

A randomized, single center, double-blind, parallel-group, placebo-controlled study assessing the effect of CSP01 on chronic idiopathic constipation and irritable bowel syndrome with constipation

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I. Background and Significance

a.) Historical background

Constipation remains one of the most common clinical conditions encountered by physicians with an estimated general population prevalence ranging from 2% to 28%¹ generating 2.5 million physician visits per year with an annual direct medical cost of more than \$230 million in the U.S. alone.² Constipation is a symptom described as infrequent stool passage often associated with straining or the sensation of incomplete evacuation.³ In addition to gastroenterological pathology such as poor bowel motility or outlet obstruction, there are many other etiologies of constipation such as secondary to a medical condition or medication. Chronic constipation without a demonstrable physiologic abnormality is classified by Rome III Criteria as chronic idiopathic constipation (CIC), a functional gastrointestinal disorder that exists on a spectrum with irritable bowel syndrome with constipation (IBS-C).⁴ The prevalence of CIC worldwide is 14%, and it is more common in women, elderly people, and those of lower socioeconomic status. Additionally, patients with chronic constipation report impaired quality of life comparable to other chronic conditions, and consequently tend to contribute considerably to physician visits and other healthcare costs.⁵ Therefore, there is a need for more effective and well-tolerated devices, as 50% of patients with constipation are not satisfied with available therapies.⁶

b.) Previous studies supporting the proposed research

Although CIC and IBS-C are common problems, the treatment of constipation symptoms is often provider-specific, and there is weak evidence to support many of the drugs that are commonly used in the treatment of this disorder.⁷ Lifestyle measures such as hydration, exercise, and increased fiber intake are an important component of the multi-faceted approach to treating chronic constipation prior to initiation of medical therapy.⁸ Notably, fiber supplementation significantly alleviates symptoms in patients without slow transit constipation⁹, the majority of patients with constipation.³

CSP01 is a non-systemic, orally administered capsule that contains thousands of

proprietary, biocompatible hydrogel particles synthesized with starting materials that are Generally Recognized as Safe by the U.S. Food and Drug Administration (FDA).¹⁰ CSP01 is similar to Gelesis100 and Gelesis200, both of which have been tested in humans and show excellent safety profiles, and differs from Gelesis200 only by the addition of the excipient sodium stearyl fumarate, which allows for the packing of more hydrogel particles into the capsule. CSP01 capsules are taken prior to a meal with water, after which the small particles within the capsules hydrate and expand in the stomach and small intestine. Gelesis100, a similar product, has undergone multiple early phase clinical trials.¹¹ The First Loss Of Weight (FLOW) study demonstrated the safety of the Gelesis100 medical device with 12 weeks of use in overweight and obese subjects. Currently, Gelesis Inc. is conducting the Gelesis Loss Of Weight (GLOW) study, a pivotal, randomized, double-blind, placebo-controlled, parallel-group study designed to assess the effect of repeated administration of Gelesis100 over six months on body weight and glycemic control parameters in overweight and obese subjects.¹²

c.) Rationale behind the proposed research

By acting as a bulking agent and possibly reducing colonic transit time through increase of colonic water content, CSP01 may contribute to constipation relief. In contrast to traditional fiber that retains water without influencing colonic water content, CSP01 absorbs water solutions up to 85 times its original weight while in the stomach, acts as a bulking agent as it moves through the small intestine, and partially degrades in the large intestine through loss of its three-dimensional matrix structure and most of its hydration capacity. By losing its water absorption capacity in the colon, colonic water content is thus increased in a mechanism of action similar to current therapies treating constipation, and CSP01 is expelled in the feces.

Given the in vitro performance of this novel, fiber-like hydrogel, it is therefore hypothesized that the device may be of benefit in patients with CIC and IBS-C, however, analysis of how it affects whole gut motility has not been conducted. This will be observed using wireless motility capsule (WMC) testing, a non-invasive diagnostic tool capable of measuring intraluminal pressure and pH through the whole GI tract, assessing both transit and contractility. WMC has been demonstrated as a safe, convenient, and reliable method of assessing whole gut transit after a dietary intervention in a more physiologic setting than traditional manometry or scintigraphy.

II. Specific Aims

This is a single center, randomized, double-blind, parallel-group, placebo-controlled pilot study. The purpose of the study is to evaluate the efficacy of the hydrogel capsule CSP01 vs active control (carboxymethylcellulose) vs placebo in accelerating colonic motility among patients with chronic idiopathic constipation. Patients who meet the Rome IV criteria for CIC or IBS-C and who meet the inclusion criteria will be offered participation in this study.

III. Subject Selection

This study aims to recruit 53 total subjects to be enrolled at one site, Massachusetts General Hospital. The 53 subjects that this study aims to recruit factors in a dropout rate of 15%, with a final sample size of 45 subjects.

INCLUSION/EXCLUSION CRITERIA:

Inclusion

1. Age 22-70 years old
2. BMI >18.5 and <35 kg/m²
3. Rome IV criteria for functional constipation or IBS-C
4. Continued IBS-C or CIC throughout Run-in period
5. Compliant with reporting during Run-in (confirm the presence of constipation during the 7-day Run-in baseline period; patients are required to report an average of <3 continuous spontaneous bowel movements [CSBMs] and ≤6 spontaneous bowel movements [SBMs] per week via the interactive web response system).

6. Ability to follow verbal and written instructions
7. Ability to record daily bowel habits, including frequency, stool consistency (BSFS), straining (EoPS), completeness of evacuation, and Patient Reported Outcomes (PROs) (abdominal discomfort, severity of constipation, bloating, overall relief)
8. Informed consent form signed by the subjects

Exclusion

1. History of loose stools
2. History of irritable bowel syndrome with diarrhea (IBS-D) or mixed irritable bowel syndrome (IBS-M)
3. Non-compliance with reporting during Run-in
4. Patients reporting laxative, enema, and/or suppository usage for >2 days or any usage of a prohibited medication during the Run-in period
5. Patients reporting watery stools for any SBM (Type 7 on the Bristol Stool Form Scale [BSFS]) or loose (mushy) stools for >1 SBM (Type 6 on the BSFS) in the absence of laxatives during Run-in
6. GI motility obstruction or GI tract structural abnormality
7. Current use of prescribed or illicit opioids
8. History of pelvic floor dysfunction
9. Need for manual maneuvers in order to achieve a BM
10. History of GI lumen surgery at any time or other GI or abdominal operations within 60 days prior to entry into the study
11. History of high-dose stimulative or cathartic laxative abuse as judged by investigator team
12. Neurological disorders, metabolic disorders, or other significant disease that would impair their ability to participate in the study
13. Cardiovascular disease, diabetes, cancer, Crohn's disease, ulcerative colitis
14. BMI of <18.5 or >35 kg/m²
15. Pregnancy (or positive serum or urine pregnancy test(s) in females of childbearing potential) or lactation
16. Absence of contraception in females of childbearing potential
17. History of allergic reaction to carboxymethylcellulose, citric acid, sodium stearyl fumarate, raw cane sugar, gelatin, or titanium dioxide
18. Administration of investigational products within 1 month prior to Screening Visit
19. Exclusion of colonic inertia with symptoms of < 1 BM per 2 weeks
20. Subjects anticipating surgical intervention during the study
21. Known history of diabetes (type 1 or 2)
22. History of eating disorders including binge eating (except mild binge eater)
23. Supine SBP > 160 mm Hg and/or supine DBP > 95 mm Hg (mean of two consecutive readings)
24. Angina, coronary bypass, or myocardial infarction within 6 months prior to Screening Visit
25. History of swallowing disorders
26. Esophageal anatomic abnormalities (e.g., webs, diverticuli, rings)
27. History of gastric bypass or any other gastric surgery

28. History of small bowel resection (except if related to appendectomy)
29. History of gastric or duodenal ulcer
30. History of gastroparesis
31. History of abdominal radiation treatment
32. History of pancreatitis
33. History of intestinal stricture (e.g., Crohn's disease)
34. History of intestinal obstruction or subjects at high risk of intestinal obstruction including suspected small bowel adhesions
35. History of malabsorption
36. History of sucrose intolerance
37. History of hepatitis B or C
38. History of human immunodeficiency virus
39. History of cancer within the past 5 years (except adequately-treated localized basal cell skin cancer or *in situ* uterine cervical cancer)
40. Any other clinically significant disease interfering with the assessments of Gelesis100, according to the Investigator (e.g., disease requiring corrective treatment, potentially leading to study discontinuation)
41. HbA1c > 8.5% (> 69 mmol/mol)
42. Positive test for drugs in the urine
43. Any relevant biochemical abnormality interfering with the assessments of Gelesis100, according to the Investigator
44. Antidiabetic medications within 1 month prior to Screening Visit (except stable dose of metformin, ≤ 1500 mg/day, for at least 1 month in subjects with type 2 diabetes)
45. Medications requiring mandatory administration with meal at lunch or dinner
46. Anticipated requirement for use of prohibited concomitant medications
47. Implanted or externally worn medical device such as, but not limited to, a pacemaker, infusion pump, or insulin pump

c.) Source of subjects and recruitment process

Subjects will be recruited from the MGH Center for Neurointestinal Health based on the following enrollment criteria. Other GI physicians at MGH will be informed of the study and can refer patients to the clinic if they are deemed appropriate for the study. Study staff will review subject's electronic medical records to confirm inclusion and exclusion criteria. Subjects may also be identified using the Research Patient Data Registry (RPDR) system. Electronic medical records of potential subjects will be reviewed to confirm inclusion and exclusion criteria. The patient's provider will be contacted to confirm the patient's eligibility as well as to gain permission to contact the patient. The recruitment letter by the PI and the patient's provider will be sent. Patients who agreed to direct contact (RODY YES) will receive a recruitment letter from the PI. If the patient does not contact the study coordinator within 1 week, they will be contacted by phone and/or email by the study coordinator. All subjects will undergo telephone prescreening by the study staff.

In addition to patients of MGH, subjects from the general greater Boston population will also be recruited. Subjects from the general population will be recruited through online advertisements run using the Galen Recruitment Service. Through this service, respondents will be filtered by qualifying questions. Contact information for qualified respondents will be provided to research study staff.

IV. Subject Enrollment

a.) Methods of enrollment

1. Patients may be approached by a research coordinator in the Neurointestinal Health clinic if they have a history of chronic constipation and agree to hear more about the trial
2. Patients may be called by the research coordinator prior to their appointment and asked if they would like to hear more about the trial
3. Any patients agreeing to hear more about the trial will learn more before beginning the informed consent process should they agree to participate as well as determining whether they meet all of the inclusion criteria
4. Patients may be contacted about the research study by their MGH physician on behalf of the research team. Afterward, patients may then be contacted by the research team directly.
5. Subjects who have provided their contact information through internet advertising may be contacted by the research team directly.

b.) Procedures for obtaining informed consent

1. Patients agreeing to participate will sign an informed consent with the study doctor at the time of enrollment, after proper informed consent has been provided by the site.

c.) Treatment assignment and randomization

1. Patients who have been enrolled and consented in the trial will be randomized with a ratio of 1:1:1 with 15 subjects per arm: 15 subjects on 3 capsules BID of CSP01, 15 subjects on 3 capsules BID (morning, evening) of carboxymethylcellulose (CMC), and 15 subjects on 3 capsules BID of placebo (sucrose).
2. We will stratify by Rome IV diagnosis of CIC vs. IBS-C to avoid clustering of IBS-C patients in one group.
3. The study personnel and patients will be blinded to treatment allocation.
4. Patients who fulfill study admission criteria and have a signed consent form will be assigned a 3-digit sequential patient number. The number will be used throughout the study.
5. Randomization will be conducted via an interactive web-based response system (IWRS). Based on the randomized treatment assignment, an unblinded pharmacist at MGH will prepare the study treatment in a manner that ensures maintenance of the blind utilizing study-specific labels and completing details pertinent to the individual patient.
6. This is a double-blind study. The individual treatment assignment will not be revealed to patients or their representatives, study staff (except for the unblinded pharmacist), or the sponsor or the sponsor's representatives, until all patients complete the study and the database is locked. The unblinded pharmacist will maintain the treatment assignment for each patient.

V. Study Procedures

a.) Study visits and parameters to be measured

1. Eligibility Screen (Day -28 to -15)

- a. Vital signs, height, weight, and physical exam will be performed.
- b. Rome IV questionnaire to screen for CIC and IBS-C
- c. Blood sample collection (CBC, Chem 7, LFTs, Thyroid Hormone, ESR, and if applicable, serum pregnancy test)
- d. Urine sample for toxicity screening

2. Run-In Period (Day -14 to 0)

Day -14: After a screening visit in which patient eligibility will be determined through use of Rome IV constipation module along with other inclusion and exclusion criteria as above, there will be a two-week run-in period.

During this time no use of contraindicated medication per exclusion criteria or medications that may affect the bowel mobility will be allowed unless the subject has been on a stable dose for the last 3 months:

- a. Laxatives
- b. Prokinetic medications
- c. Anti-Depressant medications
- d. Medications for treatment of Parkinson disease
- e. Opiates
- f. Calcium-channel Blockers
- g. Aluminium/Magnesium
- h. Hydroxides
- i. Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) as defined by a frequency of at least 3 times a week for at least 6 months. Subjects on cardiac doses of aspirin may be enrolled in the study.

Day -7: Seven days into the run-in period, patients will undergo wireless motility capsule (WMC) testing to assess baseline motility. To allow for complete passing of the capsule, there will be a 7-day period following WMC ingestion prior to initiation of treatment to coincide with the end of the two-week run-in period.

If there is an issue with capsule transit, will be monitored by investigator team and depending on location may exclude patient (i.e. if capsule transit delayed in stomach, would exclude patient based on exclusion criteria of gastroparesis). Patients with no bowel movement for 5 consecutive days, who are in need of a rescue treatment, will be instructed to contact the investigator. The following treatment is recommended, as applicable, in the following order:

1. Glycerin suppository
2. Enema
3. Laxadin/Bisacodyl tablets (3x5mg)

Administration of rescue treatment is at the discretion of the investigator based on an assessment of the subject; administration of rescue should be monitored and recorded.

3. Treatment Period (Day 0 to 22)

- a. **Day 0:** On the visit to initiate treatment, patients will return to the clinic to return their WMC monitor and be treated in a parallel-group design for 3 weeks. At this visit, the patient will return the SmartPill receiver and the study diary. Questions or concerns about the study will be discussed, including any changes in concomitant medications and new or worsening adverse events. If available, results of the SmartPill test will be reviewed by the patient's physician. If it is unclear that the capsule has passed, based on the subject's history or on the study results, erythromycin may be prescribed if the capsule is still in the stomach as a promotility medication or obtain an abdominal x-ray for verification to determine if the capsule is still in the colon. If the subject is female, then a urine pregnancy test will be performed before any abdominal xray. Issues with capsule transit will be addressed as above.

- b. Following the two-week run-in period, subjects will again complete the Rome IV Constipation module confirming that inclusion and exclusion criteria continue to be satisfied, and the patient will be randomized using the IWRS. The IWRS will notify the pharmacy to prepare the study drug (randomization output must only be seen by unblinded pharmacist).
- c. During 3-week treatment period, patients will ingest three capsules, twice daily, before breakfast and dinner (with 16 oz water).
- d. Patients will be asked to refrain from making any major lifestyle changes (e.g., starting a new diet or changing their exercise pattern) during the study.
- e. Patients will be instructed to complete a simple, web-based daily diary using the Redcap system throughout the duration of the study which includes daily recording of number and time of bowel movements, complete/incomplete evacuation, and straining, abdominal discomfort, bloating, constipation severity, and overall relief using a nominal rating scale.
- f. **Day 1:** Subjects will begin taking study device. Patients will complete the Patient Assessment of Constipation Symptoms (PAC-SYM) and Quality of Life (PAC-QOL) to determine the severity of their constipation.
- g. **Day 15:** Following 14 days of treatment, patients will return to the clinic to undergo WMC testing to establish their motility profile on treatment and complete PAC-SYM, PAC-QOL questionnaires.
- h. **Day 22:** Following 21 days of treatment, patients will return to the clinic to return the WMC monitor and complete PAC-SYM, PAC-QOL questionnaires.
- i. **Day 31 (+3 days):** There will be a post-treatment period of 7 days during which time patients will continue to complete their daily diary. The clinical coordinator will call patients at the end of this follow-up period to ensure no adverse events occurred. After completion of the study, patients will be mailed the results of their SmartPill baseline test.

4. Schedule of Events

		Study						
		Run-in period			Treatment period			Post-treatment period
Time Point	Day -28 to -15	Day -14	Day -7	Day 0	Day 1	Day 15	Day 22	Day 31
Eligibility screen	X							
Informed consent	X							
Allocation				X				
CSP01 group				—————				
CMC group				◀	—————			▶
Placebo group				—————				
Rome IV questionnaire	X			X				
Daily diary		X	X	X	X	X	X	X
PAC-SYM		X		X	X	X	X	
PAC-QOL		X		X	X	X	X	
WMC testing			X			X		
Adverse events					X	X	X	X

5. There will be no routine monitoring of labs or imaging for the purposes of the study outside of usual care. Other study monitoring activities will be conducted as per Section IX of this protocol.
6. Patients enrolled in the study will not be allowed to be given standing laxative medications for prophylactic purposes, but rescue medications will be allowed on an as-needed (PRN) basis

b.) Investigational Product (IP) to be used

1. The IP will be supplied by the Sponsor and stored in the MGH inpatient pharmacy
 - a. CSP01 is supplied in capsule form (0.79 g per capsule, 2.37 g per dose)
 - b. CMC dose is supplied in capsule form (0.70 g per capsule, 2.1 g per dose)
 - c. Matching placebo consists of an inert mixture supplied by the Sponsor in identical-appearing capsules
2. Rescue medications (in case of emergency)
 - a. If a subject experiences inadequate prevention of constipation while on the study treatment or placebo, the patient may be administered a rescue medication (laxative) at the discretion of the patient conferring with the Study physician or research NP consistent with “prn” orders or new orders from the medical team. Drugs that are available to treat constipation include: Colace (Docusate), Polyethylene glycol (Miralax), Senna (Senokot), magnesium citrate, and lactulose. Because constipation is not a side effect of the medication, all patients will be able to receive laxative doses as needed at their request throughout the study consistent with nurse’s or physician’s discretion without restriction.
 - b. Patients with no bowel movement for 5 consecutive days, who are in need of a rescue treatment, will be instructed to contact the investigator. The following treatment is recommended, as applicable, in the following order:
 - i. 1. Glycerin suppository
 - ii. 2. Enema
 - iii. 3. Laxadin/Bisacodyl tablets (3x5mg)
 - c. Administration of rescue treatment is at the discretion of the investigator based on an assessment of the subject; administration of rescue should be monitored and recorded.

c.) Data to be collected and timeline for collection

1. Primary endpoints
 - a. Colonic Transit Time (CTT)
2. Secondary endpoints
 - a. Spontaneous Bowel Movement (SBM) frequency rate
 - b. Complete Spontaneous Bowel Movement (CSBM) frequency rate
 - c. Stool consistency (Bristol Stool Form Scale)
 - d. Straining (Ease-of-Passage Scale)
 - e. Abdominal discomfort (Self Assessment on 0–10-point numerical rating scale)
 - f. Bloating (Self Assessment on 0–10-point numerical rating scale)
 - g. Constipation severity (Self Assessment on 0–10-point numerical rating scale)
 - h. Overall relief (Self Assessment on 0–10-point numerical rating scale)
 - i. Balloon Expulsion Time (BET) before and after
 - j. PAC-SYM change
 - k. PAC-QOL change
 - l. Need for rescue laxatives

c.) Adverse events

1. Definition of adverse events
 - a. An adverse event (AE) is any untoward medical occurrence (sign, symptom, illness, abnormal laboratory value, or other medical event) in a subject, whether or not related to the investigational medical device. This includes events related to the procedures involved (any procedure in the Clinical Investigation Plan).
2. A serious adverse event (SAE) is any AE that:
 - a. led to death
 - b. resulted-in a life-threatening condition
 - c. resulted-in a permanent impairment of a body structure or a body function
 - d. required inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 h (elective hospitalizations and/or hospitalizations for treatment of pre-existing conditions that did not worsen from baseline are not considered AEs and should not be reported as SAEs)
 - e. resulted-in a medical or surgical intervention to prevent permanent impairment to a body structure or a body function
 - f. led to fetal distress, fetal death or a congenital abnormality, or birth defect
3. A device deficiency is an inadequacy of the medical device with respect to its identity, quality, durability, and safety (e.g., use errors and inadequate labeling). Medical device deficiency can lead to an adverse device effect (ADE) or a serious ADE (SADE) (see below).
 - a. For the purpose of this study and for reporting purposes, all device deficiencies that could have led to SAEs, if suitable action had not been taken or intervention had not been made, or if circumstances had been less fortunate, will also be considered as SAE.

4. Adverse device event definitions:
 - a. An adverse device event (ADE) is an AE with a reasonable causal relationship to the use of the investigational medical device (i.e., an AE assessed as either “most probably related” or “possibly related” to the use of medical device) (see Section 13.1.3).
 - b. An unanticipated ADE (UADE) is an ADE not previously reported or an ADE that occurs with specificity, severity, frequency, or outcome that is not consistent with the current Investigator’s Brochure (8).
 - c. A SADE is a SAE with a reasonable causal relationship to the use of the investigational medical device (i.e., a SAE assessed as either “most probably related” or “possibly related” to the use of medical device).
 - d. An unanticipated SADE (USADE) is a SADE not previously reported or an SADE that occurs with specificity, severity, frequency, or outcome that is not consistent with the current Investigator’s Brochure. In US, this definition is equivalent to the definition of an UADE in Medical Device Reporting regulation at Title 21.

5. Adverse Event and Device Deficiency Recording, Assessment, and Reporting Procedure
 - a. All AEs regardless of seriousness or relationship to the investigational medical device including those occurring during the screening period (after the signature of the Informed Consent Form) are to be recorded in the appropriate electronic CRF.
 - b. AEs reported by subject will be discussed in details and recorded by the Investigator at each visit. AEs will be collected until 28 days after the last administration of the investigational medical device (i.e., until subject terminates his/her participation in the study).
 - c. The Investigator should specify the date of onset, severity, action taken with respect to the investigational medical device, corrective treatment, outcome, and whether or not there is a reasonable possibility that the AE may have been caused by the use of the investigational medical device.
 - d. AEs are graded as follows:
 - i. Mild: sign or symptom, usually transient, requiring no special treatment and generally not interfering with usual activities.
 - ii. Moderate: sign or symptom, which may be ameliorated by simple therapeutic measures, may interfere with usual activity.
 - iii. Severe: sign or symptom intense or debilitating and interfering with usual activities without being immediately life-threatening. Recovery is usually aided by therapeutic measures.
 - iv. Very severe: sign or symptom life-threatening. Urgent intervention indicated.
 - e. The assessment of the relationship of an AE to the use of the medical device is a clinical decision based on all available information at the time of the completion of the electronic CRF:

- i. Most probably related: follows a reasonable temporal sequence from medical device use, and cannot be reasonably explained by known characteristics of the subject's clinical data.
 - ii. Possibly related: follows a reasonable temporal sequence from medical device use, but could have been produced by the subject's clinical state regardless of the medical device.
 - iii. Probably not related: temporal association is such that the medical device use is not likely to have had any reasonable association with the observed event.
 - iv. Not related: no relationship to the use of the medical device is perceived.
- f. Abnormalities of vital signs and laboratory results are to be recorded as AEs only if they are considered by the Investigator as clinically significant (symptomatic, requiring corrective treatment, leading to discontinuation, or fulfilling a seriousness criteria).
- g. Any pre-existing conditions or signs and/or symptoms present in a subject prior to the Screening Visit should be recorded as medical/surgical history.
- h. In this study, the following events will be reported to the authorities on expedited basis:
- i. All SAEs (including SADEs) will be expeditiously reported to the relevant European Regulatory Authorities and the Ethics Committees.
 - ii. All suspected USADEs will be expeditiously reported to the Food and Drug Administration (FDA) and Institutional Review Board.
- i. All device deficiencies are to be recorded in the appropriate electronic CRF.

6. Anticipated Adverse Device Effects

- a. The ADEs anticipated with the administration of Gelesis100 in overweight or obese subjects include nausea, dyspepsia (heartburn), abdominal distension (bloating), flatulence, abdominal pain, diarrhea, defecation urgency, and constipation. These AEs were observed in the FLOW study. A comprehensive list of anticipated ADEs is provided in the Investigator's Brochure (8).\

7. Risk Analysis

- a. The Sponsor has established and maintains a process for identifying hazards associated with the use of its products, estimating, evaluating, controlling these risks and monitoring the effectiveness of the control. Detailed information regarding risk analysis is available in the Investigator's Brochure (8).

8. Precautions to Minimize Risk

- a. To minimize technical and medical complications, the investigational medical device should be used only as instructed in the Clinical Investigation Plan. This includes:
- i. administering the prescribed amount of medical device before breakfast and dinner (3 capsules at each)

- ii. drinking the prescribed volume of water (approximately 100 mL + 500 mL) at the prescribed timing before meal
- iii. consuming food at the prescribed timing (20 to 30 min after medical device administration)

9. Pregnancy

- a. In case of pregnancy, the investigational medical device use must be discontinued and the Sponsor informed. Every effort should be made to follow up the pregnancy until its outcome is available.
- b. The Contract Research Organization (CRO) Clinical Safety will provide the Investigator with the Pregnancy Reporting Form for completion. If the pregnancy is to be terminated, the anticipated date of termination should be provided.

10. Responsibilities of the Investigator

- a. to inform the Sponsor about all AEs
- b. to inform the Sponsor about all SAEs, newly discovered pregnancies or pregnancy outcomes, within 24 h of awareness of the events, by:
 - i. entering the information about the event into the electronic CRF
 - ii. in case the Investigator does not receive an automatic notification from the electronic CRF system of successful SAE submission or electronic CRF data entering is not possible:
 - 1. printing the completed section of the electronic CRF (or in case completion of electronic CRF is not possible, completion of paper SAE form)
 - 2. signing the completed SAE form
 - 3. sending the scanned SAE form by e-mail to the CRO Clinical Safety at pharmacovigilance@easthorn.eu (or in case sending a scan is not possible, faxing it to the CRO Clinical Safety at +420 244 462 271)
- c. to inform the Sponsor about all device deficiencies
- d. to make every effort to follow up the subject to a satisfactory resolution of the safety event or until the end of the study
- e. to respond to follow-up requests from the Sponsor/CRO Clinical Safety

11. Responsibilities of the Sponsor

- a. to ensure that:
 - i. all AEs are recorded and reviewed with the Investigators
 - ii. all SAEs are reported to the relevant European Regulatory Authorities/Ethics Committees as required by local regulations
 - iii. all suspected USADEs are reported to the FDA/Institutional Review Board as required by the US regulations
 - iv. all device deficiencies are recorded and reviewed with the Investigators
- b. during the course of the study, inform in writing all Investigators about all SAEs occurring at any of the participating sites

- c. to collect and maintain records of all AEs, device deficiencies, and pregnancies

VI. Biostatistical Analysis

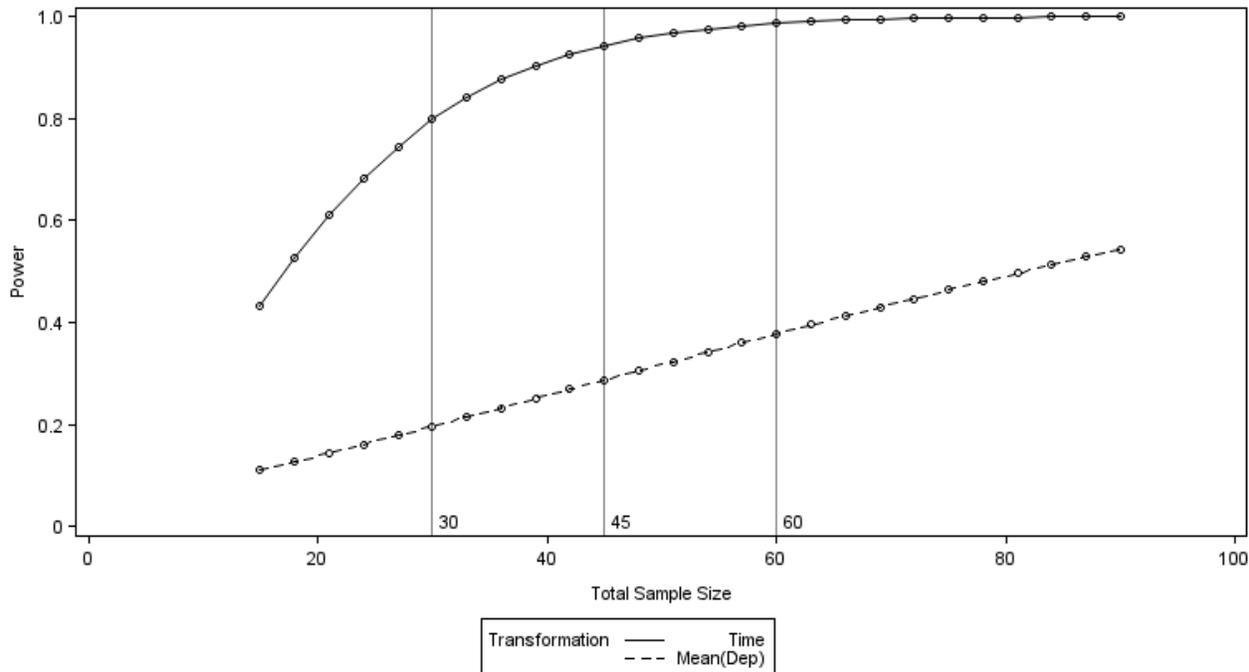
1. Specific data variables to be collected from WMC
 - a. Colonic Transit Time (CTT), Whole gut transit time (WGTT), Gastric emptying time (GET), Small bowel transit time (SBTT)
2. Specific data to be collected through patient-reported questionnaires
 - a. Spontaneous Bowel Movement (SBM) frequency rate
 - b. Complete Spontaneous Bowel Movement (CSBM) frequency rate
 - c. Stool consistency (Bristol Stool Form Scale)
 - d. Straining (Ease-of-Passage Scale)
 - e. Abdominal discomfort (Self Assessment on 0–10-point numerical rating scale)
 - f. Bloating (Self Assessment on 0–10-point numerical rating scale)
 - g. Constipation severity (Self Assessment on 0–10-point numerical rating scale)
 - h. Overall relief (Self Assessment on 0–10-point numerical rating scale)
 - i. Balloon Expulsion Time (BET) before and after
 - j. Constipation symptom severity (PAC-SYM)
 - k. Constipation quality of life (PAC-QOL)
 - l. Need for rescue laxatives
3. Study endpoints – As above
4. Statistical methods
 - a. Analysis populations
 - i. Intent-to-treat (ITT) population: all patients who are randomized will be included in the ITT population. This will be the primary population for all analyses of demographics, patient characteristics and disposition, and efficacy data.
 - ii. Safety population: All patients who are randomized and receive any study treatment will be included in the safety population. This will be the primary population for all analyses of safety data
 - iii. Per-Protocol (PP) population: All patients who are randomized and receive the study medication on each day of their hospitalization. Major protocol violations include the following:
 1. Prohibited concomitant medication usage (specifically standing laxatives during hospitalization)
 The PP population may be used for supplementary analysis of selected efficacy and safety data, as appropriate.
 - b. Endpoint analyses
 - i. Primary endpoint: Colonic transit times will be compared in a paired fashion for individual patients before and after the intervention by means of a repeated measures ANOVA using a 3x2 design to distinguish between the outcomes of the three different groups. We will also use multivariable linear regression to compare change in transit time after adjusting for confounders, specifically: presence of IBS-C, abnormal balloon expulsion testing indicating dyssynergic defecation ($BET \geq 2$ minutes), age, and sex.

ii. Secondary endpoints: The secondary endpoints will be compared in a similar fashion, with logistic regression adjusting for confounders.

c. Power analysis

This is a randomized, double-blind, single-center clinical exploratory pilot comparing treatment with CSP01 to standard control (CMC) to placebo (sucrose) for prevention of constipation in patients with chronic idiopathic constipation. Notably, there is no data either from the wireless motility capsule or from radio-opaque marker transit studies establishing a clinically-meaningful threshold for change in transit time in response to any colonic motility agent, and our hope is that transit data combined with patient-reported outcomes (our secondary endpoints) from this pilot study would provide a meaningful transit improvement threshold that may be used in future research as well. There is some data demonstrating the effect of dietary fiber on colonic transit time.⁷ If we extrapolate data from the trial of dietary fiber on colonic transit time, which demonstrated a 10-hour difference in colonic transit time with a standard deviation of 12 hours, we would assume the same effect for our standard fiber (CMC) group. Assuming that CSP01 would give an additional 3-hour decrease in colonic transit over conventional fiber, our current sample size would have 94% (with $\geq 90\%$ considered excellent) power to detect a difference. Even with 30 total subjects, we would still have 80% power (see graph below which varies the sample size).

Power Analysis/Sample Size Determination.
For a Repeated Measures Anova with Indicated Specifications, & Assuming
A Test-Retest Correlation of 0.7



If we are more conservative with the effect of CSP01 over standard fiber and decrease the additional effect to 1 hour decreased colonic transit time (1/3 of what

we would expect), we would still have 88% power with our current sample size.

VII. Risks and discomforts

1. Device side effects and adverse events

- a. The CSP01 device is constructed out of carboxymethyl cellulose cross-linked with citric acid. The device as a powder is mixed with sodium stearyl fumarate and then placed in a gelatin capsule. Construction risks, such as contaminations either from the supplier or during production, allergic reaction to the component of the device, were in most cases broadly acceptable; except two risks that were found to be intolerable (interaction with nutrients and/or drugs or mechanical crush of capsules), but after implementation of risk mitigation, these risks have been reduced to the acceptable level. The remaining risks have been found to be broadly acceptable and the benefit outweighs the risk of the device.
- b. CSP01 may contribute to constipation relief by acting as a bulking agent and possibly reducing colonic transit time through increase of colonic water content. In contrast to traditional fiber that retains water without influencing colonic water content, CSP01 absorbs water solutions up to 85 times its original weight while in the stomach, acts as a bulking agent as it moves through the small intestine, and partially degrades in the large intestine through loss of its three-dimensional matrix structure and most of its hydration capacity. Thus, CSP01 releases water in the colon increasing the colonic water content, and the CSP01 particles are expelled in the feces.

The following adverse device effects are anticipated based on the product composition (CMC), the form and route of administration (capsule taken orally), and the AEs reported in the STAGE and the FLOW studies:

- decreased appetite (lost appetite)
- dysgeusia
- nausea
- dysphagia
- dyspepsia (heartburn, pyrosis)
- reflux
- eructation (burping)
- vomiting
- abdominal distension (fullness, bloating)

- flatulence
- abdominal pain, abdominal pain upper, abdominal pain lower
- gallstone
- diarrhea (loose stools)
- defecation urgency (urgency, urge to defecation, fecal urgency)
- fecal color change
- fecal incontinence
- infrequent bowel movements (less frequent stools)
- constipation
- feces hard (hard stools)
- feces soft (soft stools)
- anorectal discomfort (anal irritation)

Because CSP01 non-invasive and does not achieve its primary intended purpose through chemical action within or on the body, and is not dependent upon being metabolized for the achievement of its primary intended purposes, it meets the definition of a medical device. CSP01 is a non-significant risk device in the US, because it does not meet the definition of a significant risk device under § 812.3(m) of the investigational device exemptions regulation (21CFR812)

- c. TSE/BSE risk from gelatin capsules found to be broadly acceptable as the Scientific Steering Committee (SSC) of the European Union (EU) in 2003 stated that the risk associated with bovine bone gelatin is very low or zero.^{14,15} In 2006, the European Food Safety Authority (EFSA) stated that the SSC opinion was confirmed, that the BSE risk of bone-derived gelatin was very small, and removed support for the 2003 request of excluding the skull and vertebrae of bovine origin older than 12 months from the material used in gelatin manufacturing.¹⁶

VIII. Potential benefits

1. It is hypothesized that it may be of benefit in patients with chronic idiopathic constipation. Potential benefits may include improved colonic transit, a decrease in self-reported abdominal discomfort, straining, bloating, and constipation severity, as well as improved quality of life and symptom severity.

IX. Monitoring and Quality Assurance

1. Good clinical practice
The investigator will ensure that this study is conducted in accordance with the principles of “Good Clinical Practice”, as outlined in Title 21 of Code of Federal Regulations (CFR), Part 312, subpart D, “Responsibilities of Sponsors and Investigators”; 21 CFR,

part 50, “Protection of Human Subjects”; 21 CFR, part 54, “Financial Disclosure by Clinical Investigators”; 21 CFR, part 56, “Institutional Review Boards”; and 21 CFR, Part 11, “Electronic Records, Electronic Signature”, are adhered to.

2. Institutional review board (IRB) approval

The protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to the MGH IRB. Approval from the IRB must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted approval. Any modifications made to the protocol after receipt of IRB approval must also be submitted to the IRB for approval before implementation.

3. Informed consent

Written informed consent, in accordance with 21 CFR Part 50, must be obtained prior to participation in the study. Within the context of the inclusion criteria, a proportion of eligible patients may be exhibiting significant cognitive impairment and the lack of capacity to provide consent. As such, all patients will require surrogate consent by a legally authorized representative. The investigator or staff will determine the appropriate family member-person to contact regarding the study, based on the standard operating procedures of MGH and local and state laws. The signed consent form must remain in the patient’s medical chart and must be available for verification at any time.

4. Liability and insurance

The civil liability of the investigator, the persons instructed by the investigator and the hospital, practice, or institute in which they are employed, and the liability of the financial loss due to personal injury and other damage which may arise as a result of the carrying out of this study are governed by the terms and conditions set forth in the Clinical Trial Agreement and applicable law.

5. Documentation of study findings

Required information will be entered into the appropriate CRFs. All CRFs are to be completed accurately and promptly, and should be updated as needed so they reflect the latest information on the patient’s file. All records are to be kept in conformance with applicable guidelines and SOPs. When the study is completed, the investigator must retain the essential documents for as long as needed to comply with regulatory authority, local regulations and sponsor requirements further detailed in Section 10.2.5. The investigator shall notify the sponsor prior to moving or destroying any of the study documents.

6. Study monitoring

- a. For Investigator-Initiated Research Studies, Investigators are responsible for ensuring proper monitoring of the investigation. The Investigator’s assigned clinical monitors are responsible for inspecting the CRFs throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of data; and adherence to GCPs. The monitors should have access to patient medical records and other study-related records needed to verify entries on the CRFs. In accordance to ICH Good Clinical Practice (ICH/GCP) guidelines, the Investigator’s assigned clinical monitors must have direct access to the

investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

- b. The monitor is responsible for routine review of the eCRFs at regular interval throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

The Sponsor may monitor Investigators' compliance and adherence to their contractual obligations related to disclosure of the Investigator's findings, agreed upon milestones, and safety information reporting.

7. Access to Information for Auditing or Inspections

Representatives of regulatory authorities, IRB, or of the Sponsor may conduct inspections or audits of this clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Sponsor immediately. The investigator agrees to provide to representatives of a regulatory agency, IRB or IEC, or Sponsor access to source documents/records, facilities, and personnel for the effective conduct of any inspection or audit.

8. Data quality assurance

Data will be entered into a secure and validated database using eCRFs. Data entered may be checked at the point of entry and through external validation checks for accuracy. After resolution of any discrepancies and automated data-review procedures, the final data sets will be subject to a quality assurance audit. When the database is declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made by written notice. The investigator will be responsible for ensuring the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRFs, which are derived from source documents, should be consistent with source documents or the discrepancies should be explained. To ensure the quality of the clinical data across all participants and sites, a clinical data management review will be performed on all patient data. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to protocol and GCPs. To resolve any questions arising from the clinical data-review process, data queries will be sent for the site to complete. The principal investigator will electronically sign and date the indicated places on the CRF. This signature will indicate that the principal investigator inspected or reviewed the data on the CRF and the data queries, and that the investigator agreed with the content.

9. Study Files and Retention of Records

- a. The investigator must maintain adequate and accurate records to fully document the conduct of the study and to ensure that study data is subsequently verified. These documents should be classified into two separate categories: (1) investigator's study file, and (2) patient clinical source documents. The investigator's study file will contain the protocol/amendments, printed (or electronically archived) copies of the patient CRFs, IRB, and governmental approval with correspondence, informed consent, drug accountability

(receipt/dispensing) records, staff curriculum vitae and authorization forms, information regarding monitoring activities, sponsor/investigator correspondence, and other appropriate documents and correspondence.

- b. Patient clinical source documents for this study would include, but are not limited to, the following:
 - i. Patient identification (name, date of birth, gender)
 - ii. Documentation that patient meets eligibility criteria, i.e., relevant medical history, physical examination, and confirmation of diagnosis
 - iii. Dated notes of the day of entry into the study including study number, patient identification number, verification that the trial was discussed and written informed consent was obtained
 - iv. Dated notes for each protocol assessment and documentation that protocol specific procedures were performed
 - v. Study drug accountability (investigator must keep blinded records of volume of study drug given and timing of each daily dose based on the hospital chart; this will not entail review of the unblinded pharmacy records for the sake of maintaining the blind)
 - vi. Documentation of all adverse events, including any action taken with regard to study drug and outcome
 - vii. Concomitant medications (including start and end date, dose if relevant)
 - viii. Date of trial completion and reason for early discontinuation, if applicable

10. Confidentiality

- a. The investigator must ensure that all participants' confidentiality will be strictly maintained and that their identities are protected from unauthorized parties. Only patient initials, date of birth, and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names and addresses for all patients screened and for all patients enrolled in the trial. On CRFs or other documents that are submitted to the sponsor, participants should be identified by an identification code and not by their names.
- b. The investigator agrees that all information received from the Sponsor, including but not limited to the Investigator Brochure, the investigational product, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11. Publication

- a. After the completion of the study and the analysis of all data, the Sponsor will support efforts by all Study Investigators to jointly publish the primary study results.

12. Protocol and Protocol Amendments

- a. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. No amendments

will be permitted to this protocol or to the conduct of the study without approval from the Sponsor and if applicable, the IRB. These communications will be documented in writing.

- b. All protocol amendments must be submitted to the IRB in accordance with local requirements. Approval must be obtained before changes are implemented.

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