Original Article

CSP01, a Novel Superabsorbent Hydrogel, Reduces Colonic Transit Time in Patients With Chronic Idiopathic Constipation in a Randomized, Double-blind, Controlled Pilot Clinical Trial

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Background/Aims

CSP01 is a novel superabsorbent hydrogel that absorbs gastrointestinal fluids and maintains high viscoelastic properties into the colon, where these fluids are released.

Methods

We conducted a single-center, randomized, double-blind, parallel-group, placebo-controlled pilot study comparing change in colonic transit time (CTT) among patients with chronic idiopathic constipation (CIC) and irritable bowel syndrome with constipation (IBS-C) treated for 21 days with either CSP01 hydrogel, active control (carboxymethylcellulose [CMC]) or placebo. CTT was measured using wireless motility capsule transit testing at pre-treatment and end-of-treatment. The primary endpoint was change in CTT.

Results

Forty subjects (20 CSP01, 11 CMC, 9 placebo) were enrolled and 38 completed the study. There was no significant change in mean CTT by treatment group ($P = 0.297$). In the placebo group, CTT increased by 15.3 minutes between baseline and end of treatment, increased by 366.4 minutes for CMC, and decreased by 727.4 minutes for CSP01. In *post hoc* analyses among those with CIC, mean CTT decreased by 1079 minutes for CSP01 ($P = 0.025$ compared to placebo), 919 minutes for CMC ($P = 0.117$ compared to placebo) and increased by 1113 minutes for placebo. Among patients with IBS-C, there was no significant difference in change in CTT for any treatment group. One subject in the CSP01 arm developed back pain attributed to constipation and withdrew without a second CTT measurement; there were no other adverse events.

Conclusion

CSP01 significantly decreased CTT compared to placebo among patients with CIC, but not in patients with IBS-C.
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Key Words

Capsules; Constipation; Gastrointestinal motility; Hydrogels; Irritable bowel syndrome

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Introduction

Chronic constipation is a highly-prevalent condition affecting approximately 14% of the population globally,[1] with substantial impact on quality of life.[2] Unlike other chronic diseases, treatment options for chronic constipation are frequently available without a prescription in the form of fiber supplements, laxatives, and herbal preparations.

Increased intake of dietary fiber or fiber supplements is often the initial recommendation for treatment of constipation, though high-quality evidence supporting its use is minimal. Previous trials using fiber supplementation in constipation have focused on a variety of subjective, symptom-based outcomes without evaluation of physiologic effects.[3] Some fibers have demonstrated specific effect in irritable bowel syndrome (IBS)[4] with others showing benefit in constipation.[5] A previous, short-term trial employing wheat dextrin demonstrated a reduction in colonic transit time (CTT) among healthy controls after 3 days of treatment.[6] Despite multiple over-the-counter options, there remains a need for more effective and well-tolerated therapeutic options.[7]

CSP01 (Gelesis Inc, Boston, MA, USA) is a novel superabsorbent hydrogel synthesized from a commonly used soluble fiber, carboxymethylcellulose (CMC), cross-linked with citric acid. The resultant 3-dimensional (3D) structure swells and absorbs 85 times its weight in water. As a result, CSP01 no longer has the properties of CMC: (1) its water-holding capacity is significantly higher, (2) its "solid-like gel" shape travels intact through the gut, and (3) it exerts more elastic response (firmness) than conventional fibers.[8] CSP01 capsules contain superabsorbent hydrogel particles that swell to form individual gel pieces that mix homogeneously with food in the stomach, and retain their 3D structure throughout the small intestine before degradation in the colon with release of absorbed fluids. We hypothesized that CSP01 may accelerate gastrointestinal (GI) transit because of its unique mechanical properties and thus aimed to determine the effect of CSP01 on CTT compared to an active control CMC (backbone of CSP01) and placebo in a double-blind, placebo-controlled randomized pilot study.

Materials and Methods

Study Design, Participants, and Medications

This study was a single-site, double-blind, placebo-controlled, parallel-group randomized study evaluating the pharmacodynamic effects of CSP01 (2.37 g), CMC (active control, 2.10 g), and placebo administered orally twice daily for 21 days among patients with chronic idiopathic constipation (CIC) and IBS with constipation (IBS-C) according to the Rome IV criteria.[9] Subjects were recruited from the gastroenterology clinic at Massachusetts General Hospital as well as from targeted, online advertisements in the local community. The study was approved by the institutional review board of Massachusetts General Hospital (IRB No. 2016P001751) and registered with ClinicalTrials.gov (NCT03054506). All patients signed informed consent. Patients were allowed to continue all medications except for laxatives or intestinal secretagogues. Exclusion criteria included colonic inertia (< 1 bowel movement/14 days), any structural or metabolic diseases/conditions that affect the GI system, or medication-induced constipation.

The study consisted of 3 periods: run-in, treatment, and post treatment follow-up (Fig. 1). After a screening visit in which patient eligibility was determined through use of Rome IV constipation

	Screening	Run-in period			Treatment period CSP01 or CMC or Placebo			
Time point (day)	−20 to −15	−14	−7	0	1	15	22	31
Efficacy								
Rome IV screen	◆			◆				
PAC-SYM	◆	◆		◆	◆	◆	◆	
PAC-QOL		◆		◆	◆	◆	◆	
Daily diary	◆————————————————————————————————————◆							
Safety	◆————————————————————————————————————◆							
WMC testing			◆			◆		
Adverse events					◆	◆	◆	◆

Figure 1. Study design. CMC, carboxymethylcellulose; WMC, wireless motility capsule; PAC-SYM, Patient Assessment of Constipation–Symptoms; PAC-QOL, Patient Assessment of Constipation–Quality of Life.

module along with other inclusion/exclusion criteria, eligible patients enrolled in a 14-day run-in period. Patients completed a daily stool diary (Day −14 to Day 0) to ensure they continued to meet criteria for CIC or IBS-C and underwent wireless motility capsule (WMC) testing (Day −7 to Day 0) to assess baseline CTT. If still meeting inclusion criteria, patients were randomized (simple randomization) to 1 of the 3 groups: CSP01 2.10 g, matching CMC 2.37 g (corresponding to the amount of CMC hydrogel precursor contained in the CSP01 dose), or matching placebo. Thus, the agents differed primarily on their rheological properties (inherent material properties that govern elastic response to an applied force) with a similar CMC backbone. The randomization code was generated by the Massachusetts General Hospital research pharmacy, with study medication distributed to study staff in a blinded fashion. All study personnel and patients were blinded throughout the study until database lock and data analyses. For the following 21 days of treatment, patients took 3 capsules of either placebo, CMC or CSP01 twice a day (before breakfast and dinner) with 2 glasses of water (16 oz) and completed a daily stool diary.

A second WMC test was done on Day 15 to Day 21 of the treatment period. The patient completed daily stool diaries and adverse event (AE) monitoring for an additional 7 ± 3 days (Day 22 to Day 31) after the last dose of treatment. Safety monitoring was conducted throughout the study.

Colonic Transit Testing and Analysis

The primary endpoint was the change in CTT from pre-treatment (Day −7 to Day 0) to last week of treatment (Day 15 to Day 21). We used the established WMC technique (SmartPill; Medtronic plc, Fridley, MN, USA), a reliable means of measuring CTT[10,11] previously used in a clinical trial to assess treatment with fiber.[6] CTT was defined as the time interval between the points of entry into the cecum and capsule exit from the body. CTT ≥ 59 hours is classified as slow-transit constipation.

Daily Stool Diaries

Each patient noted the exact time of each bowel movement during the run-in and treatment periods along with the following descriptions: stool consistency according to the Bristol stool form scale (ranging from 1, "hard lumps" to 7, "watery"),[12,13] ease of passage (ranging from 1, "manual disimpaction" to 7, "incontinence"), and answered whether or not they felt completely evacuated (yes/no). Additionally, patients completed daily ratings of global constipation severity, bloating severity, and abdominal discomfort severity, all assessed on a 0-10 scale (higher values indicate more severe

symptoms). Finally, patients completed the Patient Assessment of Constipation–Symptoms (PAC-SYM)[14] and the Patient Assessment of Constipation–Quality of Life (PAC-QOL)[15] at the beginning of the run-in period (Day −14) and on Days 0, 15, and 22 of the treatment period.

Statistical Methods

For the primary outcome, change in CTT from baseline to Day 21 of treatment, we employed a modified intention-to-treat analysis where all patients with pre- and post-treatment CTT data were included in the analysis. In cases where the primary outcome was unavailable but secondary outcome information was available, we performed an intention-to-treat analysis as planned prior to study initiation. In order to assess the effects of treatment (CSP01 vs CMC vs Placebo) on CTT, we employed a mixed between subject and within subject repeated measures analysis of covariance (ANCOVA). Between subject factors selected based on clinical relevance were treatment group, diagnosis (CIC or IBS-C), gender, and age, whereas the within subject factor crossed with each of the above was a 2-level time factor (7 days pre-treatment or Day 15 of treatment). In addition, the interactions of treatment with gender and with IBS were also tested (and each further crossed with time). A backward elimination algorithm was applied to the full saturated model. *Post hoc* analyses specifically examined CTTs among patients with CIC vs IBS. For the secondary outcomes, the analysis of the daily diary data, we first computed the mean scores per 2-week period (baseline and last 2 weeks of active treatment) in each subject. Between subject factors selected based on clinical relevance were treatment group, Rome IV diagnosis (CIC or IBS-C), gender, and age, whereas the within subject factor crossed with each of the above was a 2-level time factor (average scores over 2 weeks of pre-treatment or over the last 2 weeks of active treatment). Similar analyses were performed with the addition of baseline slow-transit constipation (baseline CTT ≥ 59 hours) to the between-subject factors in the group as a whole and with IBS status factored in. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Sample Size

Sample sizes planned for the study were based on mean and co-efficient of variation data from a prior study evaluating the effects of fiber on CTT using the WMC.[6] From this previous data, there was a 10-hour difference in CTT with a standard deviation of 12 hours, which we assumed would be similar to the effect of our active control CMC group. Assuming that CSP01 would give an additional

3-hour decrease in CTT over conventional fiber, we anticipated enrolling 15 subjects per arm where the calculated sample size would have 94% power to detect a significant difference at an alpha level of 0.05. More conservatively, with 10 subjects per arm, we would have 80% power to detect a significant difference between groups.
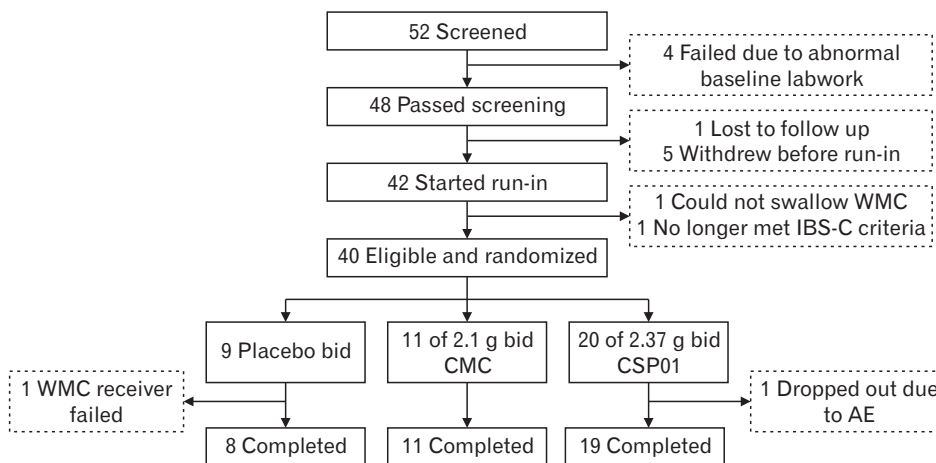

Figure 2. Study flow chart. WMC, wireless motility capsule; IBS-C, irritable bowel syndrome with constipation; bid, twice a day; CMC, carboxymethylcellulos; AE, adverse event.

Table 1. Demographic and Baseline Characteristics, Intention to Treat Population

Patient characteristics	Treatment assignment		
	Placebo (n = 9)	Carboxymethylcellulose (n = 11)	CSP01 (n = 20)
Age (yr)	51.9 ± 12.7	41.5 ± 17.7	44.9 ± 18.1
Sex			
Female	7 (77.8)	9 (81.8)	19 (95.0)
Male	2 (22.2)	2 (18.2)	1 (5.0)
Race			
White	8 (88.9)	8 (72.7)	16 (80.0)
Non-white	1 (11.1)	3 (27.3)	4 (20.0)
Body mass index (kg/m^2)	24.2 ± 4.6	25.4 ± 3.0	25.9 ± 4.8
Rome IV diagnosis			
CIC	4 (44.4)	9 (81.8)	14 (70.0)
IBS-C	5 (55.6)	2 (18.2)	6 (30.0)
Colonic transit time (min)	3088 ± 2083	3524 ± 2792	3288 ± 1838
Slow-transit constipation[a]	3.0 ± 33.3	5.0 ± 45.5	7.0 ± 35.0
Stool frequency per day	0.8 ± 0.4	0.7 ± 0.4	0.8 ± 0.3
Stool consistency per BM (BSFS 1-7)	2.6 ± 1.1	3.1 ± 1.1	3.0 ± 1.2
Ease of passage scale per BM (1-7)	3.9 ± 0.7	3.5 ± 0.5	3.6 ± 0.6
Number of CSBMs per day	0.2 ± 0.3	0.2 ± 0.2	0.2 ± 0.2
Daily constipation severity (1-10)[b]	4.2 ± 2.5	4.0 ± 1.3	4.1 ± 2.1
Daily abdominal discomfort severity (1-10)[b]	3.8 ± 2.2	3.6 ± 1.4	3.9 ± 1.8
Daily bloating severity (1-10)[b]	4.7 ± 2.5	4.4 ± 1.4	4.4 ± 2.2

[a]Slow-transit constipation defined as colonic transit time ≥ 59 hours at baseline.

[b]Higher values indicate increased severity of symptoms.

CIC, chronic idiopathic constipation; IBS-C, irritable bowel syndrome with constipation; BM, bowel movement; BSFS, Bristol Stool Form Scale; CSBM, complete spontaneous bowel movement.

P-values were calculated with the use of analysis of variance for continuous data and chi square tests for categorical data.

Data are presented as mean ± SD or n (%).

Results

Participants and Study Flow

Fifty-two patients were screened for the study, as shown in Figure 2 between March 7, 2017 and March 22, 2018. Four were ineligible because of baseline abnormal lab values (positive toxicology screen or abnormal liver function tests). Six were not randomized to treatment because of loss to follow up or subject withdrawal and a further 2 were not randomized (1 due to an inability to swallow the WMC and 1 subject not meeting Rome IV IBS-C criteria during the run-in period). Recruitment was stopped prematurely due to slower than expected enrollment. Because a simple randomization scheme was used rather than block randomization, there was an unequal allocation of patients to treatment arms by chance. Demographic and baseline data of all randomized patients are shown in Table 1. The CMC, CSP01, and placebo groups were all similar regarding baseline characteristics and CTT. Two randomized patients were not included in the primary endpoint analysis, 1 CSP01-treated (CIC group) patient dropped out because of an AE and the other (placebo-treated, IBS-C group) because the WMC recorder malfunctioned—providing no data on follow-up colonic transit. This left 38 total subjects, slightly below our anticipated recruitment level but above our threshold of 30 subjects to achieve 80% power to detect an effect. All patients received all doses of study medication, except for the patient who dropped out in the CSP01 group due to an AE, who completed 27 doses.

Effect of Carboxymethylcellulose and CSP01 on Colonic Transit

There was no significant change in mean CTT by treatment ($P = 0.297$) (Table 2). In the placebo group, CTT increased by
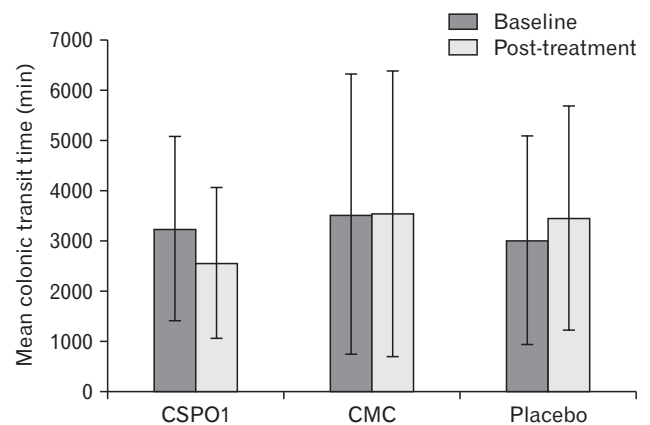

Figure 3. Baseline and post-treatment colonic transit times for all trial patients. CMC, carboxymethylcellulose.

Table 2. Change in Colonic Transit Time by Treatment Assignment and Diagnosis, Modified Intention-to-Treat Population

Diagnosis group	Treatment assignment			P-value
	Placebo	Carboxymethylcellulose	CSP01	
Overall (min)	(n = 8)	(n = 11)	(n = 19)	
Change in CTT	+367	+15	−727	0.297[a]
Baseline CTT	3088 ± 2083	3524 ± 2792	3288 ± 1838	
On treatment CTT	3455 ± 2227	3539 ± 2841	2560 ± 1505	
CIC (min)	(n = 4)	(n = 9)	(n = 13)	
Change in CTT	+1113	−97	−263	0.025 (CSP01 vs placebo)[b]
Baseline CTT	3193 ± 1728	3044 ± 2816	3334 ± 1963	0.117 (CMC vs placebo)[b]
On treatment CTT	4306 ± 2717	2611 ± 2146	2254 ± 1235	
IBS-C (min)	(n = 4)	(n = 2)	(n = 6)	
Change in CTT	−92	+2035	+35	0.712 (CSP01 vs placebo)[c]
Baseline CTT	2984 ± 2665	5684 ± 1757	3189 ± 1701	0.103 (CMC vs placebo)[c]
On treatment CTT	2604 ± 2125	7719 ± 1085	3224 ± 1929	

[a]P-value obtained from a mixed between subject and within subject repeated measures analysis of covariance (ANCOVA) including treatment group, diagnosis (chronic idiopathic constipation [CIC] or irritable bowel syndrome with constipation [IBS-C]), gender, and age. The within subject factor crossed with each of the above was a 2-level Time factor (7 days pre-treatment or Day 15 of treatment).

[b]Post hoc analysis using above ANCOVA model specifically among subsets of patients with CIC.

[c]Post hoc analysis using above ANCOVA model specifically among subsets of patients with IBS-C.

Data are presented as mean ± SD.

367 minutes between baseline and end of treatment, increased by 15 minutes for CMC, and decreased by 727.4 minutes (12 hours, 7 minutes) for CSP01 (Fig. 3). A *post hoc* analysis demonstrated of the overall ANCOVA analysis of CTT demonstrated a complex, 3-way interaction of treatment group (placebo, CMC, or CSP01), time (before vs after treatment), and Rome diagnosis (CIC vs IBS-C) at a significance level of $P = 0.058$, reflecting a tendency for CTT to decline after treatment with CMC and especially CSP01, but only among patients with CIC. Additional *post hoc* analyses suggested that overall treatment differences (for CMC and CSP01)

occurred for people with CIC, but not IBS-C ($P = 0.080$).

Among CIC patients (n = 26), the decline in CTT for treatment with CSP01 was significantly different from placebo ($P = 0.025$), and there was no significant difference between CMC and placebo (Fig. 4). Among patients with IBS-C (n = 12), the decline in CTT for treatment with CSP01 and CMC were not significantly different from placebo ($P = 0.712$ and $P = 0.103$, respectively)(Table 2).

Among patients with baseline slow-transit constipation, mean CTT increased by 553.3 minutes (9 hours, 13 minutes) in the placebo group, decreased by 733.0 minutes (12 hours, 13 minutes) in
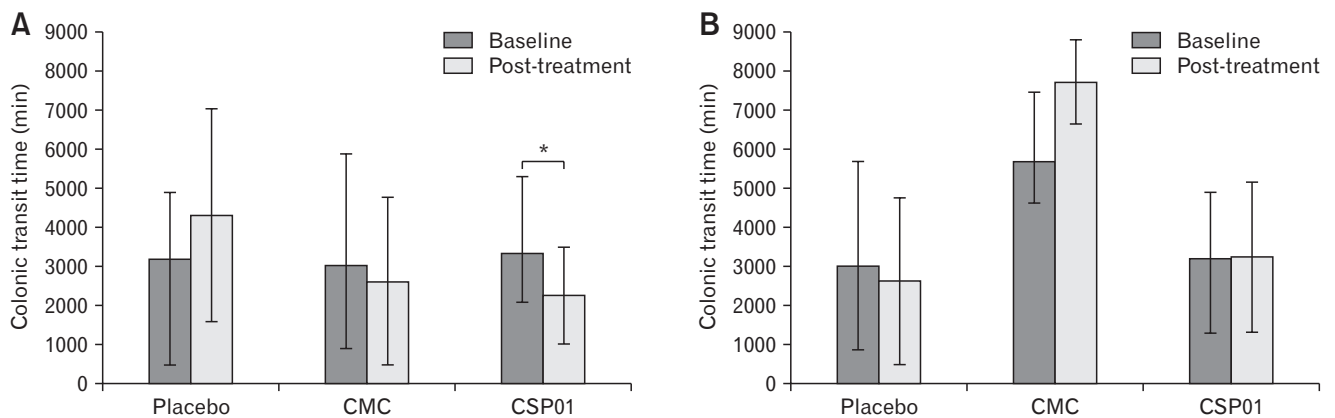

Figure 4. Baseline and post-treatment colonic transit times for patients with chronic idiopathic constipation (A) and irritable bowel syndrome with constipation (B). CMC, carboxymethylcellulose. *$P < 0.05$.

Table 3. Effects of Carboxymethylcellulose and CSP01 on Bowel Symptoms, Patients Completing Study

Variables	Placebo (n = 9)		Carboxymethylcellulose (n = 11)		CSP01 (n = 19)		P-value[a]
	Baseline	Post-Tx	Baseline	Post-Tx	Baseline	Post-Tx	
Stool frequency per day	0.8 ± 0.4	0.9 ± 0.6	0.7 ± 0.4	0.8 ± 0.4	0.8 ± 0.3	1.0 ± 0.4	0.641
Stool consistency per BM (BSFS 1-7)	2.6 ± 1.1	2.7 ± 1.4	3.1 ± 1.1	3.6 ± 1.6	3.0 ± 1.2	3.8 ± 0.9	0.509
Ease of passage scale per BM (1-7)	3.9 ± 0.7	3.9 ± 0.6	3.5 ± 0.5	3.6 ± 0.6	3.6 ± 0.6	3.8 ± 0.4	0.098
Number of CSBMs/day	0.2 ± 0.3	0.3 ± 0.3	0.2 ± 0.2	0.3 ± 0.2	0.2 ± 0.2	0.3 ± 0.3	0.896
Daily constipation severity (1-10)[b]	4.2 ± 2.5	3.9 ± 2.5	4.0 ± 1.3	3.3 ± 1.2	4.1 ± 2.1	3.5 ± 1.8	0.586
Daily abdominal discomfort severity (1-10)[b]	3.8 ± 2.2	3.6 ± 2.6	3.6 ± 1.4	3.1 ± 1.4	3.9 ± 1.8	3.7 ± 1.9	0.796
Daily bloating severity (1-10)[b]	4.7 ± 2.5	4.0 ± 2.8	4.4 ± 1.4	3.9 ± 1.2	4.4 ± 2.2	4.2 ± 2.2	0.443
PAC-SYM[b]	15.3 ± 7.1	13.0 ± 8.0	17.5 ± 4.6	10.5 ± 4.8	18.0 ± 8.2	12.2 ± 7.3	0.422
PAC-QOL[c]	30.9 ± 14.1	28.6 ± 16.1	31.4 ± 6.0	21.0 ± 4.1	39.7 ± 16.6	27.7 ± 18.4	0.161

[a]P-values were calculated for effect of treatment type × time (pre-treatment vs last week of treatment) with the use of analysis of covariance with adjustment for age and sex.
[b]Higher values indicate increased severity of symptoms.
[c]Higher values indicate lower quality of life.
Tx, treatment; BM, bowel movement; BSFS, Bristol Stool Form Scale; CSBMs, complete spontaneous bowel movements; PAC-SYM, Patient Assessment of Constipation–Symptoms; PAC-QOL, Patient Assessment of Constipation–Quality of Life.
One patient in the placebo-treated irritable bowel syndrome with constipation group did not have a second wireless motility capsule colonic transit time because of a technical malfunction but did complete the symptom diary and was included in this analysis.

the CMC group, and decreased by 1425.7 minutes (23 hours, 46 minutes) in the CSP01 group. When baseline slow-transit constipation was included in the model as an additional covariate, it was not found to be significantly associated with a decrease in CTT overall ($P = 0.540$) or when IBS status was included ($P = 0.120$) across the 3 treatment groups.

Effect of Carboxymethylcellulose and CSP01 on Bowel Symptoms

There were no significant effects of treatment with either CMC or CSP01 on any bowel symptoms or disease-specific symptom severity or quality of life for the 39 patients completing the diaries and questionnaires (Table 3). Notably, 1 patient in the placebo-treated, IBS-C group did not have a second CTT because of a technical malfunction but did complete the symptom diary and was included in this analysis. *Post hoc* analyses for symptoms stratified by CIC (Supplementary Table 1) and IBS-C (Supplementary Table 2) demonstrated numeric improvements in bowel movement frequency, constipation symptoms, symptom severity, and quality of life for CIC. However, there was no statistically significant difference in any of the indices.

Adverse Events

There were no serious AEs, but 1 patient in the CSP01 group had to stop treatment because of an AE, described as back pain attributed to worsening of her underlying constipation. There were no other recorded AEs.

Discussion

In this randomized, double-blind, placebo-controlled, 3-arm pilot trial of a novel superabsorbent hydrogel (CSP01) for patients with CIC and IBS-C, we found that CSP01 accelerates CTT in patients with CIC alone. Despite improvements in CTT among those with CIC, however, there were no significant improvements in stool consistency, frequency, complete spontaneous bowel movements or symptoms among patients in either group, nor any significant AEs.

Our results add additional support to the limited evidence examining the role of fiber-like compounds in the treatment of constipation. Although CSP01 has characteristics of both soluble and insoluble compounds, most traditional fibers fall predominantly into one of the two categories. Two previous trials of insoluble fiber in CIC were conflicting. One trial found increased stool frequency, softer stool consistency, and decreased difficulty in defecation among 15 patients consuming fiber-enriched rye bread,[16] while the other showed no difference in straining during defecation among 9 patients treated with bran.[17] In contrast, numerous trials of soluble fiber for CIC have demonstrated limited treatment benefit for constipation symptoms, but each trial suffered from significant methodological concerns.[3] Importantly, none of these trials measured colonic transit as an outcome.

Our results suggest that solubility is just one aspect in the efficacy of a fiber supplement, as our active control group (CMC) demonstrated no significant reduction in CTT compared to placebo. We hypothesized 2 potential reasons why CMC failed to show benefit while CSP01 (made of 90% CMC) treatment had a significant reduction in CTT compared to placebo. First, CMC lacks the 3D structure of the superabsorbent hydrogel, and therefore creates significantly lower elastic response (firmness). In an experiment simulating the in vitro gastric, small bowel, and colonic digestion of various fibers, a superabsorbent hydrogel prototype to CSP01 was found to have viscoelastic properties similar to masticated vegetables that were well in excess of those of soluble fibers such as guar gum and psyllium.[8] Thus, it is possible that the inherent resistance of CSP01 to deformation applies a mechanical force to the gut wall that stimulates the mechanosensitive cells and enterochromaffin cells of the gut myenteric plexus and mucosa, respectively—initiating and maintaining the basic circuit responsible for bolus propulsion in the GI tract and improving motility. Second, because of its 3D structure, CSP01 has greater water-holding capacity than fiber products like CMC.

The improvement in CTT compared to placebo seen with CSP01 only occurred in the subset of patients with CIC and was not seen with IBS-C. Although many experts view CIC and IBS-C as a spectrum of disease with the latter more associated with abdominal pain, the exact relationship between these 2 entities remains to be seen when using the newer Rome IV criteria utilized in the current study. Indeed, patients fulfilling the Rome IV criteria for IBS-C are thought to represent a more severe subset of Rome III IBS-C patients and therefore may suffer more visceral hypersensitivity than CIC patients.[18] On the whole, patients with CIC are more likely to have delayed colonic transit than those with IBS-C, but not definitively so.[19] However, there is some imaging evidence suggesting differences in response to laxatives in these 2 groups that may explain part of the differential response seen in our study.[20]

It should be noted that despite a significant decrease in CTT among patients with CIC treated with CSP01, there were no significant improvements noted in any specific bowel symptoms compared to placebo among those treated with CSP01. There are

several possible reasons for the discordance between physiologic improvement and symptom-based improvements: (1) among patients with functional GI disease, the placebo effect is significantly higher than for many other GI conditions such that it can be difficult to adequately power clinical trials to detect therapeutic gain,[21] and this trial was powered to detect differences in colonic transit rather than symptoms; (2) there is likely only a weak relationship between colonic transit and symptom report akin to what is seen with gastric emptying in functional dyspepsia[22] and retention of radiopaque markers in constipation;[23] and (3) we recruited subjects primarily from a tertiary referral population, likely selecting subjects with more severe disease and who may have been more refractory to fiber in comparison to a laxative. Nevertheless, lubiprostone, approved by the Food and Drug Administration for treatment of CIC, found an 11.7 hours reduction in CTT from baseline after 2 weeks of treatment using the same WMC methodology, consistent with the findings from the CSP01 group, and reported a significant correlation between increased bowel movement frequency and shorter CTT.[24]

We acknowledge several limitations. Our study was closed before randomization of 15 patients per arm as was required to attain > 90% power in our predetermined power calculations. Nevertheless, our recruited sample size of approximately 10 patients per arm achieved more than 80% power to detect a difference in colonic transit. Additionally, our positive findings occurred in a *post hoc* analysis of CTT according to CIC vs IBS-C, rather than an overall treatment effect for the group as a whole. Although our goal was a pure intention-to-treat analysis, we could not obtain on-treatment CTTs from 2 patients (1 from placebo and 1 from CSP01 group) enrolled in the study, somewhat limiting the robustness of our results. Because we did not track dietary habits of participants, we could not account for dietary fiber intake among trial participants, which could have affected our final results. Finally, we did not account for concomitant rectal evacuation disorders, which can occur in both CIC and IBS-C patients and are associated with prolonged CTTs.[25]

The current trial has several notable strengths. With a total of 40 subjects, this is one of the larger fiber trials in this population and one of the few trials to utilize an objective physiologic endpoint as a primary outcome. However, patients with IBS-C were underrepresented (n = 12). Additionally, we made use of an active control group (CMC) to give context to any positive findings seen with CSP01.

In summary, CSP01, a novel superabsorbent hydrogel, significantly decreases CTT among patients with CIC. The results of this study add a physiologic rationale to the use of superabsorbent hydrogels in patients with constipation, and CSP01 appears to be a promising agent in CIC. Further randomized trials of adequate power are warranted to determine whether CSP01 improves constipation symptoms and could become a treatment option for CIC.

Supplementary Materials

Note: To access the supplementary tables mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm20001.

Author contributions: Kyle Staller and Braden Kuo planned and designed the study; Abbey Bailey enrolled patients; Joseph J Locascio performed the statistical analysis; and Kyle Staller drafted the manuscript and had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis as a guarantor of article. All authors interpreted the results and contributed to critical review of the manuscript, and approved the final version of the article, including the authorship list.

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