.6%) participants received active treatment. A large majority of participants were female (85.8%) and 43.4% of the cohort was Caucasian.

Black and Latino participants comprised 23.8% and 17% of the cohort, respectively, providing a broad ethnic distribution of the American population of CIC patients. Patients had significant symptoms of CIC with <1 Complete Spontaneous Bowel Movement (CSBM) per week and decreased stool consistency (Table 2). Patients included in these studies had been suffering with constipation for >10 years on average.

Adverse event profile:

Overall adverse event rates were low and similar between active and sham / placebo treatment groups (Table 3). Diarrhea occurred in only 15 of the 800 patients (1.9%). Similar rates of adverse events were seen for nausea (2.3%), abdominal distention/bloating/flatulence (2.9%), and abdominal pain/discomfort (2.9%). In the safety study (V-111) and exploratory study (V-179) there were increased incidences of headaches (12% and 7.1% respectively) but these rates were not identified in subsequent trials. 12% of patients described feeling a `sensation of vibration` in the active cohort while only 2% expressed this feeling in the sham / placebo cohort. When assessing subjective experiences of side effects, only 1.2% of the patients treated found the side effects to be bothersome.

No serious adverse events or Emergency Department visits directly attributable to capsule administration were reported during any of the six trials. No patients withdrew from the studies prematurely due to adverse events and all patients completed 8 weeks of therapy. No episodes of capsule retention were reported during the trial however this was not formally assessed with abdominal imaging at the conclusion of the studies.

Functionality and Ease of use/tolerability:

The ease of use of the Vibrating Capsule and its activation system were assessed at week 4 and week 8 throughout trials V240, V250, V300, and V270 (Table 4). A majority (83%) of the patients found the treatment convenient (not disruptive to daily routine). Similarly, 87% of patients found it easy to plan the time of treatment. When asked if they found the treatment easy to use, 87% of patients indicated that the system was easy to use in its current form while only 4% found it extremely difficult. A majority of the

patients (71%) reported satisfaction with the capsule treatment compared with 29% of patients who were dissatisfied.

Discussion

In this analysis of 800 patients with CIC treated across six studies, we found that the Vibrating Capsule was safe and well tolerated. Adverse events were limited, mostly insignificant when compared to sham / placebo capsules, and no serious adverse events were reported. Most patients found the system easy to use.

Importantly, no instances of capsule retention requiring endoscopic retrieval or surgical extraction occurred during these studies. This is especially noteworthy as similar devices, such as the video endoscopy capsule, have infrequently been associated with retention requiring endoscopic or surgical removal (¹²). For this reason, patency capsules have been developed to reduce the risk of capsule retention (¹⁶). With the Vibrating Capsule system, patients took 2-5 capsules per week without evidence of capsule retention. This may give providers some comfort in recommending this technology for the treatment of constipation. Patient selection likely accounts for this discrepancy between retention rates for the Vibrating Capsule and the video endoscopy capsule. The video capsule is used in patients with suspected small bowel pathology, such as Crohn's disease, which would be an exclusion for the use of the Vibrating Capsule. It is not realistic or cost effective to perform interventions such as patency capsules, enterography, or anorectal manometry prior to initiation of the vibrating capsule in most clinical settings which underscores the importance of safety data such as this analysis. Vibrating capsules should not be used in a patient with a history of complex intestinal surgeries, adhesions, bowel obstruction, intestinal stricture or stenosis, Crohn's disease or complicated diverticular disease. In this analysis where 800 patients were given either a vibrating or a sham / placebo capsule, there were no instances of capsule retention suggesting that in the appropriate patient population, the capsule is unlikely to be retained in the small intestine. Prolonged retention in the colon is possible given the nature of the patient population. It is unknown how long the capsules remain in the colon and what is an approximate transit or exit time for these

capsules is since patients were not asked to document passage of capsules, and it is often hard to see them if they are encased in stool.

Any population of patients that suffers from constipation will be quite diverse and include those with altered anatomy resulting from prior surgery, individuals taking medications such as opioids, as well as those with more diffuse motility disorders (¹⁷⁻¹⁸). The Vibrating Capsule is contraindicated in patients with anatomy-altering surgeries such as gastric bypass or a prior history of bowel resection. Conditions or medications that cause gastroparesis or otherwise slow proximal gut transit could decrease the efficacy of the Vibrating Capsule by delaying its arrival into the colon with premature activation in the small intestine. All patients in these studies were pre-screened for colon cancer using current best practices (¹⁹). The role of pre-treatment motility studies such as small bowel follow-through, sitz marker study, or whole gut transit study are yet to be elucidated, as they were not performed in the clinical trials. Notably, in the V111 study, patients were required to collect their expelled capsule. Therefore, until they passed the capsule, they could not take an additional capsule; 26 patients completed the entire study and expelled the capsule without difficulty (²⁰). At this time, in considering Vibrant therapy in a patient with CIC who does not have any of the aforementioned medical history, age appropriate colon cancer screening is the only pre-treatment testing that should be considered before initiating therapy. Dysphagia is another possible challenge to treatment as the Vibrating Capsules are larger than most pharmacologic pills. Patients with significant esophageal or oropharyngeal dysphagia should likely avoid the Vibrating Capsule and undergo appropriate endoscopic or radiographic workup for this. It should be noted that dysphagia due to the capsules was not a major adverse event in this analysis.

About 12% of patients reported feeling a vibrating sensation during administration of the active capsule. In the spirit of complete transparency, we have classified this feeling as an adverse event. However, it is arguable whether this truly represents an 'adverse event' as most patients did not find the sensation bothersome, and none of the patients withdrew due to this sensation. Interestingly, a small portion of the sham / placebo /control patients also reported feeling a sensation of vibration which

emphasizes the subjectivity of this finding or presence of concomitant visceral hypersensitivity.

Constipation therapies commonly cause side effects, most notably diarrhea, which has been shown to limit their use (^{21, 22}). In a recent online study, BURDEN-CIC, in which responses to a questionnaire were obtained from 1223 patients, 59% of current CIC prescription users were dissatisfied with current therapies, and 35% of these patients reported side effects, especially diarrhea (25%). Also 55% of health care providers surveyed reported inadequate treatment response to pharmacologic therapies, and 34% described managing treatment-emergent diarrhea as most challenging (²¹). In this analysis of 6 combined studies with 800 participants, diarrhea occurred in less than 2% of our patients, in sharp contrast to many of the prescription therapies for CIC. For example, diarrhea was reported in 14-16% of patients on linaclotide, a guanylate cyclase agonist (²³). In comparison, the rate of diarrhea in the Vibrating Capsule treatment arm of the Pivotal Study was 1.2% (¹⁰). Furthermore, in the linaclotide studies 3.8 – 4.7% discontinued treatment due to diarrhea, compared to only 0.5% who received placebo) (²³⁻²⁵). In our analysis of studies using the Vibrating Capsule, no patient withdrew from the trial because of side effects.

Another vibrating capsule called the Vibravot, has been developed and tested in China and is not FDA approved. The eligibility criteria for the Vibravot patient population studied, and its mode of operation, is unclear but may achieve symptomatic relief from constipation based on direct vibration in the colon (²⁶). Vibravot demonstrated a much greater adverse event rate of 43.4% including identification of fecal occult blood and unexplained fevers. Two patients withdrew from the Vibravot study (²⁶). The Vibravot system employs a larger capsule and a longer activation time compared to the Vibrating Capsule which could explain the higher adverse event rate. Other non-pharmacologic treatments for CIC have also been described (²⁷⁻²⁹). Intermittent Colonic Exo-Peristalsis is a system that stimulates the large intestine via a device that is worn by the patient exteriorly and has shown some efficacy in treating chronic constipation in small trials (²⁷). This system had an adverse event of 8.7%. Acupuncture and Inferential Stimulation

have also been investigated and yielded adverse events rates that were comparable to the Vibrating Capsule (^{28,29}).

This strength of this post-hoc analysis includes the large sample size of CIC patients analyzed across 6 individual studies that were completed across more than 100 sites (93 of them in US; 7 in Israel) incorporating a sufficiently diverse patient population that was representative of the a typical CIC population in the US.

Limitations of this post-hoc analysis include the relatively strict inclusion criteria which is typical of most clinical studies. Many patients that seek medical attention for constipation may have other comorbidities: for example, neurologic conditions such as Parkinson's disease, opiate-induced constipation or have undergone a surgical procedure that could impact the efficacy and safety of the Vibrating Capsule (^{30,31}). Another limitation is the length of the study period. All the trials included in this analysis lasted for 8 weeks. Constipation is a chronic illness that lasts years or decades and has significant effects on quality of life (³²). Long-term safety data from use of the Vibrating Capsule in a less selected population are required and are currently being generated.

In conclusion, we found that the Vibrating Capsule, a first in class treatment for CIC, was safe, well tolerated and easy to use. No patient discontinued treatment because of an adverse event, providing reassurance to a treating physician regarding this new therapy. Future research, including long-term post-marketing studies should provide valuable insights into the incidence and prevalence of adverse events of the Vibrating Capsule in the "real world".

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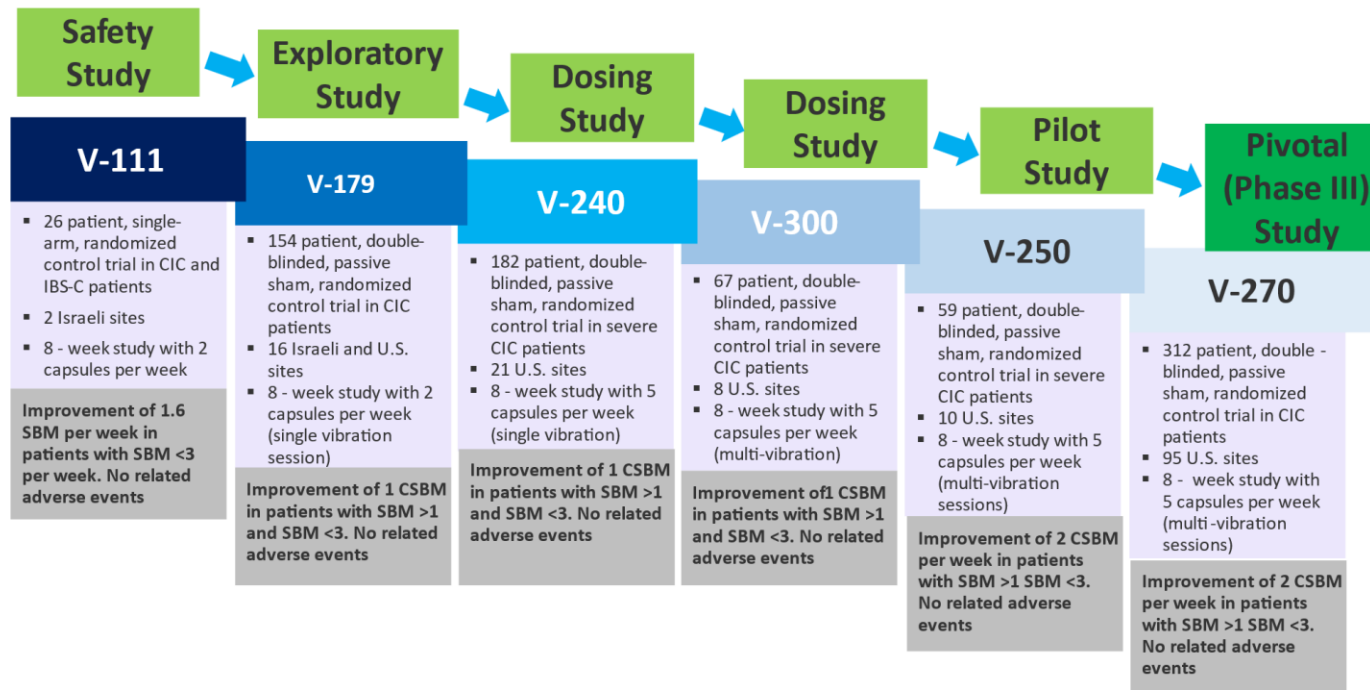
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Figure 1: Summary description of clinical trials using vibrating capsule that were analyzed for safety and tolerability

Clinical Development Program For Vibrating Capsules in CIC Patients



Flow diagram representing the clinical trials included in the analysis. This included 6 separate studies with a total of 800 patients. Patients received vibrating capsules or sham / placebo capsules 2-5x a week depending on the study.

Table 1: Demographic Characteristics of Patients Included in the Analysis

Studies		V111	V179		V240		V250		V300			V270		All Studies
Characteristic		Vibrant (N=26)	Vibrant (N=77)	Sham / placebo (N=77)	Active (N=89)	Sham / placebo (N=93)	Active (N=31)	Placebo (N=28)	Active Mode 1 (N=22)	Active Mode 2 (N=21)	Sham / placebo (N=24)	Active Mode (N=163)	Placebo (N=149)	All Arms (N=800)
Age Mean (SD)		47.0 (12.6)	45.7 (12.3)	47.0 (13.4)	45.4 (13.1)	42.7 (11.2)	46.9 (11.9)	46.0 (15.0)	44.4 (12.7)	41.9 (10.7)	41.3 (13.6)	47.1 (13.3)	45.9 (13.4)	Mean range: 41.3-47.1
Gender N (%)	Male	2 (7.7%)	8 (10.4%)	9 (11.7%)	18 (20.2%)	22 (23.7%)	1 (3.2%)	1 (3.6%)	3 (14.3%)	4 (18.2%)	3 (12.5%)	20 (12.3%)	23 (15.4%)	114 (14%)
	Female	24 (92.3%)	69 (89.6%)	68 (88.3%)	71 (79.8%)	71 (76.3%)	30 (96.4%)	27 (96.4%)	18 (85.7%)	18 (81.8%)	21 (87.5%)	143 (87.7%)	126 (84.6%)	686 (86%)
Ethnicity N (%)	Caucasian	26 (100%)	59 (76.6%)	63 (81.8%)	37 (41.6%)	29 (31.2%)	15 (48.4%)	9 (32.1%)	6 (28.6%)	5 (22.7%)	9 (37.5%)	77 (47.2%)	60 (40.3%)	395 (49%)
	Hispanic/Latino	-	-	-	17 (19.1%)	22 (23.7%)	4 (12.9%)	10 (35.7%)	4 (19.1%)	8 (36.4%)	6 (25%)	31 (19.0%)	34 (22.8%)	136 (17%)
	Black/African American	-	-	-	32 (36.0%)	33 (35.5%)	11 (35.5%)	8 (28.6%)	10 (47.6%)	7 (31.8%)	9 (37.5%)	41 (25.2%)	39 (26.2%)	190 (24%)
	Native American	-	-	-	1 (1.1%)	4 (4.3%)	-	-	1 (4.8%)	1 (4.6%)	-	-	-	7 (1%)
	Asian/Pacific Islander	-	-	-	1 (1.1%)	3 (3.2%)	-	-	-	1 (4.6%)	-	10 (6.1%)	12 (8.1%)	27 (3%)
	Other	-	18 (23.4)	14 (18.2%)	1 (1.1%)	2 (2.2%)	1 (3.2%)	1 (3.6%)	-	-	-	4 (2.5%)	4 (2.7%)	45 (6%)

SD -Standard deviation.

Table 2: Baseline Bowel Symptoms, Stool Characteristics and Quality of Life Scores for CIC Patients Included in this Analysis

Characteristic Mean (SD)	V111	V179		V240		V250		V300			V270	
	Vibrant	Vibrant	Sham / placebo	Active	Sham / placebo	Active	Placebo	Active Mode 1	Active Mode 2	Sham / placebo	Active	Placebo
	N=26	N=77	N=77	N=89	N=93	N=31	N=28	N=22	N=21	N=24	N=163	N=149
No. of SBMs/week	2.21 (0.74)	1.99 (0.89)	1.89 (1.01)	1.79 (0.59)	1.78 (0.57)	1.54 (0.65)	1.63 (0.87)	1.51 (0.59)	1.57 (0.57)	1.82 (0.72)	1.73 (0.51)	1.63 (0.49)
No. of CSBMs/week	Not collected	0.59 (0.86)	0.60 (0.81)	0.45 (0.70)	0.40 (0.59)	0.42 (0.49)	0.46 (0.59)	0.44 (0.71)	0.46 (0.74)	0.60 (0.62)	0.38 (0.51)	0.39 (0.59)
Duration of constipation (years)	Not collected	Not collected	Not collected	11.67 (12.46)	13.09 (12.19)	18.06 (13.00)	21.36 (12.32)	14.86 (10.79)	8.45 (6.70)	11.15 (12.33)	17.9 (14.5)	14.5 (12.35)
Stool Consistency score ^a	Not collected	1.70 (0.75)	1.82 (1.03)	2.36 (1.29)	2.24 (1.13)	2.84 (1.41)	2.36 (1.06)	2.18 (1.27)	2.50 (1.53)	2.47 (1.28)	2.13 (1.10)	2.14 (1.06)
Straining Score ^b	Not collected	5.48 (2.27)	5.72 (2.70)	4.33 (2.30)	5.00 (10.00)	3.87 (2.37)	4.46 (2.46)	4.36 (2.22)	4.26 (2.33)	3.92 (2.07)	4.66 (2.44)	4.87 (2.30)
Bloating Score ^c	Not collected	5.06 (2.98)	4.92 (2.64)	3.44 (2.54)	3.84 (2.44)	4.09 (3.02)	4.06 (2.90)	3.16 (2.50)	2.83 (2.34)	3.16 (1.92)	3.52 (2.59)	3.61 (2.74)
PAC-QOL score	Not collected	2.15 (0.74)	2.20 (0.74)	2.60 (0.80)	2.77 (0.69)	2.81 (0.83)	2.80 (0.84)	Not collected	Not collected	Not collected	2.67 (0.74)	2.67 (0.76)

SD -Standard
deviation.

^a Stool consistency range of scores (1=hard lumpy stool, 7 = loose watery stools),

^b Straining score (no straining =0; unbearable straining=10)

^c Bloating score (no bloating=0; unbearable bloating=10)

Table 3: Adverse Events Reported by the Patients Who Were Participating in Each of the Clinical Trials of the Vibrating Capsule

Studies	V111*	V179		V240		V250		V300			V270		Total	
Adverse Events N (%)	Vibrant (N=26)	Vibrant (N=77)	Sham / placebo (N=77)	Active (N=89)	Sham / placebo (N=93)	Active (N=31)	Placebo (N=28)	Active Mode 1 (N=22)	Active Mode 2 (N=21)	Sham / placebo (N=24)	Active Mode (N=163)	Placebo (N=149)	Active (N=429)	Placebo (N=371)
All Adverse Events	12(46%)	35(45%)	20(26%)	37(42%)	23(25%)	6(19%)	8(29%)	6(27%)	8(38%)	5(21%)	44(27%)	26(17%)	148(34%)	82(22%)
Sensation of Vibration	-	14(17%)	2(3%)	15(17%)	2(2%)	-	-	1(5%)	2(10%)	3(13%)	18(11%)	-	50(12%)	7(2%)
Headache	3(12%)	7(9%)	4(5%)	5(6%)	3(3%)	1(3%)	1(4%)	1(5%)	2(10%)	1(4%)	3(2%)	4(3%)	22(5%)	13(4%)
UTI	-	1(1%)	1(1%)	2(2%)	-	-	-	-	1(5%)	-	3(2%)	2(1%)	7(2%)	3(1%)
Abdominal pain/discomfort	3(12%)	2(3%)	1(1%)	-	2(2%)	1(3%)	-	1(5%)	1(5%)	-	4(2%)	8(5%)	12(3%)	11(3%)
Emesis/Vomiting	-	1(1%)	1(1%)	-	2(2%)	-	1(4%)	-	-	-	2(1%)	1(1%)	3(1%)	5(1%)
Nausea	-	1(1%)	3(4%)	7(8%)	2(2%)	-	1(4%)	-	-	-	3(2%)	1(1%)	11(3%)	7(2%)
Abdominal distension/Bloating	2(8%)	2(3%)	7(9%)	2(2%)	3(3%)	-	-	2(9%)	1(5%)	-	2(1%)	2(1%)	11(3%)	12(3%)
Anorectal discomfort	-	-	-	-	-	-	-	-	-	-	-	1(1%)	0(0%)	1(0%)
Diarrhea	2(8%)	2(3%)	1(1%)	1(1%)	3(3%)	1(3%)	1(4%)	-	1(5%)	1(4%)	2(1%)	-	9(2%)	6(2%)
Other	2(8%)	5(6%)	-	5(6%)	6(6%)	3(10%)	4(14%)	1(5%)	-	-	7(4%)	7(5%)	23(5%)	17(5%)

NOTE. Data shown for adverse events in at least 1% of the subjects. * V111 was an open label study that included IBS-C & Functional Constipation patients.

Table 4: Functionality and Ease of use/ Tolerability:

Studies TSQM parameter ^a		V240 N ^b =145	V250 N ^b =54	V300 N ^b =63	V270 N ^b =312	All studies N ^b =574
Treatment Convenience ^c	N (%)	121 (83%)	44 (82%)	59 (94%)	255 (82%)	479 (83%)
Total Convenience Score	Mean (SD)	4.81 (1.48)	5.02 (1.54)	5.83 (1.34)	4.96 (1.69)	5.02 (1.61)
Ease of planning the treatment ^c	N (%)	127 (88%)	46 (85%)	59 (94%)	267 (86%)	499 (87%)
Total Treatment Planning Score	Mean (SD)	5.17 (1.38)	5.13 (1.43)	5.81 (1.24)	5.23 (1.51)	5.27 (1.45)
Ease of Use ^c	N (%)	111 (77%)	47 (87%)	51 (81%)	292 (94%)	501 (87%)
Total Ease of Use Score	Mean (SD)	4.38 (1.61)	5.30 (1.74)	4.60 (1.51)	5.58 (1.42)	5.15 (1.6)
Overall Treatment Satisfaction ^c	N (%)	89 (61%)	35 (65%)	40 (64%)	241 (77%)	405 (71%)
Total treatment satisfaction Score	Mean (SD)	3.64 (1.25)	4.39 (2.13)	3.68 (1.38)	4.81 (1.8)	4.35 (1.75)

SD -Standard deviation.

^a Treatment Satisfaction Questionnaire for Medication (TSQM) range of scores (1=Extremely Dissatisfied, 7 = Extremely Satisfied).

^b N: Number of patients from Active and Placebo/sham / placebo arms that completed the TSQM questionnaire

^c Satisfaction rate: represents the incidence of satisfied patients (score 4 and above).

Graphical Abstract Text

The Vibrating Capsule, a first in class treatment for CIC, was found to be safe and well tolerated in over 800 patients observed in six clinical trials.

The Vibrating Capsule: Safety and Tolerability in Patients with Chronic Idiopathic Constipation

Short Running Title: Vibrating Capsule is Safe and Tolerable in CIC

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Keywords: Constipation, Capsules, Equipment Safety, Equipment Design
Defecation

Key Points:

1. The Vibrating Capsule treatment for Chronic Idiopathic Constipation was associated with a low adverse event rate across 6 trials in this post-hoc analysis
2. There were no severe adverse events or recorded capsule retentions across all 6 trials
3. The Vibrating Capsule was well tolerated with no patient stopping treatment early during any of the 6 trials.

Declarations:

Consent for publication: No individual data was used in this study

Availability of Data and Materials: The analyzed data from the current study are not publicly available due to the novelty of the treatment but are available from the corresponding author upon reasonable request.

Competing Interests:

Bryan F Curtin, William D. Chey, Brennan M.R. Spiegel, Darren Brenner, Anthony Lembo: Served on a scientific advisory board for Vibrant Gastro

Satish SC Rao and Eamonn M M Quigley: Served on Vibrant advisory board and received research grant support for Vibrant clinical trials

Authors Contributions:

Bryan F Curtin: Concept, preparation of the article and revision.

Satish SC Rao: Concept, manuscript writing and revision.

Eamonn MM Quigley: manuscript writing and revision. William D. Chey: manuscript writing and revision. Darren M. Brenner: manuscript writing and critical revision

Abstract:

BACKGROUND: Chronic Idiopathic Constipation (CIC) remains a significant problem globally with increasing estimates for disease burden. In a Phase 3 placebo-controlled trial, a novel treatment using the Vibrating Capsule was recently shown to be effective in treating patients with CIC. However, its safety and tolerability has not been described in detail.

METHODS: We analyzed safety data from six trials encompassing the development of the Vibrating Capsule, including, dose-ranging and pivotal studies. The incidence of adverse events, treatment discontinuation, tolerability and satisfaction were assessed.

KEY RESULTS: A total of 800 patients who took either an active vibrating capsule or a sham / placebo (non-vibrating) but similar capsule from 6 studies were included in this post-hoc analysis. The most common adverse gastrointestinal events were bloating (2.9%), abdominal pain (2.9%), nausea (2.3%) and diarrhea (1.9%). A sensation of vibration was reported by 11.7% of patients. The adverse events rates were low, and investigators categorized most of them as unrelated to treatment. There were no serious adverse events such as retention of therapeutic capsules and no patient stopped therapy or withdrew due to adverse effects. The majority of patients (83%) found the system convenient, with an overall treatment satisfaction rate of 71%.

CONCLUSIONS AND INFERENCES: The Vibrating Capsule, a first in class treatment for CIC was found to be safe and well tolerated by patients in clinical trials. No patient discontinued treatment due to adverse events.

Introduction:

Chronic Idiopathic Constipation (CIC) is a global problem. Recent studies suggest that the global prevalence of CIC is approximately 11.7% ⁽¹⁾. This significant disease burden leads to loss of productivity and decreased quality of life for sufferers ⁽²⁻⁵⁾. There are currently more therapeutic options for CIC than ever before, yet patients report significant dissatisfaction with these options due to either lack of efficacy or side effects such as nausea, diarrhea and abdominal discomfort ^(6, 7). For these reasons, many patients express interest in non-pharmacologic options for their constipation ⁽⁸⁾. This underscores the unmet need for novel treatment modalities for patients with CIC.

More recently there has been interest in utilizing non-pharmacologic, mechanical stimulation devices that would treat CIC via a different mechanism. These devices offer the potential for improving CIC symptoms while avoiding many of the side effects associated with pharmacological treatments ⁽⁹⁾. The novel Vibrating Capsule is an orally ingested device that was recently proven to significantly improve constipation symptoms in CIC patients in a placebo-controlled phase 3 trial ⁽¹⁰⁾. This trial showed a greater percentage of patients receiving the vibrating capsule achieved its primary efficacy end point of an increase in 1 Complete Spontaneous Bowel Movement (CSBM) per week with the Vibrating Capsule compared to sham / placebo capsules. The proposed mechanism of action is augmentation of peristalsis in sync with the circadian rhythm of colonic motility ⁽¹¹⁾.

Despite previously demonstrated efficacy, concerns remain about the safety and tolerability of this novel intervention. Capsule devices have been utilized in the GI tract for some time, with video capsule endoscopy established as a vital component of the evaluation of occult bleeding from the gastrointestinal tract or in the diagnosis of tumors of the small intestine. Over several decades of use in clinical practice the retention rate of the video capsule has been approximately 2% ⁽¹²⁾. The novel Vibrating Capsule requires patients to take a similar sized non-dissolvable capsule five times per week so

concerns regarding retention or other side effects require an assessment. Here, we conducted an extended post-hoc analysis of the safety and tolerability data of the use of vibrating capsule in the treatment of patients with CIC across multiple clinical trials.

Methods

Study Design

From 2011-2021, six studies were performed to assess the safety and efficacy of the Vibrating Capsule (Figure 1), and all were included in this analysis (V111, V179, V240, V250, V300, V270). Studies were conducted for 8 weeks at multiple sites in the United States and Israel. Participants were assessed 4 times throughout the trial period including initial screening, a baseline visit after 14 days of run-in, week 4, and a close out visit at week 8. Depending on the specific trial, an in-person questionnaire or an app-based diary was used to track factors such as frequency of bowel movements, stool consistency via the Bristol Stool Form Scale, Patient Assessment of Constipation Quality of Life (PAC-QOL), treatment satisfaction scores, and ease-of-use questionnaires. Adverse events and side effects were also recorded at these visits as well as throughout the clinical trials. All participants signed an informed consent document that was approved by a central or local institutional review board, as appropriate. All patients, study evaluators, treating clinicians, and sponsors were blinded to the treatment allocations (excluding the single-arm safety study (V111)). Participants were recruited from clinics and through local advertisement at each site.

Participants

Participants included in this analysis were aged 22 years or older, met Rome III criteria for CIC and had failed to experience relief of their symptoms following at least one month of treatment with osmotic or stimulant laxatives ⁽¹³⁾. Patients with an average of ≥ 1 spontaneous bowel movements (SBMs) per week and ≤ 2.5 SBMs per week, during screening were eligible. All patients were required to have had a colonoscopy within the previous 5 years unless they were < 50 years old and had no alarm features ⁽¹⁴⁾. Patients with a history of complicated/obstructing diverticular disease, intestinal

obstruction, inflammatory bowel disease, gastrointestinal malignancy, gastroparesis, Zenker's diverticulum, dysphagia, esophageal stricture, pelvic floor dysfunction, megarectum, history of bariatric surgery, significant systemic illnesses, pregnancy/lactation, or with a pacemaker were excluded from the study. Patients with constipation secondary to drugs including opiates or who satisfied criteria for IBS-C (Rome III) were excluded (¹³).

Treatment Description

The Vibrating Capsule (Vibrant®, Vibrant Ltd, Hakochav Yokneam, Israel) requires an activation pod that programs the capsule to time the onset of the treatment protocol. Details of capsule activation and treatment paradigms have been previously described (¹⁰). The capsule measures 24.2 mm x 11.3 mm and contains a vibrating trigger, a medical grade energy source, a computer activation chip, and a latex-free biocompatible shell. Activation protocols varied across trials with 2-5 capsules ingested per week during the treatment periods. Vibration protocols led to activation for approximately 1-2 hours at 3 oscillation cycles per minute with periods of rest in between. The capsule was designed to be expelled in stool.

All the trials included in this analysis used an inactive sham / placebo capsule (Excluding the single-arm safety study (V111)). It is important to note that the sham / placebo capsule looked identical to the active vibrating capsule, and had similar dimensions. Given the similar constitution of the capsules and the primary purpose here was to address safety (rather than efficacy), we felt that it would be appropriate to include patients from multiple clinical trials in the total analysis, similar to other previous safety studies in CIC patients (¹⁵).

Results

Demographics:

A total of 800 patients were treated with a Vibrating Capsule or a sham / placebo control capsule in the six trials and were included in the analysis (Table 1). Four hundred and twenty-nine (53.6%) participants received active treatment. A large majority of participants were female (85.8%) and 43.4% of the cohort was Caucasian.

Black and Latino participants comprised 23.8% and 17% of the cohort, respectively, providing a broad ethnic distribution of the American population of CIC patients. Patients had significant symptoms of CIC with <1 Complete Spontaneous Bowel Movement (CSBM) per week and decreased stool consistency (Table 2). Patients included in these studies had been suffering with constipation for >10 years on average.

Adverse event profile:

Overall adverse event rates were low and similar between active and sham / placebo treatment groups (Table 3). Diarrhea occurred in only 15 of the 800 patients (1.9%). Similar rates of adverse events were seen for nausea (2.3%), abdominal distention/bloating/flatulence (2.9%), and abdominal pain/discomfort (2.9%). In the safety study (V-111) and exploratory study (V-179) there were increased incidences of headaches (12% and 7.1% respectively) but these rates were not identified in subsequent trials. 12% of patients described feeling a `sensation of vibration` in the active cohort while only 2% expressed this feeling in the sham / placebo cohort. When assessing subjective experiences of side effects, only 1.2% of the patients treated found the side effects to be bothersome.

No serious adverse events or Emergency Department visits directly attributable to capsule administration were reported during any of the six trials. No patients withdrew from the studies prematurely due to adverse events and all patients completed 8 weeks of therapy. No episodes of capsule retention were reported during the trial however this was not formally assessed with abdominal imaging at the conclusion of the studies.

Functionality and Ease of use/tolerability:

The ease of use of the Vibrating Capsule and its activation system were assessed at week 4 and week 8 throughout trials V240, V250, V300, and V270 (Table 4). A majority (83%) of the patients found the treatment convenient (not disruptive to daily routine). Similarly, 87% of patients found it easy to plan the time of treatment. When asked if they found the treatment easy to use, 87% of patients indicated that the system was easy to use in its current form while only 4% found it extremely difficult. A majority of the

patients (71%) reported satisfaction with the capsule treatment compared with 29% of patients who were dissatisfied.

Discussion

In this analysis of 800 patients with CIC treated across six studies, we found that the Vibrating Capsule was safe and well tolerated. Adverse events were limited, mostly insignificant when compared to sham / placebo capsules, and no serious adverse events were reported. Most patients found the system easy to use.

Importantly, no instances of capsule retention requiring endoscopic retrieval or surgical extraction occurred during these studies. This is especially noteworthy as similar devices, such as the video endoscopy capsule, have infrequently been associated with retention requiring endoscopic or surgical removal (¹²). For this reason, patency capsules have been developed to reduce the risk of capsule retention (¹⁶). With the Vibrating Capsule system, patients took 2-5 capsules per week without evidence of capsule retention. This may give providers some comfort in recommending this technology for the treatment of constipation. Patient selection likely accounts for this discrepancy between retention rates for the Vibrating Capsule and the video endoscopy capsule. The video capsule is used in patients with suspected small bowel pathology, such as Crohn's disease, which would be an exclusion for the use of the Vibrating Capsule. It is not realistic or cost effective to perform interventions such as patency capsules, enterography, or anorectal manometry prior to initiation of the vibrating capsule in most clinical settings which underscores the importance of safety data such as this analysis. Vibrating capsules should not be used in a patient with a history of complex intestinal surgeries, adhesions, bowel obstruction, intestinal stricture or stenosis, Crohn's disease or complicated diverticular disease. In this analysis where 800 patients were given either a vibrating or a sham / placebo capsule, there were no instances of capsule retention suggesting that in the appropriate patient population, the capsule is unlikely to be retained in the small intestine. Prolonged retention in the colon is possible given the nature of the patient population. It is unknown how long the capsules remain in the colon and what is an approximate transit or exit time for these

capsules is since patients were not asked to document passage of capsules, and it is often hard to see them if they are encased in stool.

Any population of patients that suffers from constipation will be quite diverse and include those with altered anatomy resulting from prior surgery, individuals taking medications such as opioids, as well as those with more diffuse motility disorders (¹⁷⁻¹⁸). The Vibrating Capsule is contraindicated in patients with anatomy-altering surgeries such as gastric bypass or a prior history of bowel resection. Conditions or medications that cause gastroparesis or otherwise slow proximal gut transit could decrease the efficacy of the Vibrating Capsule by delaying its arrival into the colon with premature activation in the small intestine. All patients in these studies were pre-screened for colon cancer using current best practices (¹⁹). The role of pre-treatment motility studies such as small bowel follow-through, sitz marker study, or whole gut transit study are yet to be elucidated, as they were not performed in the clinical trials. Notably, in the V111 study, patients were required to collect their expelled capsule. Therefore, until they passed the capsule, they could not take an additional capsule; 26 patients completed the entire study and expelled the capsule without difficulty (²⁰). At this time, in considering Vibrant therapy in a patient with CIC who does not have any of the aforementioned medical history, age appropriate colon cancer screening is the only pre-treatment testing that should be considered before initiating therapy. Dysphagia is another possible challenge to treatment as the Vibrating Capsules are larger than most pharmacologic pills. Patients with significant esophageal or oropharyngeal dysphagia should likely avoid the Vibrating Capsule and undergo appropriate endoscopic or radiographic workup for this. It should be noted that dysphagia due to the capsules was not a major adverse event in this analysis.

About 12% of patients reported feeling a vibrating sensation during administration of the active capsule. In the spirit of complete transparency, we have classified this feeling as an adverse event. However, it is arguable whether this truly represents an 'adverse event' as most patients did not find the sensation bothersome, and none of the patients withdrew due to this sensation. Interestingly, a small portion of the sham / placebo /control patients also reported feeling a sensation of vibration which

emphasizes the subjectivity of this finding or presence of concomitant visceral hypersensitivity.

Constipation therapies commonly cause side effects, most notably diarrhea, which has been shown to limit their use (^{21, 22}). In a recent online study, BURDEN-CIC, in which responses to a questionnaire were obtained from 1223 patients, 59% of current CIC prescription users were dissatisfied with current therapies, and 35% of these patients reported side effects, especially diarrhea (25%). Also 55% of health care providers surveyed reported inadequate treatment response to pharmacologic therapies, and 34% described managing treatment-emergent diarrhea as most challenging (²¹). In this analysis of 6 combined studies with 800 participants, diarrhea occurred in less than 2% of our patients, in sharp contrast to many of the prescription therapies for CIC. For example, diarrhea was reported in 14-16% of patients on linaclotide, a guanylate cyclase agonist (²³). In comparison, the rate of diarrhea in the Vibrating Capsule treatment arm of the Pivotal Study was 1.2% (¹⁰). Furthermore, in the linaclotide studies 3.8 – 4.7% discontinued treatment due to diarrhea, compared to only 0.5% who received placebo) (²³⁻²⁵). In our analysis of studies using the Vibrating Capsule, no patient withdrew from the trial because of side effects.

Another vibrating capsule called the Vibravot, has been developed and tested in China and is not FDA approved. The eligibility criteria for the Vibravot patient population studied, and its mode of operation, is unclear but may achieve symptomatic relief from constipation based on direct vibration in the colon (²⁶). Vibravot demonstrated a much greater adverse event rate of 43.4% including identification of fecal occult blood and unexplained fevers. Two patients withdrew from the Vibravot study (²⁶). The Vibravot system employs a larger capsule and a longer activation time compared to the Vibrating Capsule which could explain the higher adverse event rate. Other non-pharmacologic treatments for CIC have also been described (²⁷⁻²⁹). Intermittent Colonic Exo-Peristalsis is a system that stimulates the large intestine via a device that is worn by the patient exteriorly and has shown some efficacy in treating chronic constipation in small trials (²⁷). This system had an adverse event of 8.7%. Acupuncture and Inferential Stimulation

have also been investigated and yielded adverse events rates that were comparable to the Vibrating Capsule (^{28,29}).

This strength of this post-hoc analysis includes the large sample size of CIC patients analyzed across 6 individual studies that were completed across more than 100 sites (93 of them in US; 7 in Israel) incorporating a sufficiently diverse patient population that was representative of the a typical CIC population in the US.

Limitations of this post-hoc analysis include the relatively strict inclusion criteria which is typical of most clinical studies. Many patients that seek medical attention for constipation may have other comorbidities: for example, neurologic conditions such as Parkinson's disease, opiate-induced constipation or have undergone a surgical procedure that could impact the efficacy and safety of the Vibrating Capsule (^{30,31}). Another limitation is the length of the study period. All the trials included in this analysis lasted for 8 weeks. Constipation is a chronic illness that lasts years or decades and has significant effects on quality of life (³²). Long-term safety data from use of the Vibrating Capsule in a less selected population are required and are currently being generated.

In conclusion, we found that the Vibrating Capsule, a first in class treatment for CIC, was safe, well tolerated and easy to use. No patient discontinued treatment because of an adverse event, providing reassurance to a treating physician regarding this new therapy. Future research, including long-term post-marketing studies should provide valuable insights into the incidence and prevalence of adverse events of the Vibrating Capsule in the "real world".

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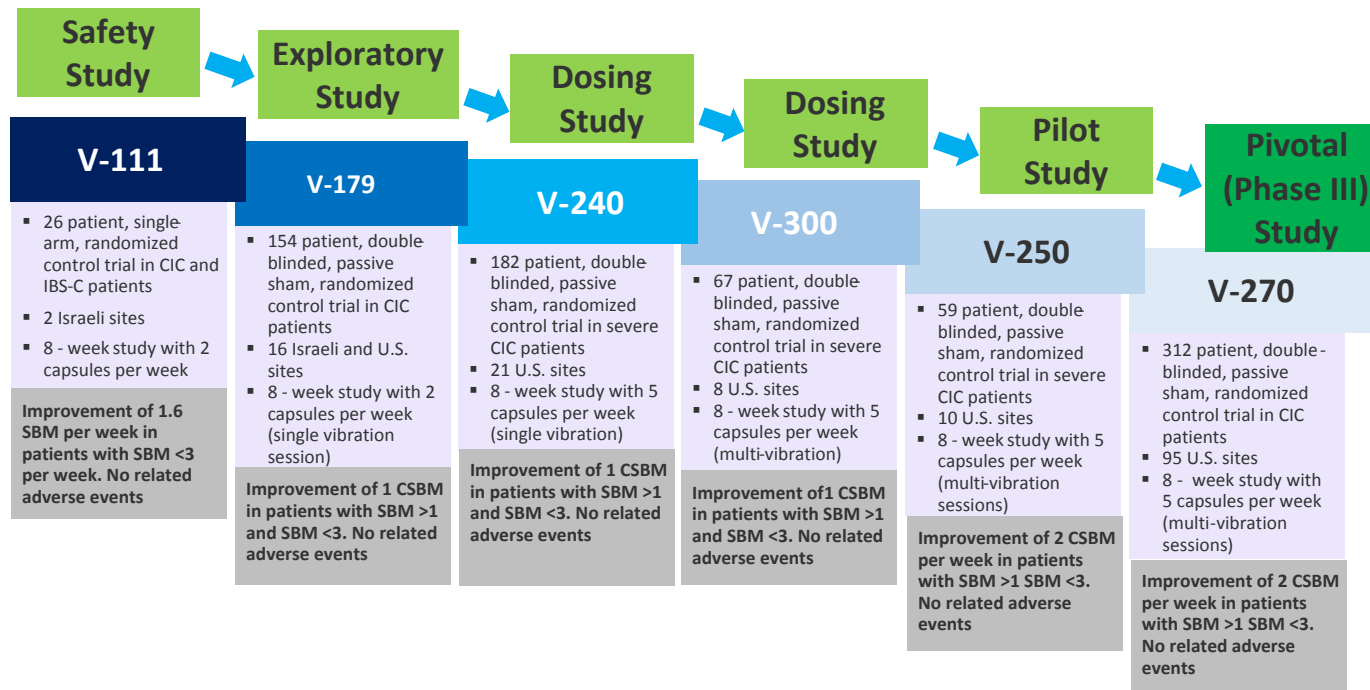
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Figure 1: Summary description of clinical trials using vibrating capsule that were analyzed for safety and tolerability

Clinical Development Program For Vibrating Capsules in CIC Patients



Flow diagram representing the clinical trials included in the analysis. This included 6 separate studies with a total of 800 patients. Patients received vibrating capsules or sham / placebo capsules 2-5x a week depending on the study.

Table 1: Demographic Characteristics of Patients Included in the Analysis

Studies		V111	V179		V240		V250		V300			V270		All Studies
Characteristic		Vibrant (N=26)	Vibrant (N=77)	Sham / placebo (N=77)	Active (N=89)	Sham / placebo (N=93)	Active (N=31)	Placebo (N=28)	Active Mode 1 (N=22)	Active Mode 2 (N=21)	Sham / placebo (N=24)	Active Mode (N=163)	Placebo (N=149)	All Arms (N=800)
Age Mean (SD)		47.0 (12.6)	45.7 (12.3)	47.0 (13.4)	45.4 (13.1)	42.7 (11.2)	46.9 (11.9)	46.0 (15.0)	44.4 (12.7)	41.9 (10.7)	41.3 (13.6)	47.1 (13.3)	45.9 (13.4)	Mean range: 41.3-47.1
Gender N (%)	Male	2 (7.7%)	8 (10.4%)	9 (11.7%)	18 (20.2%)	22 (23.7%)	1 (3.2%)	1 (3.6%)	3 (14.3%)	4 (18.2%)	3 (12.5%)	20 (12.3%)	23 (15.4%)	114 (14%)
	Female	24 (92.3%)	69 (89.6%)	68 (88.3%)	71 (79.8%)	71 (76.3%)	30 (96.4%)	27 (96.4%)	18 (85.7%)	18 (81.8%)	21 (87.5%)	143 (87.7%)	126 (84.6%)	686 (86%)
Ethnicity N (%)	Caucasian	26 (100%)	59 (76.6%)	63 (81.8%)	37 (41.6%)	29 (31.2%)	15 (48.4%)	9 (32.1%)	6 (28.6%)	5 (22.7%)	9 (37.5%)	77 (47.2%)	60 (40.3%)	395 (49%)
	Hispanic/Latino	-	-	-	17 (19.1%)	22 (23.7%)	4 (12.9%)	10 (35.7%)	4 (19.1%)	8 (36.4%)	6 (25%)	31 (19.0%)	34 (22.8%)	136 (17%)
	Black/African American	-	-	-	32 (36.0%)	33 (35.5%)	11 (35.5%)	8 (28.6%)	10 (47.6%)	7 (31.8%)	9 (37.5%)	41 (25.2%)	39 (26.2%)	190 (24%)
	Native American	-	-	-	1 (1.1%)	4 (4.3%)	-	-	1 (4.8%)	1 (4.6%)	-	-	-	7 (1%)
	Asian/Pacific Islander	-	-	-	1 (1.1%)	3 (3.2%)	-	-	-	1 (4.6%)	-	10 (6.1%)	12 (8.1%)	27 (3%)
	Other	-	18 (23.4)	14 (18.2%)	1 (1.1%)	2 (2.2%)	1 (3.2%)	1 (3.6%)	-	-	-	4 (2.5%)	4 (2.7%)	45 (6%)

SD -Standard deviation.

Table 2: Baseline Bowel Symptoms, Stool Characteristics and Quality of Life Scores for CIC Patients Included in this Analysis

Characteristic Mean (SD)	V111	V179		V240		V250		V300			V270	
	Vibrant	Vibrant	Sham / placebo	Active	Sham / placebo	Active	Placebo	Active Mode 1	Active Mode 2	Sham / placebo	Active	Placebo
	N=26	N=77	N=77	N=89	N=93	N=31	N=28	N=22	N=21	N=24	N=163	N=149
No. of SBMs/week	2.21 (0.74)	1.99 (0.89)	1.89 (1.01)	1.79 (0.59)	1.78 (0.57)	1.54 (0.65)	1.63 (0.87)	1.51 (0.59)	1.57 (0.57)	1.82 (0.72)	1.73 (0.51)	1.63 (0.49)
No. of CSBMs/week	Not collected	0.59 (0.86)	0.60 (0.81)	0.45 (0.70)	0.40 (0.59)	0.42 (0.49)	0.46 (0.59)	0.44 (0.71)	0.46 (0.74)	0.60 (0.62)	0.38 (0.51)	0.39 (0.59)
Duration of constipation (years)	Not collected	Not collected	Not collected	11.67 (12.46)	13.09 (12.19)	18.06 (13.00)	21.36 (12.32)	14.86 (10.79)	8.45 (6.70)	11.15 (12.33)	17.9 (14.5)	14.5 (12.35)
Stool Consistency score ^a	Not collected	1.70 (0.75)	1.82 (1.03)	2.36 (1.29)	2.24 (1.13)	2.84 (1.41)	2.36 (1.06)	2.18 (1.27)	2.50 (1.53)	2.47 (1.28)	2.13 (1.10)	2.14 (1.06)
Straining Score ^b	Not collected	5.48 (2.27)	5.72 (2.70)	4.33 (2.30)	5.00 (10.00)	3.87 (2.37)	4.46 (2.46)	4.36 (2.22)	4.26 (2.33)	3.92 (2.07)	4.66 (2.44)	4.87 (2.30)
Bloating Score ^c	Not collected	5.06 (2.98)	4.92 (2.64)	3.44 (2.54)	3.84 (2.44)	4.09 (3.02)	4.06 (2.90)	3.16 (2.50)	2.83 (2.34)	3.16 (1.92)	3.52 (2.59)	3.61 (2.74)
PAC-QOL score	Not collected	2.15 (0.74)	2.20 (0.74)	2.60 (0.80)	2.77 (0.69)	2.81 (0.83)	2.80 (0.84)	Not collected	Not collected	Not collected	2.67 (0.74)	2.67 (0.76)

SD -Standard
deviation.

^a Stool consistency range of scores (1=hard lumpy stool, 7 = loose watery stools),

^b Straining score (no straining =0; unbearable straining=10)

^c Bloating score (no bloating=0; unbearable bloating=10)

Table 3: Adverse Events Reported by the Patients Who Were Participating in Each of the Clinical Trials of the Vibrating Capsule

Studies	V111*	V179		V240		V250		V300			V270		Total	
Adverse Events N (%)	Vibrant (N=26)	Vibrant (N=77)	Sham / placebo (N=77)	Active (N=89)	Sham / placebo (N=93)	Active (N=31)	Placebo (N=28)	Active Mode 1 (N=22)	Active Mode 2 (N=21)	Sham / placebo (N=24)	Active Mode (N=163)	Placebo (N=149)	Active (N=429)	Placebo (N=371)
All Adverse Events	12(46%)	35(45%)	20(26%)	37(42%)	23(25%)	6(19%)	8(29%)	6(27%)	8(38%)	5(21%)	44(27%)	26(17%)	148(34%)	82(22%)
Sensation of Vibration	-	14(17%)	2(3%)	15(17%)	2(2%)	-	-	1(5%)	2(10%)	3(13%)	18(11%)	-	50(12%)	7(2%)
Headache	3(12%)	7(9%)	4(5%)	5(6%)	3(3%)	1(3%)	1(4%)	1(5%)	2(10%)	1(4%)	3(2%)	4(3%)	22(5%)	13(4%)
UTI	-	1(1%)	1(1%)	2(2%)	-	-	-	-	1(5%)	-	3(2%)	2(1%)	7(2%)	3(1%)
Abdominal pain/discomfort	3(12%)	2(3%)	1(1%)	-	2(2%)	1(3%)	-	1(5%)	1(5%)	-	4(2%)	8(5%)	12(3%)	11(3%)
Emesis/Vomiting	-	1(1%)	1(1%)	-	2(2%)	-	1(4%)	-	-	-	2(1%)	1(1%)	3(1%)	5(1%)
Nausea	-	1(1%)	3(4%)	7(8%)	2(2%)	-	1(4%)	-	-	-	3(2%)	1(1%)	11(3%)	7(2%)
Abdominal distension/Bloating	2(8%)	2(3%)	7(9%)	2(2%)	3(3%)	-	-	2(9%)	1(5%)	-	2(1%)	2(1%)	11(3%)	12(3%)
Anorectal discomfort	-	-	-	-	-	-	-	-	-	-	-	1(1%)	0(0%)	1(0%)
Diarrhea	2(8%)	2(3%)	1(1%)	1(1%)	3(3%)	1(3%)	1(4%)	-	1(5%)	1(4%)	2(1%)	-	9(2%)	6(2%)
Other	2(8%)	5(6%)	-	5(6%)	6(6%)	3(10%)	4(14%)	1(5%)	-	-	7(4%)	7(5%)	23(5%)	17(5%)

NOTE. Data shown for adverse events in at least 1% of the subjects. * V111 was an open label study that included IBS-C & Functional Constipation patients.

Table 4: Functionality and Ease of use/ Tolerability:

Studies TSQM parameter ^a		V240 N ^b =145	V250 N ^b =54	V300 N ^b =63	V270 N ^b =312	All studies N ^b =574
Treatment Convenience ^c	N (%)	121 (83%)	44 (82%)	59 (94%)	255 (82%)	479 (83%)
Total Convenience Score	Mean (SD)	4.81 (1.48)	5.02 (1.54)	5.83 (1.34)	4.96 (1.69)	5.02 (1.61)
Ease of planning the treatment ^c	N (%)	127 (88%)	46 (85%)	59 (94%)	267 (86%)	499 (87%)
Total Treatment Planning Score	Mean (SD)	5.17 (1.38)	5.13 (1.43)	5.81 (1.24)	5.23 (1.51)	5.27 (1.45)
Ease of Use ^c	N (%)	111 (77%)	47 (87%)	51 (81%)	292 (94%)	501 (87%)
Total Ease of Use Score	Mean (SD)	4.38 (1.61)	5.30 (1.74)	4.60 (1.51)	5.58 (1.42)	5.15 (1.6)
Overall Treatment Satisfaction ^c	N (%)	89 (61%)	35 (65%)	40 (64%)	241 (77%)	405 (71%)
Total treatment satisfaction Score	Mean (SD)	3.64 (1.25)	4.39 (2.13)	3.68 (1.38)	4.81 (1.8)	4.35 (1.75)

SD -Standard deviation.

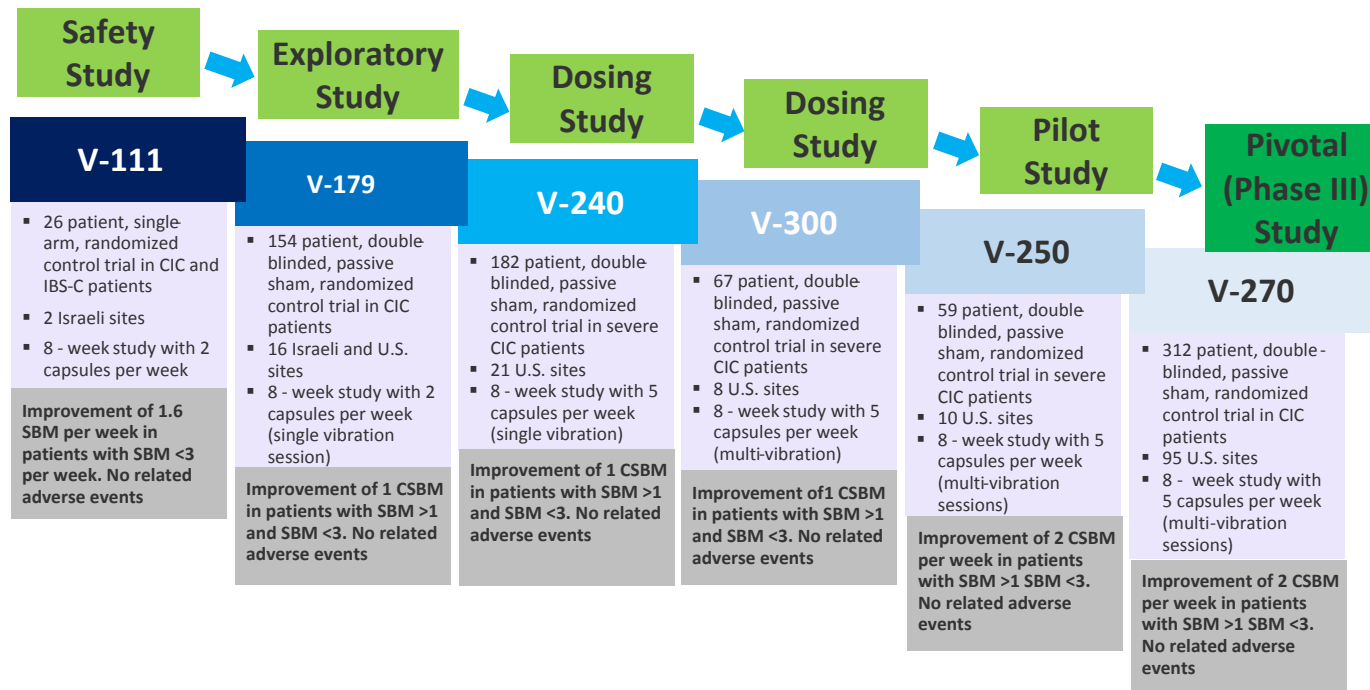
^a Treatment Satisfaction Questionnaire for Medication (TSQM) range of scores (1=Extremely Dissatisfied, 7 = Extremely Satisfied).

^b N: Number of patients from Active and Placebo/sham / placebo arms that completed the TSQM questionnaire

^c Satisfaction rate: represents the incidence of satisfied patients (score 4 and above).

Figure 1: Summary description of clinical trials using vibrating capsule that were analyzed for safety and tolerability

Clinical Development Program For Vibrating Capsules in CIC Patients



Flow diagram representing the clinical trials included in the analysis. This included 6 separate studies with a total of 800 patients. Patients received vibrating capsules or sham / placebo capsules 2-5x a week depending on the study.

Table 1: Demographic Characteristics of Patients Included in the Analysis

Studies		V111	V179		V240		V250		V300			V270		All Studies
Characteristic		Vibrant (N=26)	Vibrant (N=77)	Sham / placebo (N=77)	Active (N=89)	Sham / placebo (N=93)	Active (N=31)	Placebo (N=28)	Active Mode 1 (N=22)	Active Mode 2 (N=21)	Sham / placebo (N=24)	Active Mode (N=163)	Placebo (N=149)	All Arms (N=800)
Age Mean (SD)		47.0 (12.6)	45.7 (12.3)	47.0 (13.4)	45.4 (13.1)	42.7 (11.2)	46.9 (11.9)	46.0 (15.0)	44.4 (12.7)	41.9 (10.7)	41.3 (13.6)	47.1 (13.3)	45.9 (13.4)	Mean range: 41.3-47.1
Gender N (%)	Male	2 (7.7%)	8 (10.4%)	9 (11.7%)	18 (20.2%)	22 (23.7%)	1 (3.2%)	1 (3.6%)	3 (14.3%)	4 (18.2%)	3 (12.5%)	20 (12.3%)	23 (15.4%)	114 (14%)
	Female	24 (92.3%)	69 (89.6%)	68 (88.3%)	71 (79.8%)	71 (76.3%)	30 (96.4%)	27 (96.4%)	18 (85.7%)	18 (81.8%)	21 (87.5%)	143 (87.7%)	126 (84.6%)	686 (86%)
Ethnicity N (%)	Caucasian	26 (100%)	59 (76.6%)	63 (81.8%)	37 (41.6%)	29 (31.2%)	15 (48.4%)	9 (32.1%)	6 (28.6%)	5 (22.7%)	9 (37.5%)	77 (47.2%)	60 (40.3%)	395 (49%)
	Hispanic/Latino	-	-	-	17 (19.1%)	22 (23.7%)	4 (12.9%)	10 (35.7%)	4 (19.1%)	8 (36.4%)	6 (25%)	31 (19.0%)	34 (22.8%)	136 (17%)
	Black/African American	-	-	-	32 (36.0%)	33 (35.5%)	11 (35.5%)	8 (28.6%)	10 (47.6%)	7 (31.8%)	9 (37.5%)	41 (25.2%)	39 (26.2%)	190 (24%)
	Native American	-	-	-	1 (1.1%)	4 (4.3%)	-	-	1 (4.8%)	1 (4.6%)	-	-	-	7 (1%)
	Asian/Pacific Islander	-	-	-	1 (1.1%)	3 (3.2%)	-	-	-	1 (4.6%)	-	10 (6.1%)	12 (8.1%)	27 (3%)
	Other	-	18 (23.4)	14 (18.2%)	1 (1.1%)	2 (2.2%)	1 (3.2%)	1 (3.6%)	-	-	-	4 (2.5%)	4 (2.7%)	45 (6%)

SD -Standard deviation.

Table 2: Baseline Bowel Symptoms, Stool Characteristics and Quality of Life Scores for CIC Patients Included in this Analysis

Characteristic Mean (SD)	V111	V179		V240		V250		V300			V270	
	Vibrant	Vibrant	Sham / placebo	Active	Sham / placebo	Active	Placebo	Active Mode 1	Active Mode 2	Sham / placebo	Active	Placebo
	N=26	N=77	N=77	N=89	N=93	N=31	N=28	N=22	N=21	N=24	N=163	N=149
No. of SBMs/week	2.21 (0.74)	1.99 (0.89)	1.89 (1.01)	1.79 (0.59)	1.78 (0.57)	1.54 (0.65)	1.63 (0.87)	1.51 (0.59)	1.57 (0.57)	1.82 (0.72)	1.73 (0.51)	1.63 (0.49)
No. of CSBMs/week	Not collected	0.59 (0.86)	0.60 (0.81)	0.45 (0.70)	0.40 (0.59)	0.42 (0.49)	0.46 (0.59)	0.44 (0.71)	0.46 (0.74)	0.60 (0.62)	0.38 (0.51)	0.39 (0.59)
Duration of constipation (years)	Not collected	Not collected	Not collected	11.67 (12.46)	13.09 (12.19)	18.06 (13.00)	21.36 (12.32)	14.86 (10.79)	8.45 (6.70)	11.15 (12.33)	17.9 (14.5)	14.5 (12.35)
Stool Consistency score ^a	Not collected	1.70 (0.75)	1.82 (1.03)	2.36 (1.29)	2.24 (1.13)	2.84 (1.41)	2.36 (1.06)	2.18 (1.27)	2.50 (1.53)	2.47 (1.28)	2.13 (1.10)	2.14 (1.06)
Straining Score ^b	Not collected	5.48 (2.27)	5.72 (2.70)	4.33 (2.30)	5.00 (10.00)	3.87 (2.37)	4.46 (2.46)	4.36 (2.22)	4.26 (2.33)	3.92 (2.07)	4.66 (2.44)	4.87 (2.30)
Bloating Score ^c	Not collected	5.06 (2.98)	4.92 (2.64)	3.44 (2.54)	3.84 (2.44)	4.09 (3.02)	4.06 (2.90)	3.16 (2.50)	2.83 (2.34)	3.16 (1.92)	3.52 (2.59)	3.61 (2.74)
PAC-QOL score	Not collected	2.15 (0.74)	2.20 (0.74)	2.60 (0.80)	2.77 (0.69)	2.81 (0.83)	2.80 (0.84)	Not collected	Not collected	Not collected	2.67 (0.74)	2.67 (0.76)

SD -Standard
deviation.

^a Stool consistency range of scores (1=hard lumpy stool, 7 = loose watery stools),

^b Straining score (no straining =0; unbearable straining=10)

^c Bloating score (no bloating=0; unbearable bloating=10)

Table 3: Adverse Events Reported by the Patients Who Were Participating in Each of the Clinical Trials of the Vibrating Capsule

Studies	V111*	V179		V240		V250		V300			V270		Total	
Adverse Events N (%)	Vibrant (N=26)	Vibrant (N=77)	Sham / placebo (N=77)	Active (N=89)	Sham / placebo (N=93)	Active (N=31)	Placebo (N=28)	Active Mode 1 (N=22)	Active Mode 2 (N=21)	Sham / placebo (N=24)	Active Mode (N=163)	Placebo (N=149)	Active (N=429)	Placebo (N=371)
All Adverse Events	12(46%)	35(45%)	20(26%)	37(42%)	23(25%)	6(19%)	8(29%)	6(27%)	8(38%)	5(21%)	44(27%)	26(17%)	148(34%)	82(22%)
Sensation of Vibration	-	14(17%)	2(3%)	15(17%)	2(2%)	-	-	1(5%)	2(10%)	3(13%)	18(11%)	-	50(12%)	7(2%)
Headache	3(12%)	7(9%)	4(5%)	5(6%)	3(3%)	1(3%)	1(4%)	1(5%)	2(10%)	1(4%)	3(2%)	4(3%)	22(5%)	13(4%)
UTI	-	1(1%)	1(1%)	2(2%)	-	-	-	-	1(5%)	-	3(2%)	2(1%)	7(2%)	3(1%)
Abdominal pain/discomfort	3(12%)	2(3%)	1(1%)	-	2(2%)	1(3%)	-	1(5%)	1(5%)	-	4(2%)	8(5%)	12(3%)	11(3%)
Emesis/Vomiting	-	1(1%)	1(1%)	-	2(2%)	-	1(4%)	-	-	-	2(1%)	1(1%)	3(1%)	5(1%)
Nausea	-	1(1%)	3(4%)	7(8%)	2(2%)	-	1(4%)	-	-	-	3(2%)	1(1%)	11(3%)	7(2%)
Abdominal distension/Bloating	2(8%)	2(3%)	7(9%)	2(2%)	3(3%)	-	-	2(9%)	1(5%)	-	2(1%)	2(1%)	11(3%)	12(3%)
Anorectal discomfort	-	-	-	-	-	-	-	-	-	-	-	1(1%)	0(0%)	1(0%)
Diarrhea	2(8%)	2(3%)	1(1%)	1(1%)	3(3%)	1(3%)	1(4%)	-	1(5%)	1(4%)	2(1%)	-	9(2%)	6(2%)
Other	2(8%)	5(6%)	-	5(6%)	6(6%)	3(10%)	4(14%)	1(5%)	-	-	7(4%)	7(5%)	23(5%)	17(5%)

NOTE. Data shown for adverse events in at least 1% of the subjects. * V111 was an open label study that included IBS-C & Functional Constipation patients.

Table 4: Functionality and Ease of use/ Tolerability:

Studies TSQM parameter ^a		V240 N ^b =145	V250 N ^b =54	V300 N ^b =63	V270 N ^b =312	All studies N ^b =574
Treatment Convenience ^c	N (%)	121 (83%)	44 (82%)	59 (94%)	255 (82%)	479 (83%)
Total Convenience Score	Mean (SD)	4.81 (1.48)	5.02 (1.54)	5.83 (1.34)	4.96 (1.69)	5.02 (1.61)
Ease of planning the treatment ^c	N (%)	127 (88%)	46 (85%)	59 (94%)	267 (86%)	499 (87%)
Total Treatment Planning Score	Mean (SD)	5.17 (1.38)	5.13 (1.43)	5.81 (1.24)	5.23 (1.51)	5.27 (1.45)
Ease of Use ^c	N (%)	111 (77%)	47 (87%)	51 (81%)	292 (94%)	501 (87%)
Total Ease of Use Score	Mean (SD)	4.38 (1.61)	5.30 (1.74)	4.60 (1.51)	5.58 (1.42)	5.15 (1.6)
Overall Treatment Satisfaction ^c	N (%)	89 (61%)	35 (65%)	40 (64%)	241 (77%)	405 (71%)
Total treatment satisfaction Score	Mean (SD)	3.64 (1.25)	4.39 (2.13)	3.68 (1.38)	4.81 (1.8)	4.35 (1.75)

SD -Standard deviation.

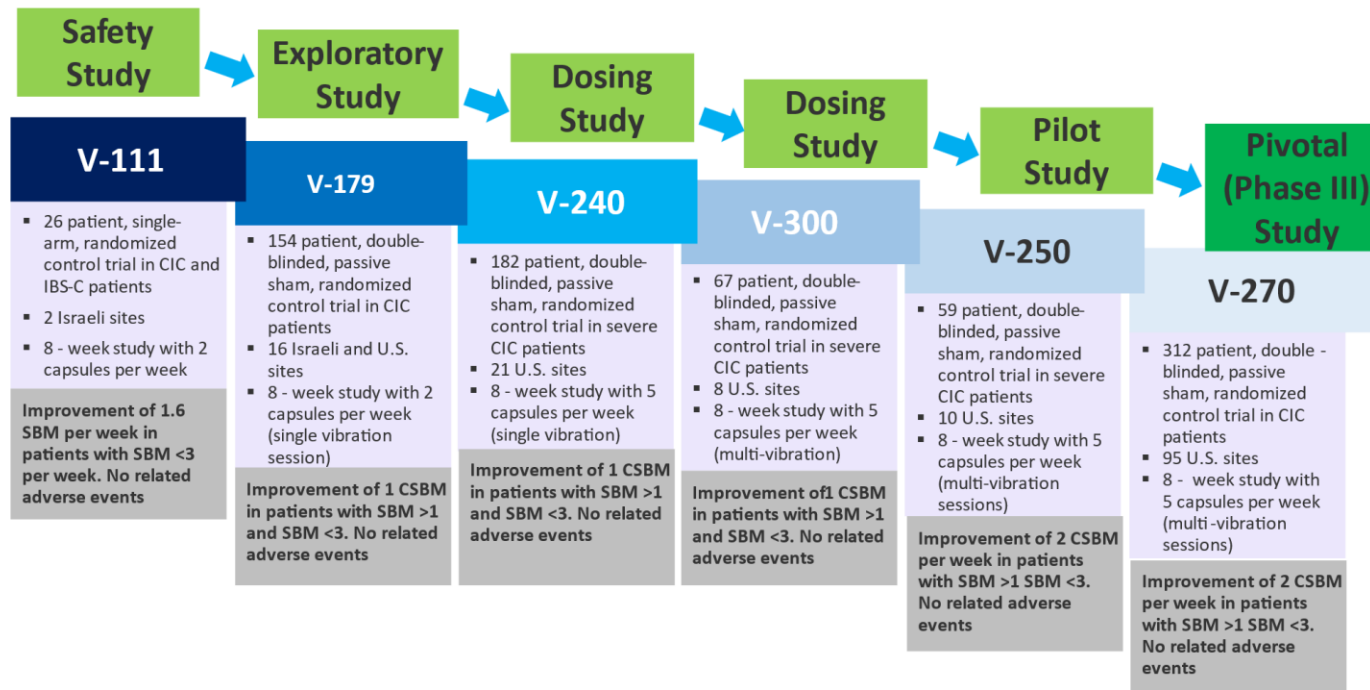
^a Treatment Satisfaction Questionnaire for Medication (TSQM) range of scores (1=Extremely Dissatisfied, 7 = Extremely Satisfied).

^b N: Number of patients from Active and Placebo/sham / placebo arms that completed the TSQM questionnaire

^c Satisfaction rate: represents the incidence of satisfied patients (score 4 and above).

Figure 1: Summary description of clinical trials using vibrating capsule that were analyzed for safety and tolerability

Clinical Development Program For Vibrating Capsules in CIC Patients



Flow diagram representing the clinical trials included in the analysis. This included 6 separate studies with a total of 800 patients. Patients received vibrating capsules or sham / placebo capsules 2-5x a week depending on the study.

Table 1: Demographic Characteristics of Patients Included in the Analysis

Studies		V111	V179		V240		V250		V300			V270		All Studies
Characteristic		Vibrant (N=26)	Vibrant (N=77)	Sham / placebo (N=77)	Active (N=89)	Sham / placebo (N=93)	Active (N=31)	Placebo (N=28)	Active Mode 1 (N=22)	Active Mode 2 (N=21)	Sham / placebo (N=24)	Active Mode (N=163)	Placebo (N=149)	All Arms (N=800)
Age Mean (SD)		47.0 (12.6)	45.7 (12.3)	47.0 (13.4)	45.4 (13.1)	42.7 (11.2)	46.9 (11.9)	46.0 (15.0)	44.4 (12.7)	41.9 (10.7)	41.3 (13.6)	47.1 (13.3)	45.9 (13.4)	Mean range: 41.3-47.1
Gender N (%)	Male	2 (7.7%)	8 (10.4%)	9 (11.7%)	18 (20.2%)	22 (23.7%)	1 (3.2%)	1 (3.6%)	3 (14.3%)	4 (18.2%)	3 (12.5%)	20 (12.3%)	23 (15.4%)	114 (14%)
	Female	24 (92.3%)	69 (89.6%)	68 (88.3%)	71 (79.8%)	71 (76.3%)	30 (96.4%)	27 (96.4%)	18 (85.7%)	18 (81.8%)	21 (87.5%)	143 (87.7%)	126 (84.6%)	686 (86%)
Ethnicity N (%)	Caucasian	26 (100%)	59 (76.6%)	63 (81.8%)	37 (41.6%)	29 (31.2%)	15 (48.4%)	9 (32.1%)	6 (28.6%)	5 (22.7%)	9 (37.5%)	77 (47.2%)	60 (40.3%)	395 (49%)
	Hispanic/Latino	-	-	-	17 (19.1%)	22 (23.7%)	4 (12.9%)	10 (35.7%)	4 (19.1%)	8 (36.4%)	6 (25%)	31 (19.0%)	34 (22.8%)	136 (17%)
	Black/African American	-	-	-	32 (36.0%)	33 (35.5%)	11 (35.5%)	8 (28.6%)	10 (47.6%)	7 (31.8%)	9 (37.5%)	41 (25.2%)	39 (26.2%)	190 (24%)
	Native American	-	-	-	1 (1.1%)	4 (4.3%)	-	-	1 (4.8%)	1 (4.6%)	-	-	-	7 (1%)
	Asian/Pacific Islander	-	-	-	1 (1.1%)	3 (3.2%)	-	-	-	1 (4.6%)	-	10 (6.1%)	12 (8.1%)	27 (3%)
	Other	-	18 (23.4)	14 (18.2%)	1 (1.1%)	2 (2.2%)	1 (3.2%)	1 (3.6%)	-	-	-	4 (2.5%)	4 (2.7%)	45 (6%)

SD -Standard deviation.

Table 2: Baseline Bowel Symptoms, Stool Characteristics and Quality of Life Scores for CIC Patients Included in this Analysis

Characteristic Mean (SD)	V111	V179		V240		V250		V300			V270	
	Vibrant	Vibrant	Sham / placebo	Active	Sham / placebo	Active	Placebo	Active Mode 1	Active Mode 2	Sham / placebo	Active	Placebo
	N=26	N=77	N=77	N=89	N=93	N=31	N=28	N=22	N=21	N=24	N=163	N=149
No. of SBMs/week	2.21 (0.74)	1.99 (0.89)	1.89 (1.01)	1.79 (0.59)	1.78 (0.57)	1.54 (0.65)	1.63 (0.87)	1.51 (0.59)	1.57 (0.57)	1.82 (0.72)	1.73 (0.51)	1.63 (0.49)
No. of CSBMs/week	Not collected	0.59 (0.86)	0.60 (0.81)	0.45 (0.70)	0.40 (0.59)	0.42 (0.49)	0.46 (0.59)	0.44 (0.71)	0.46 (0.74)	0.60 (0.62)	0.38 (0.51)	0.39 (0.59)
Duration of constipation (years)	Not collected	Not collected	Not collected	11.67 (12.46)	13.09 (12.19)	18.06 (13.00)	21.36 (12.32)	14.86 (10.79)	8.45 (6.70)	11.15 (12.33)	17.9 (14.5)	14.5 (12.35)
Stool Consistency score ^a	Not collected	1.70 (0.75)	1.82 (1.03)	2.36 (1.29)	2.24 (1.13)	2.84 (1.41)	2.36 (1.06)	2.18 (1.27)	2.50 (1.53)	2.47 (1.28)	2.13 (1.10)	2.14 (1.06)
Straining Score ^b	Not collected	5.48 (2.27)	5.72 (2.70)	4.33 (2.30)	5.00 (10.00)	3.87 (2.37)	4.46 (2.46)	4.36 (2.22)	4.26 (2.33)	3.92 (2.07)	4.66 (2.44)	4.87 (2.30)
Bloating Score ^c	Not collected	5.06 (2.98)	4.92 (2.64)	3.44 (2.54)	3.84 (2.44)	4.09 (3.02)	4.06 (2.90)	3.16 (2.50)	2.83 (2.34)	3.16 (1.92)	3.52 (2.59)	3.61 (2.74)
PAC-QOL score	Not collected	2.15 (0.74)	2.20 (0.74)	2.60 (0.80)	2.77 (0.69)	2.81 (0.83)	2.80 (0.84)	Not collected	Not collected	Not collected	2.67 (0.74)	2.67 (0.76)

SD -Standard
deviation.

^a Stool consistency range of scores (1=hard lumpy stool, 7 = loose watery stools),

^b Straining score (no straining =0; unbearable straining=10)

^c Bloating score (no bloating=0; unbearable bloating=10)

Table 3: Adverse Events Reported by the Patients Who Were Participating in Each of the Clinical Trials of the Vibrating Capsule

Studies	V111*	V179		V240		V250		V300			V270		Total	
Adverse Events N (%)	Vibrant (N=26)	Vibrant (N=77)	Sham / placebo (N=77)	Active (N=89)	Sham / placebo (N=93)	Active (N=31)	Placebo (N=28)	Active Mode 1 (N=22)	Active Mode 2 (N=21)	Sham / placebo (N=24)	Active Mode (N=163)	Placebo (N=149)	Active (N=429)	Placebo (N=371)
All Adverse Events	12(46%)	35(45%)	20(26%)	37(42%)	23(25%)	6(19%)	8(29%)	6(27%)	8(38%)	5(21%)	44(27%)	26(17%)	148(34%)	82(22%)
Sensation of Vibration	-	14(17%)	2(3%)	15(17%)	2(2%)	-	-	1(5%)	2(10%)	3(13%)	18(11%)	-	50(12%)	7(2%)
Headache	3(12%)	7(9%)	4(5%)	5(6%)	3(3%)	1(3%)	1(4%)	1(5%)	2(10%)	1(4%)	3(2%)	4(3%)	22(5%)	13(4%)
UTI	-	1(1%)	1(1%)	2(2%)	-	-	-	-	1(5%)	-	3(2%)	2(1%)	7(2%)	3(1%)
Abdominal pain/discomfort	3(12%)	2(3%)	1(1%)	-	2(2%)	1(3%)	-	1(5%)	1(5%)	-	4(2%)	8(5%)	12(3%)	11(3%)
Emesis/Vomiting	-	1(1%)	1(1%)	-	2(2%)	-	1(4%)	-	-	-	2(1%)	1(1%)	3(1%)	5(1%)
Nausea	-	1(1%)	3(4%)	7(8%)	2(2%)	-	1(4%)	-	-	-	3(2%)	1(1%)	11(3%)	7(2%)
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Anorectal discomfort	-	-	-	-	-	-	-	-	-	-	-	1(1%)	0(0%)	1(0%)
Diarrhea	2(8%)	2(3%)	1(1%)	1(1%)	3(3%)	1(3%)	1(4%)	-	1(5%)	1(4%)	2(1%)	-	9(2%)	6(2%)
Other	2(8%)	5(6%)	-	5(6%)	6(6%)	3(10%)	4(14%)	1(5%)	-	-	7(4%)	7(5%)	23(5%)	17(5%)

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^a Treatment Satisfaction Questionnaire for Medication (TSQM) range of scores (1=Extremely Dissatisfied, 7 = Extremely Satisfied).

^b N: Number of patients from Active and Placebo/sham / placebo arms that completed the TSQM questionnaire

^c Satisfaction rate: represents the incidence of satisfied patients (score 4 and above).