Long-term safety and efficacy study of a medical device containing xyloglucan, pea protein reticulated with tannins and xylo-oligosaccharides, in patients with diarrhoea-predominant irritable bowel syndrome

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Abstract

Background: Irritable bowel syndrome with diarrhoea (IBS-D) is a frequent problem associated with a significant socioeconomic implication. Increased gut permeability is an important pathophysiological mechanism. A medical device containing xyloglucan (XG), pea protein and tannins (PPT) from grape-seed extract, and xylo-oligosaccharides (XOS) has proven restoration of intestinal barrier function. Our objective was to evaluate the efficacy and safety of treatment with the medical device XG + PPT + XOS (XG-PPT-XOS) in adult patients with IBS-D in a clinical setting for 6 months.

Material and methods: This was a multicentre, open-label, prospective, observational study conducted to evaluate long-term safety and efficacy of XG-PPT-XOS. IBS-D adult patients (Rome IV criteria) were included and received two tablets twice daily for 6 months. IBS Symptom Severity Score (IBS-SSS) and bowel habit were registered at baseline and monthly, until the end of follow up. Efficacy was evaluated by comparison of mean scores at each time point.

Results: 50 patients were included, of which 19 completed the 6 months. IBS-SSS score decreased from 312.2 ± 82.2 to 213.6 ± 109.9 ($p < 0.0001$) at 1 month and 192.0 ± 108.9 at the last visit completed; diarrhoea score decreased from 45.6 ± 17.9 to 25.7 ± 17.7 and 25.3 ± 17.2 at 1 month and at the last visit completed, respectively. Pain score decreased from 107.8 ± 49.9 at baseline to 73.2 ± 57.3 ($p < 0.0001$) at 1 month and bloating score from 56.4 ± 28.8 at baseline to 42.8 ± 32.6 ($p < 0.001$) at 1 month, reaching 62.4 ± 56.0 and 40.4 ± 34.3, respectively, at the last visit completed. Adverse effects were mild and mostly not related to treatment.

Conclusion: Treating IBS-D patients with XG-PPT-XOS is effective and safe in the long term within a clinical setting, improving all IBS-D symptoms from the first month of treatment and showing a sustained response over the term of therapy.

Keywords: diarrhoea, gut permeability, irritable bowel syndrome, mucoprotectants, xyloglucan, xylo-oligosaccharides

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Introduction

Irritable bowel syndrome with diarrhoea (IBS-D) is a frequent problem that affects a large percentage of the population.[1] It is also associated with substantial healthcare resource use and has a significant socioeconomic impact on society.[2] It is a frequent cause for medical consultation, but unfortunately, current options for treatment are

limited.[3] One of the underlying reasons for this is that there are multiple mechanisms that participate in its pathophysiology and not all of them are involved in all patients to the same extent.[4] The complex pathophysiology of IBS is based on the brain–gut–microbiome axis which involves the nervous system, the modulation of gut microbiota, the intestinal barrier function and the immune system.[5]

Current therapeutic alternatives for IBS-D are limited, including loperamide or a bile-acid sequestrant (effective for diarrhoea but not for pain), antispasmodics (effective for pain but with mild efficacy for diarrhoea), rifaximin (effective for bloating and partly for diarrhoea and pain) and tricyclic antidepressants (effective for both symptoms but with relevant side effects).[6]

Disruption of the epithelial barrier function with alterations in tight junctions has been demonstrated in IBS-D and post-infectious IBS, leading to an abnormally permeable epithelium.[7] Intestinal proteases may mediate the effects of microbial dysbiosis on the pathophysiology of IBS and favour intestinal barrier disruption by affecting epithelial tight junctions.[8]

In this context, there is increasing interest in strategies that can prevent or reverse the mucosal intestinal barrier disruption produced by various factors. The use of compounds with barrier-protective properties in IBS-D has previously been established.[9] Xyloglucan (XG), a natural polysaccharide derived from tamarind seeds, possesses a 'mucin like' molecular structure that confers muco-adhesive properties allowing it to act as a physical barrier protecting the integrity of mucosal cells against different damaging agents, such as micro-organisms, allergens, and pro-inflammatory compounds. This effect would reduce bacterial adherence and invasion, and also acts to preserve tight junctions and paracellular flux.[10] Additionally, the prebiotic mixture of vegetable xylo-oligosaccharides could play a role in the composition of microbiota.[9]

The compound containing XG, pea protein reticulated in tannins and xylo-oligosaccharides (XG-PPT-XOS) has shown its ability to normalize permeability in several animal models, in both *in vitro* and *in vivo* studies.[11] It is also effective in the treatment of acute diarrhoea in adults.[12] A randomized double-blind clinical trial in IBS-D patients treated with XG has shown there was a significant reduction of diarrhoea, increased pain relief and less bloating.[13] No adverse effects were observed, and due to its composition and mechanism of action, it has been considered safe by regulatory authorities.

We aimed to evaluate the efficacy and safety of 6 months' treatment with the medical device Gelsectan®, containing XG-PPT-XOS in adult patients with IBS-D, and prove sustained response in real clinical practice.

Material and methods
This was a multicentre, open-label, prospective, and observational study conducted from November 2017 to December 2018 (inclusion period) to evaluate the long-term safety and efficacy of XG-PPT-XOS (Gelsectan®).

Patients
Patients aged 18 and above with confirmed diagnosis of IBS-D, according to Rome IV, having symptoms at inclusion (IBS Severity Score, IBS-SSS >70) were enrolled. Patients were excluded if they had had any prior abdominal surgery (except hysterectomy or appendectomy), heart, lung, renal, hepatic, oncological and neurological diseases (in the researcher's opinion), allergy to any of the product ingredients or were unable to give informed consent.

Previous treatment in stable doses for IBS for at least 2 months prior to enrolment without complete response (persistence of symptoms) was not an exclusion criterion. Rescue medication was not allowed during the study.

Patients were treated with two tablets XG-PPT-XOS (Gelsectan®) twice daily (before breakfast and dinner) for 6 months. Assessments were conducted at screening and at 6 monthly visits. Baseline characteristics were recorded at inclusion and then at every monthly visit. The information recorded in every visit included the validated Spanish version of IBS-SSS,[14] self-assessment of symptomatic improvement using the Likert scale (much better, better, unchanged, worse, much worse) in comparison with the previous visit, and a medical interview by a gastroenterologist specifying the number of daily bowel movements (BMs) and consistency of stools using the Bristol Stool Form Scale (BSFS), the

percentage of BMs with urgency in the previous week and the occurrence of faecal incontinence episodes in the previous month. Adverse events were recorded at each visit. Relation with study product (non-related, possible or probable) and severity (mild, moderate or severe) of adverse events (AEs) were defined by the investigator.

Definitions, variables and outcomes. Clinical response was defined at each visit as a reduction of 50 points or more in IBS-SSS compared with baseline visit. Normal bowel habit was defined as three or less BMs daily and BSFS score less than 5 in the week before the visit. Subjective improvement was evaluated as follows: (a) initial subjective improvement, defined as the reporting of better or much better after the first month of treatment; and (b) sustained subjective improvement, defined as reporting of no change, better or much better in all subsequent visits, after an initial subjective improvement.

Individual symptoms were evaluated as follows: pain was defined as the sum of individual scores for IBS-SSS for frequency and severity of pain; bloating as the individual score of IBS-SSS; defecatory frequency as the reported number of daily BMs in the week before the visit; stool consistency as the reported mean BSFS in the week before the visit; and defaecatory urgency as the reported percentage of BMs with urgency in the week before the visit. Faecal incontinence was considered if any episode of incontinence occurred in the previous 4 weeks, regardless of its number, quantity, or quality (gas, liquid, solid faeces).

A composite score was constructed to evaluate the severity and impact of diarrhoea for this study, using a weighting system for symptoms that are usually considered in clinical practice. This was developed after using an informal questionnaire asking 10 patients and 5 experienced gastroenterologists to evaluate the weight of each symptom for defining the severity of diarrhoea in IBS. The severity of diarrhoea score was calculated by multiplying the mean number of BMs (with a maximum of seven) by the mean Bristol score; 10 points were added if urgency occurred in more than 25% of BMs; an additional 10 points were added if faecal incontinence occurred within the previous month and 5 points if incontinence had occurred previously but not during the last month. The score was normalized to a 0–100-point scale. The composite score did not undergo any formal validation, though it was considered supportive for the outcome.

Statistical analysis. An intention-to-treat analysis was performed. For patients withdrawing from the study or lost to follow up, Last Observation Carried Forward was used to account for the worst outcomes all along the monthly analysis.

Qualitative variables are described as frequency, and quantitative variables as mean plus standard deviation. Quantitative variables at each visit are compared with baseline value using the paired Student's *t* test.

Association of patients' baseline characteristics with clinical response and normal bowel habit at 1 month and at last visit completed was evaluated by logistic regression, considering potential predictive variables age, sex, baseline IBS-SSS and baseline diarrhoea score.

Statistical analysis was performed using SPSS 25 (SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Ethical aspects. The study was conducted according to the Helsinki declaration and all ethical boards of participants' centres approved the study. One centre only participated during the first month of the study. All patients were fully informed and signed the informed consent containing all relevant information about the study before their inclusion. The study was approved by the Hospital Clínico San Carlos Ethical Committee as a reference review board, confirmed by ethical committees of participating centres.

Results
Patient disposition, demographics, and baseline characteristics. A total of 50 patients were included. The mean age of the patients was 41.2 ± 15.4 years (range 19.7–73.2 years) and 68% of them were female. All patients had previously been diagnosed with IBS for a mean duration of 65.4 ± 59.4 months, and the global IBS-SSS at baseline was 312.2 ± 82.2 (range 110–470); three of them were considered as post-infectious IBS. Table 1 details the baseline characteristics of patients included.

From the initial 50 patients, 13 of them only provided consent for participating in the first month

Table 1. Patient demographics and characteristics at baseline.

	Mean ± SD (range)
Age	41.2 ± 15.4 (19.7–73.2)
BMI	25.5 ± 5.9 (17.0–44.9)
Time of evolution of IBS (months)	65.4 ± 59.4 (1–216)
IBS-SSS	312.2 ± 82.2 (110–470)
IBS-SSS: pain severity	54.8 ± 25.8 (10–100)
IBS-SSS: pain frequency	53.0 ± 33.0 (10–100)
Pain score (frequency + severity)	107.8 ± 49.9 (20–200)
IBS-SSS: bloating severity	56.4 ± 28.8 (0–100)
IBS-SSS: dissatisfaction with bowel habit	73.2 ± 25.2 (0–100)
IBS-SSS: interference with daily life	74.8 ± 19.9 (20–100)
Daily number of BMs	4.0 ± 1.6 (1–10)
Bristol score	5.9 ± 0.8 (4–7)
Defaecatory urgency (%)	59.6 ± 30.9 (0–100)
Severity of diarrhoea score	45.6 ± 17.9 (7.6–113.9)
History of faecal incontinence	22 (44%)
Faecal incontinence in the prior month	13 (26%)

BM, bowel movement; BMI, body mass index; IBS, irritable bowel syndrome; IBS-SSS, IBS Symptom Severity Score; SD, standard deviation.

of the study. Of the remaining 37 patients, 18 discontinued the treatment at some point during follow up. Reasons for discontinuation included AE ($n = 1$), withdrawal of consent ($n = 7$), protocol deviation ($n = 2$) and lack of efficacy ($n = 8$). Two patients withdrew their consent due to them becoming asymptomatic with treatment and not wanting to continue the study; four of the remaining five patients who withdrew their consent did not specify a reason, but at their last visit completed they reported subjective change to be 'better' on the Likert scale. Two patients began to take the product on demand, as they reported feeling better; nonetheless, they were considered as protocol deviation. Nineteen patients completed the 6-month treatment phase. Eight patients were taking drugs in stable doses (six were taking antispasmodics, one cholestyramine and one amitriptyline).

Main and global outcomes

Clinical response was achieved in 33 of the 50 patients (66%) after 1 month of treatment, and 35 (70%) at the last visit completed. IBS-SSS score decreased from 312.2 ± 82.2 to 213.6 ± 109.9 ($p < 0.0001$) at 1 month, and 192.0 ± 108.9 at the last visit completed; diarrhoea score decreased from 45.6 ± 17.9 to 25.7 ± 17.7 at 1 month and 25.3 ± 17.2 at the last visit completed (Table 2). Figure 1 shows the evolution of IBS-SSS and diarrhoea scores in each single patient; most patients showed a clear initial reduction in IBS-SSS and diarrhoea scores within the first month and maintained the same level in subsequent months. Only five patients showed no change or increase in IBS-SSS at 1 month and six patients at the last visit completed. Figure 2 shows the IBS-SSS score of the 50 patients throughout the study period.

At 1 month, 24 of the 33 patients (72.7%) who achieved clinical response reported normal bowel habit; in addition, 9 of the 17 (52.9%) patients who did not achieve clinical response reported normal bowel habit. At last visit completed, 27 of the 35 (77.1%) patients who achieved clinical response reported normal bowel habit; in addition, 5 of the 15 (33.3%) patients who did not achieve clinical response reported normal bowel habit. Therefore, 33 and 32 patients reported normal bowel habit at 1 month and at the last visit completed, respectively.

A total of 38 of 50 patients (76%) had an initial subjective response at 1 month. Among 25 patients with initial subjective response who completed at least 2 months of treatment, 15 (60%) had sustained subjective response.

Factors associated with clinical response. Age, sex, severity of IBS-SSS or severity of diarrhoea at baseline were not indicators of clinical response at 1 month or at the last visit completed (data not shown).
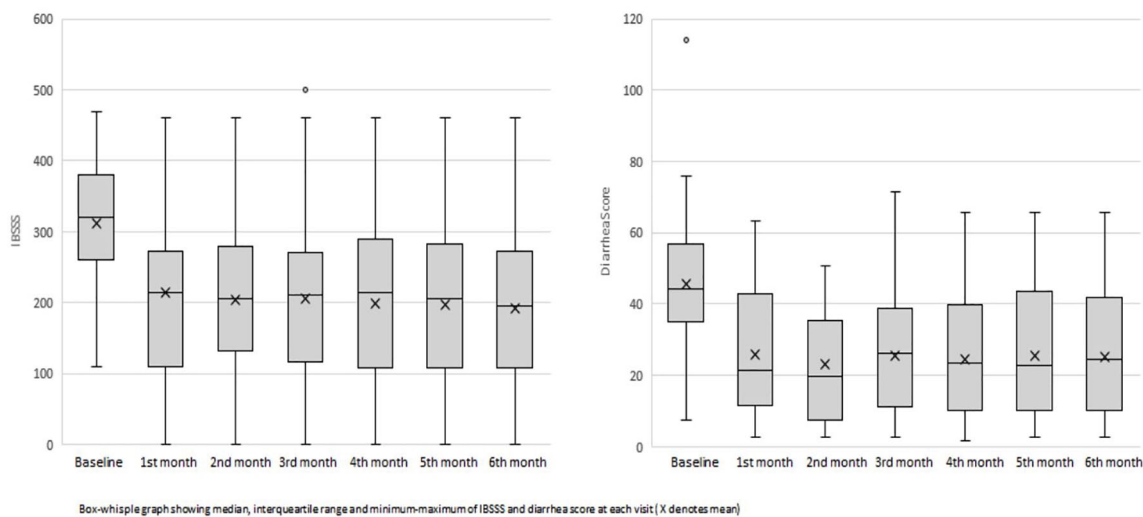
Symptoms and bowel habit

Individual symptom scores and self-reported bowel habit improved consistently during the treatment (Table 3). Pain and bloating scores decreased from 107.8 ± 49.9 and 56.4 ± 28.8 at baseline to 73.2 ± 57.3 ($p < 0.0001$) and 42.8 ± 32.6 ($p < 0.001$) at

Table 2. Changes in IBS-SSS score and diarrhea score along the study.

	IBS-SSS score	Mean difference with previous visit (95%CI)	Diarrhoea score	Mean difference with previous visit (95%CI)
	Mean ± SD		Mean ± SD	
Baseline	312.2 ± 82.2		45.6 ± 17.9	
1 month	213.6 ± 109.9	98.6 (71.8–125.4)**	25.7 ± 17.7	19.9 (14.1–25.7)**
2 months	204.2 ± 104.5	9.4 (–5.4 to 24.2)	23.0 ± 15.5	2.7 (–0.4 to 5.8)
3 months	205.2 ± 111.2	–1.0 (–16.8 to 14.8)	25.7 ± 17.1	–2.7 (–5.7 to 0.4)
4 months	199.6 ± 110.9	5.6 (–6.8 to 18.0)	24.6 ± 16.4	1.1 (–1.5 to 3.7)
5 months	197.4 ± 114.2	2.2 (–12.2 to 16.6)	25.4 ± 17.6	–0.8 (–3.4 to 1.9)
6 months	192.0 ± 108.9	5.4 (–4.6 to 15.4)	25.3 ± 17.2	0.1 (–2.0 to 2.2)

$**p < 0.0001$ (paired Student's *t* test).
95%CI, 95% confidence interval; IBS-SSS, Irritable Bowel Syndrome Symptom Severity Score; SD, standard deviation.

Box-whisple graph showing median, interqueartile range and minimum-maximum of IBSSS and diarrhea score at each visit (X denotes mean)

Figure 1. Change in IBS-SSS and diarrhoea score along the study.
IBS-SSS, Irritable Bowel Syndrome Symptom Severity Score.

1 month, respectively, reaching 62.4 ± 56.0 and 40.4 ± 34.3, respectively, at the last visit completed. Mean number of BMs decreased by 1.4 BM daily, and consistency of stools increased, showing a 1.4 decrease in BSFS at 1 month.

The change in pain, bloating, number of BMs, BSFS and urgency from baseline to subsequent visits is summarized in Figure 3.

Among 13 patients who reported faecal incontinence during the previous month at baseline, 6 did not report faecal incontinence after 1 month of treatment and at the last visit completed.

Safety
Among the patients included, 14 (28%) reported a total of 23 AEs (Table 4). Subjective constipation
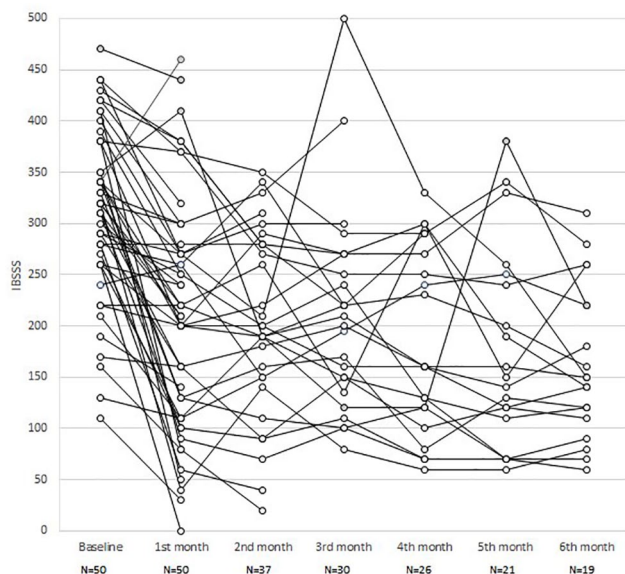
Figure 2. IBS-SSS score of the participating patients along the study period.
IBS-SSS, Irritable Bowel Syndrome Symptom Severity Score.

was reported at 1 month by three patients; this AE was considered related to the study treatment; two of these events were considered mild and the third as moderate. When changes in bowel habit associated with these events were analyzed, defaecatory frequency decreased from 4–6 BMs daily to 2–0.5 and BSFS from 6–6.5 to 4–6.

Other AEs reported are shown in Table 4. All of them were categorized as mild and considered not related to the study treatment, except one patient reporting nausea, which was considered by the investigator as possibly related. No serious AEs or deaths occurred.

Discussion

Our study provides the expected results of XG-PPT-XOS with a protocol mirroring real-life practice, showing its efficacy and safety in patients with moderate-to-severe IBS-D from the first month of treatment, which are sustained during the observed period of treatment for up to 6 months. Around 70% of recruited patients obtain significant benefit, as shown by the improvement in global outcomes (reduction of IBS-SSS by 50 points or more, reduction in diarrhoea score, normalization of bowel habit). Moreover, all individual symptoms, including pain and bloating, evolved satisfactorily under

treatment with XG-PPT-XOS. Also, the treatment was safe with a small number of AEs, most of them mild.

IBS is a highly prevalent gastrointestinal disorder with remarkable health, social and economic consequences.[3,15] Therefore, effective, safe treatment for this disorder is needed.

Promising treatments include mucoprotectants, such as XG and gelatin tannate, whose mechanism of action is the formation of a protective layer over the intestinal mucosa; mucoprotectants can help by restoring normal function to a deficient intestinal barrier, and consequently normalize mucosal permeability.[11] Previous studies suggest that mucoprotectants are safe and effective in the treatment of both adults and children with acute diarrhoea.[12,16,17] Alexea *et al*.[9] compared the clinical response and safety for a combination of oligo- and polysaccharides and reticulated protein (a precursor of the product evaluated in this study) *versus* placebo (four oral tablets/day for 56 days) in 128 patients with IBS-D. They found a significant improvement in symptoms and quality of life in the patients treated with oligo- and polysaccharides and reticulated protein compared with those that received placebo, and showed that 70% of patients normalized bowel habit, with a 30% benefit over placebo.

Trifan *et al*.[13] reported that 28 days of treatment with XG-PPT-XOS in patients with IBS-D was superior to placebo, improving diarrhoea, but also subjective assessments of abdominal pain, bloating, quality of life and general health. Our findings are in accordance with this good response from the first month of treatment. However, IBS is a chronic disorder that is characterized by the presence of recurrent gastrointestinal symptoms whose duration varies among patients.[18] Therefore, a significant proportion of IBS-D patients may have symptomatic episodes for years that possibly need long-term treatment. Our study demonstrated the sustained response of XG-PPT-XOS treatment in clinical practice in all IBS-D symptoms. All individual symptoms improved at first month of treatment and thereafter. A very consistent effect on both defaecatory frequency and stool consistency was observed; moreover, patients showed a remarkable decrease in defaecatory urgency (from around 60% of BMs to close to 25%), a symptom especially disturbing for IBS-D patients. Although

Table 3. Changes in individual symptoms and bowel habit.

	Pain score Mean ± SD	Mean difference with previous visit (95%CI)	Bloating score Mean ± SD	Mean difference with previous visit (95%CI)	Number of daily BMs Mean ± SD	Mean difference with previous visit (95%CI)	BSFS score Mean ± SD	Mean difference with previous visit (95%CI)	Defaecatory urgency (%) Mean ± SD	Mean difference with previous visit (95%CI)
Baseline	107.8 ± 49.9		56.4 ± 28.8		4.0 ± 1.6		5.9 ± 0.8		59.6 ± 30.9	
1 month	73.2 ± 57.3	34.6 (19.6–49.6)**	42.8 ± 32.6	13.6 (5.8–21.4)*	2.6 ± 1.4	1.4 (0.9–1.9)**	4.4 ± 0.9	1.4 (1.1–1.8)**	34.3 ± 31.7	25.3 (15.0–35.5)**
2 months	69.6 ± 54.1	3.6 (–4.5–11.7)	42.4 ± 33.1	0.4 (–4.0 to 4.8)	2.4 ± 1.3	0.1 (–0.1 to 0.3)	4.2 ± 1.0	0.2 (0.0–0.4)	26.0 ± 26.0	8.3 (0.8–15.8)
3 months	69.8 ± 57.3	–0.2 (–9.6–9.2)	44.4 ± 35.1	–2.0 (–5.9 to 1.9)	2.5 ± 1.4	–0.1 (–0.2 to 0.1)	4.5 ± 1.1	–0.3 (–0.5 to 0.0)	35.2 ± 32.1	–9.2 (–15.8 to –2.6)
4 months	71.4 ± 55.0	–1.6 (–7.6–4.4)	42.2 ± 34.8	2.2 (–0.3 to 4.7)	2.4 ± 1.4	0.1 (0.0–0.2)	4.5 ± 1.0	0.0 (–0.2 to 0.2)	31.7 ± 28.9	3.5 (–1.3 to 8.3)
5 months	66.2 ± 56.2	5.2 (–2.7–13.1)	43.6 ± 33.5	–1.4 (–6.0 to 3.2)	2.5 ± 1.4	–0.1 (–0.3 to 0.1)	4.5 ± 1.1	0.0 (–0.2 to 0.2)	32.9 ± 32.3	–1.2 (–5.3 to 2.9)
6 months	62.4 ± 56.0	3.8 (–3.0–10.6)	40.4 ± 34.3	3.2 (–1.6 to 8.0)	2.5 ± 1.4	0.0 (–0.2 to 0.2)	4.5 ± 1.0	0.0 (–0.1 to 0.2)	34.3 ± 33.1	–1.4 (–6.0 to 3.2)

*$p < 0.001$.
**$p < 0.0001$.
Paired Student's t test.
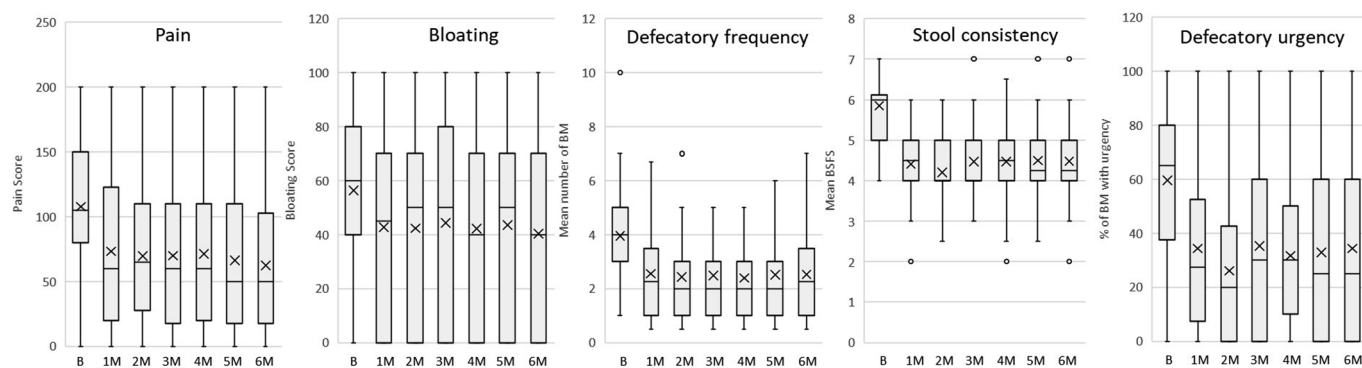95%CI, 95% confidence interval; BM, bowel movement; BSFS, Bristol Stool Form Scale; SD, standard deviation.

Figure 3. Change in pain, bloating, number of BMs, BSFS and urgency.
BM, bowel movement; BSFS, Bristol Stool Form Scale.

Table 4. Summary of AEs occurring during the study period.

System	AE (*n*)	Severity	Relation to study product
Digestive	Constipation (3)	Mild (2)	Probably related (3)
		Moderate (1)	
	Nausea (2)	Mild	Possibly related (1)
			Not related (1)
	Epigastric pain (2)	Mild	Not related
	Acute infectious diarrhoea (2)	Mild	Not related
	Dyspepsia (1)	Mild	Not related
ENT	Allergic rhinitis (1)	Mild	Not related
	Tonsillitis (1)	Mild	Not related
	Aphthous stomatitis (1)	Mild	Not related
	Oral ambulatory surgery (1)	Mild	Not related
	Otitis (1)	Mild	Not related
	Otalgia (1)	Mild	Not related
	Flu-like syndrome (1)	Mild	Not related
Others	Headache (2)	Mild	Not related
	Vulvar itching (1)	Mild	Not related
	Vaginal candidiasis (1)	Mild	Not related
	Back pain (1)	Mild	Not related

AE, adverse event; ENT, ear, nose and throat.

not specifically targeted in the design, faecal incontinence was also controlled in a significant proportion of patients. It is noteworthy there was good response not only for diarrhoea but also for pain and bloating. Bloating is a frequent symptom reported by around 16–31% of the general population and is a common complaint in individuals with functional gastrointestinal disorders.[19] Interestingly, this beneficial effect on functional bloating has also been detected in a previous study of XG-containing medical devices in accordance with our results.[19]

Safety is an important aspect to consider, as IBS patients usually requires long-term treatments. In our study, AEs within the study period were reported by 28% of the patients, similar to another real-life study performed in a clinical setting.[20] Most AEs were mild and not related to the treatment, in accordance with other clinical studies with mucoprotectants.[9,13] Constipation was the only relevant AE reported by three patients at 1 month; however, it seems to represent a perception of constipation, since the number of daily BMs and BSFS did not correspond to what would be expected in true constipation. In our view, rather than an AE, it reinforces the efficacy of the product in improving the bowel habit, which may lead some patients accustomed to a diarrhoeal habit to consider the improvement as inconvenient; whether these patients could benefit from dose reduction was not evaluated but could be a successful strategy.

The main limitation of our study was the sample size and number of withdrawals during the study period. Recruiting IBS patients in a long-term study with monthly visits with an already marketed product sold over the counter is a challenge for inclusion, as many patients prefer prescriptions out of a study protocol. Also, it is challenging obliging them to attend planned visits, as those not obtaining any benefit tend to withdraw, while those obtaining benefit tend to obtain the product directly from the pharmacist, avoiding regular displacements to the office for visits; in fact, that seemed to be the case in eight of the patients included. In this respect, we observed a similar rate of drop out in a study with IBS-CONSTIPATION patients on linaclotide for 12 weeks, trying to reproduce as much as possible a real clinical practice situation.[20] The third limitation of our study was its uncontrolled, open-label and non-randomized design, so we cannot exclude that some patients' improvement was due to improvement in the natural course of the disease or a placebo effect. Nevertheless, our results are consistent with the findings of previous randomized clinical trials that have evaluated XG-PPT-XOS, and demonstrated that the efficacy and safety of XG-PPT-XOS goes beyond 28 days of treatment. Therefore, assessment of efficacy focused on what we would normally see in a real clinical practice, as the benefit over placebo had been previously shown.

In summary, treating IBS-D patients with XG-PPT-XOS is effective and safe in a clinical setting in the long term. This treatment significantly reduced diarrhoea, pain and bloating sensation from the first month of treatment and response was sustained in long-term therapy.

Conflict of interest statement
The authors declare that there is no conflict of interest.

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