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Open label study to assess the safety and efficacy of IQP-PO-101 in regulating bowel movement frequency

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ABSTRACT

This study was conducted to assess the efficacy and safety of IQP-PO-101 (also known as Chiasyll™) in regulating bowel movement and relief of other constipation symptoms. Frequency of bowel movements was evaluated in 50 adults, aged between 18 and 65 years old, who were constipated and had 2 to 4 bowel movements per week. The open-label study had a 2-week run-in period, 4-week intervention period, and a 2-week post-treatment period. In addition to weekly measurement of bowel movement frequency, subjects had to self-assess and record the consistency of their stools, evaluate straining, pain, and evacuation completeness using a Visual Analogue Scale (VAS) in the subject diaries. When constipation was assessed by frequency of bowel movement, laxation was restored from a mean of 3.56 (SD 1.23) times at Week 0 to 6.14 (SD 2.34) times at Week 4 during the treatment period ($p < 0.001$). At Week 6 during the post-treatment period, subjects experienced bowel movements 4.78 (SD 2.01) times ($p < 0.001$). At the end of the treatment period, IQP-PO-101 was also shown to reduce the proportion of constipated stools (Type 1 and Type 2 on Bristol Stool Chart) by two-fold, indicating improvement of the hard and lumpy stool texture ($p < 0.001$). Subjects also experienced an increase in frequency of feeling of complete evacuation during bowel movements, from 33.0% at Week 0 to 64.2% at Week 4. Pain during defecation was also reduced at the end of the treatment period. The absence of a comparator arm is a relevant limit of the study. Overall, the administration of IQP-PO-101 resulted in significant improvement in subjects' bowel regularity with minimal gastrointestinal side effects.

Keywords: Bowel movement, constipation, psyllium husk, chia seed.

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INTRODUCTION

Constipation is one of the most common gastrointestinal complaints, recording a prevalence rate of 17.1% of Europeans and 14.7% of the general population in the United States (Higgins and Johanson, 2004; Peppas et al., 2008). Consequently, in the United States alone, there are 2.5 million physician visits that occur every year (Sonnenberg and Koch, 1989). The most prevalent complaint of constipation is the formation of hard stools; other common associated symptoms include straining, bloating and a sense of incomplete evacuation of the bowel (Bharucha et al., 2006; Longstreth et al., 2006).

A normal bowel movement differs widely between individuals, varying from three times a day to three times a week; depending on the lifestyle adopted by the individuals. Constipation occurs when irregular bowel movement causes a reduction in the frequency of bowel movements to below three times a week, and/or difficulty in passing stools (Longstreth et al., 2006). Common causes of constipation are lack of dietary fibre intake, lack of physical activity, side effects of medications, and also irritable bowel syndrome (Bharucha, 2007; Kamm, 2003). One major aim in the treatment of idiopathic constipation is to provide a significant stool softening through swelling and bulking effects in the gastrointestinal tract. Current guidelines from national and international gastroenterology organisations advocate the use of fibres as first-line therapy for constipation (Locke et al., 2000).

The intake of fibre is known to prevent bowel movement irregularity, difficulties in defecation and slow

colonic transit. Generally, the two types of fibre; soluble fibre and insoluble fibre complement each other in their mechanism of action for regular bowel movement. While soluble fibre increases the absorption of water and forms a gel that softens the stool, insoluble fibre assists by adding bulk to stools and increasing acceleration of food passage, thereby promoting regularity (Bosaeus, 2004).

According to systematic reviews, among available OTC laxatives or fibres supplements, psyllium offers the strongest supporting evidence in treatment of constipation (Brandt et al., 2005; Ramkumar and Rao, 2005; Singh, 2007). Psyllium husk is known to increase the water contents in stool, thereby softening it and leading to an increase of bowel movements (McRorie et al., 1998). Use of psyllium was also reported to be beneficiary in idiopathic constipation, where stool frequency and stool weight were increased and stool consistency and pain on defecation were improved (Ashraf et al., 1995; Davies et al., 1998).

IQP-PO-101 is a proprietary combination of psyllium (*Plantago psyllium* L.) husk and chia (*Salvia hispanica* L.) seed. Psyllium husk is rich in soluble fibre (Davidson et al., 1996; Gelissen et al., 1994; Natural Standard Monograph, 2011), when combined with chia seed which is rich in insoluble fibre (Alfredo et al., 2009). IQP-PO-101 provides a fibre matrix with excellent water-holding capacity. In water, the fibre matrix of IQP-PO-101 is able to swell more than 40 times (ml/g) into a gelatinous mass. Its swelling capacity has been shown to be superior compared to psyllium alone (Council of Europe, 2014; InQpharm internal data). Hence, it was hypothesized that the daily consumption of IQP-PO-101 over the course of 4 weeks would improve bowel function in constipated adults.

MATERIALS AND METHODS

Subjects

Subjects for this open-label study were to meet the inclusion criteria: 1) age 18 to 65 years, 2) having 2 to 4 bowel movements per week (self-reported at least two of the following symptoms over the preceding 3 months: excessive straining, lumpy or hard stool, sensation of anorectal obstruction, a sense of incomplete evacuation of bowel movements, and a need for digital manipulation to facilitate evacuation), 3) recorded between 4 to 9 defecations in the bowel movement diary during the 14-day run-in period, 4) completed a minimum of 14 consecutive days stool diary during run-in period, 5) use of appropriate contraceptive methods during the study period for subjects of childbearing potential, 6) commitment to avoid the use of laxatives and/or other medicinal products/supplements that may affect bowel movement, and 7) commitment to refrain from making any major life-style changes (new diet or change of exercise pattern) during the run-in and treatment period.

The exclusion criteria were: 1) known hypersensitivity to the ingredients of the investigational product, 2) history of or concurrent gastrointestinal diseases, 3) use of other laxative/products to ease bowel movements within seven days prior to the screening visit, 4) drug-induced constipation, 5) constipation other than idiopathic constipation, that is, presence of secondary causes of constipation including endocrine disorders, metabolic disorders and neurologic disorders, 6) history of previous abdominal surgery, 7) clinically relevant abnormalities in colonoscopy within the last 2 years prior to the run-in period, 8) known illnesses or conditions such as severe cardiovascular or lung disease, neurologic or psychiatric disorders (including active alcohol or drug abuse), cancer, AIDS, or other gastrointestinal or endocrine disorders, 9) pregnancy or nursing, 10) excursions of safety parameters.

All subjects provided written informed consent before any study-related procedures were carried out.

Study intervention

This clinical trial was performed according to EN ISO 14155:2011, the principles of the World Medical Association (Declaration of Helsinki), as well as the EU recommendations for Good Clinical Practice (CPMP/ICH/135/95), ICH E6 (R1) and ICH E3. Safety reporting also complied with the German national GCP-V (2004, revised 2006). The study was approved by the ethics committee of the Charité Universitätsmedizin before initiation.

This open label clinical trial investigating the efficacy and safety of IQP-PO-101 was conducted from March 2013 to August 2013 in Berlin, Germany. The study included a 2-week run-in period, a 4-week intervention period, and a 2-week post-treatment period. During the 2-week run-in period, subjects were requested to complete a stool diary, which records the number of bowel movements, stool consistency and subjective measures of efficacy like straining at the beginning and end of defecation, feeling of pain during defecation, and frequency of the feeling of complete evacuation. Data collected was used as baseline values for data analyses. There was no investigation product administered during this period.

Subjects that fulfilled the inclusion and exclusion criteria entered the 4-week treatment period, with the instruction to start the intake of the investigational product, 1QP-PO-101, on the day after the clinic visit (Day 1). The 4-weeks treatment period was followed by a 2-week post-treatment (treatment-free) period, where subjects continued keeping records in the stool diary. At the end of the 2-week post-treatment period, subjects returned to the clinic for a final visit.

IQP-PO-101 (supplied in powder sachet by manufacturer, InQpharm) was taken with the following dosages: 1) Week 1 (Day 1 to Day 7) – One sachet twice a day (higher initial dosage to quickly relieve constipation) mixed in 250 ml of water; 2) Week 2 to 4 (Day 8 to Day 28) – One sachet once a day (maintenance dosage), mixed in 250 ml of water. Each sachet of IQP-PO-101 contains 4 g of psyllium husk and 0.5 g of chia seed as the active ingredients. There was no comparator arm in this study.

Efficacy parameters

All efficacy endpoints related to bowel movement were assessed by the subjects using the daily stool diary.

The primary efficacy parameter was the difference in the number of bowel movements per week, from baseline (first 2 weeks without treatment) to Week 4.

Secondary efficacy parameters included objective measures like bowel movement frequency, the time from first dose of investigational product to first defecation and subjective measures like patient ratings using Bristol Stool Form Scale (7-point scales) of stool consistency, straining and pain during bowel movement, and feeling of incomplete evacuation. Subjective measurements were performed using VAS scales provided in the diaries. Global evaluation of efficacy was assessed by the investigators and the subjects at the end of the treatment phase.

Safety parameters

Vital signs and physical examination results were recorded at every visit. Venous blood samples were obtained at the screening visit and at the final visit of the study. Full blood count (including hemoglobin, hematocrit, erythrocytes, thrombocytes and leucocytes), and clinical chemistry were analyzed in a central laboratory. Clinical chemistry parameters included the protein metabolism parameter uric acid, the lipid metabolism parameters total cholesterol, HDL- and LDL-cholesterol and triglycerides as well as the carbohydrate metabolism parameter HbA1c. Additionally, global evaluation of safety by the investigator and the subjects were assessed at the end of the treatment phase and adverse events (AEs) were requested and recorded at every visit.

Statistical analysis

The null hypothesis assumed no difference in weekly bowel movements from Week 0 to Week 4, and was tested at the significance level of 2.5% (one-tailed) using non-parametric Wilcoxon test for dependent groups.

The sample size was estimated based on Davies et al. (1998), considering the similarities in study design and treatment duration. A total of 50 subjects were expected to be adequate for this study.

Demographic and baseline characteristics of the efficacy and safety variables were first assessed based on a descriptive analysis. For metric data (continuous data), statistical characteristics were given (number, mean, standard deviation, median, extremes, quartiles). For ordinal data (discrete data), the frequency distribution was performed. All nominal data (categorical data) were summarized using frequency tables.

The testing of secondary endpoints was performed with non-parametric procedures: Mann-Whitney U test for independent (Sub-) groups, Wilcoxon test for dependent group analysis (pre-post), and Chi^2-test for comparison of rates. In cases of small sample sizes, exact tests were used. All tests were performed with a significance level (type I error) of 5.0% (two-tailed test) or of 2.5% for the one-tailed test. All values are presented as mean and standard deviation (SD) unless otherwise indicated. All data were analyzed using the SPSS Statistic software, version 19.0 (SPSS, Chicago, IL).

RESULTS

Demographics

All 50 subjects screened and enrolled completed the study. Of the 50 subjects, all were Caucasian and there were 12 males (24.0%) and 38 females (76.0%). The youngest included patient was 23 years, the oldest 65 years. Their baseline characteristics are listed in Table 1.

Efficacy endpoints

Weekly bowel movements

All 50 subjects presented symptoms of constipation, with reported defecations of between 4 and 9 episodes during the 2-week run-in period.

The mean bowel movements during Week 0 were 3.56 (SD 1.23) times. Following treatment with IQP-PO-101, subjects reported an increase of mean bowel movements to 6.14 (SD 2.34) times during Week 4 (Figure 1), the increase of 2.58 bowel movements/week (SD 2.41) is statistically significant ($p < 0.001$). Across the 4-week treatment period, bowel movements have been maintained at above 6 times weekly. Overall, 39 out of 50 subjects (78%; CI: 64.0 to 88.5%) had an increase in weekly bowel movements. Additionally, 29 subjects out of 50 subjects (58.0%) achieved at least 6 bowel movements per week at Week 4, representing a normalization of bowel movements.

The number of weekly bowel movements for the post-treatment period during Week 5 (5.06 times, SD 2.29) and Week 6 (4.78 times, SD 2.01) were still elevated with statistically significant increase compared with Week 0 (3.56 times, SD 1.23) despite a slight decline ($p < 0.001$ for both Weeks 5 and 6) (Figure 1).

Stool consistency

Subjects were asked to self-assess the stool consistency as described in the Bristol Stool Form Scale. The types of stool pattern were documented for all 2052 bowel movements during the 8 weeks of the study (2052 of 2052; 100%).

IQP-PO-101 was shown to produce softer stools during the treatment period. The proportion of Type 1 and Type 2 stool (indicating constipation) decreased from 70% at Week 0 (baseline) to below 35% at Week 4. The difference in the proportion of Type 1 and Type 2 stool between Week 0 and Weeks 1 to 6 was statistically significant (all $p < 0.001$) (Table 2). The mean stool consistency score was higher at Week 4 compared to baseline (3.43, SD 1.56 vs 2.21, SD 1.43). During the post-treatment period at Week 6, subjects produced slightly harder stools (mean score 2.78, SD 1.58).

Straining and feeling of pain

Both straining at the beginning and end of defecation were improved during the treatment. By Week 4, 44 subjects (88.0%; CI: 75.6 to 95.5%) reported that they had experienced less straining at the beginning of defecation relative to Week 0. The same number of subjects also experienced less straining at the end of defecation in the same period. Straining at the beginning and ending of defecation during the treatment period, yielded a mean VAS score of 37.0 and 32.5 respectively, compared to 64.3 and 55.3 at baseline (both $p < 0.001$) (Figure 2).

Similarly, there was an improvement on feeling of pain during defecation. 41 subjects (82.0%; CI: 68.5 to 91.5%) reported that they felt less pain during defecation after the 4-week treatment, compared to Week 0. The mean VAS score for pain decreased to 21.9 (SD 20.3) at Week 4 from 43.7 (SD 24.6) at baseline. The mean pain VAS scores were significantly lower relative to baseline (all p <

Table 1. Subjects baseline characteristics (n = 50).

Parameter	Mean	SD	Min	Max
Age (year)	46.3	13.2	23	65
Height (cm)	169.0	7.1	156	186
Weight (kg)	69.3	13.4	50.0	129.0
BMI (kg/m^2)	24.3	4.7	18.2	43.6

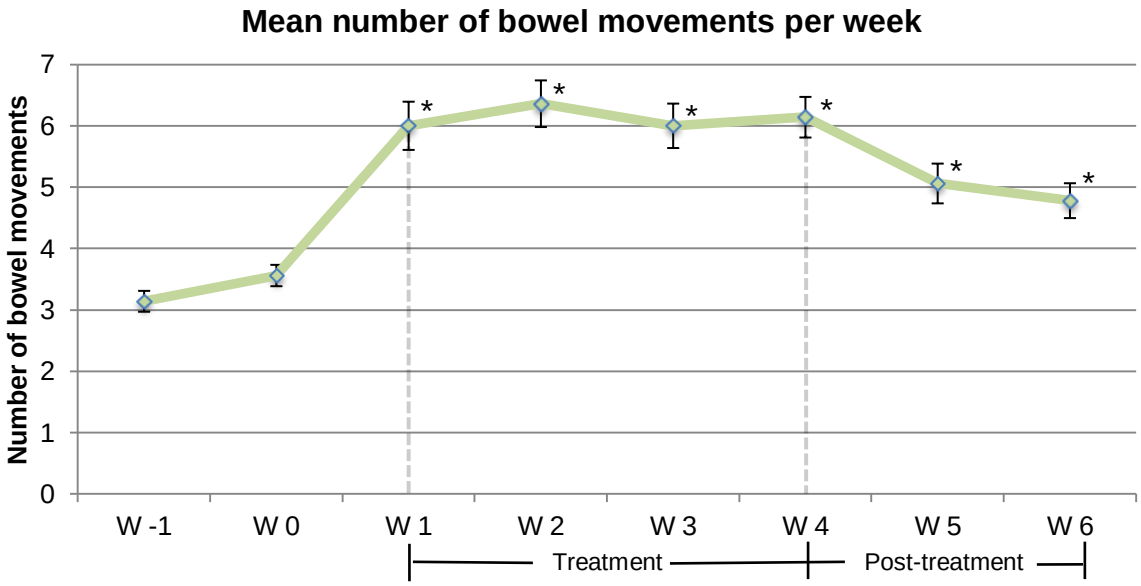

Figure 1. Mean number of bowel movements per week for each subject. * = p < 0.001 compared to Week 0 (W 0) (non-parametric Wilcoxon test).

Table 2. Stool consistency (according to Bristol stool form scale)[a].

Stool pattern	Total number of stool	Type 1 & Type 2		Type 3 & Type 4	
		Number	%	Number	%
Week -1	157	118	75.2	25	15.9
Week 0	178	125	70.2	39	21.9
Week 1	300	112	37.3*	122	40.7*
Week 2	318	108	34.0*	114	35.8*
Week 3	300	93	31.0*	115	38.3*
Week 4	307	107	34.9*	124	40.4*
Week 5	253	105	41.5*	100	39.5*
Week 6	239	122	51.0*	76	31.8**

[a] Type 5, Type 6 and Type 7 were not plotted in Table 2, as the percentage was relatively lower than the percentage of Types 1 to 4.
* p ≤ 0.001 compared to Week 0
** p = 0.027 compared to Week 0

0.001) across Weeks 1 to 6. Notably, despite a slight increase in mean pain VAS scores during Week 6 of the post treatment period compared to the treatment period, pain in Week 6 was still significantly lower than pain at baseline.

Feeling of complete evacuation

During 97.8% (2006 of 2052) of the defecations recorded, subjects responded to the question regarding the feeling

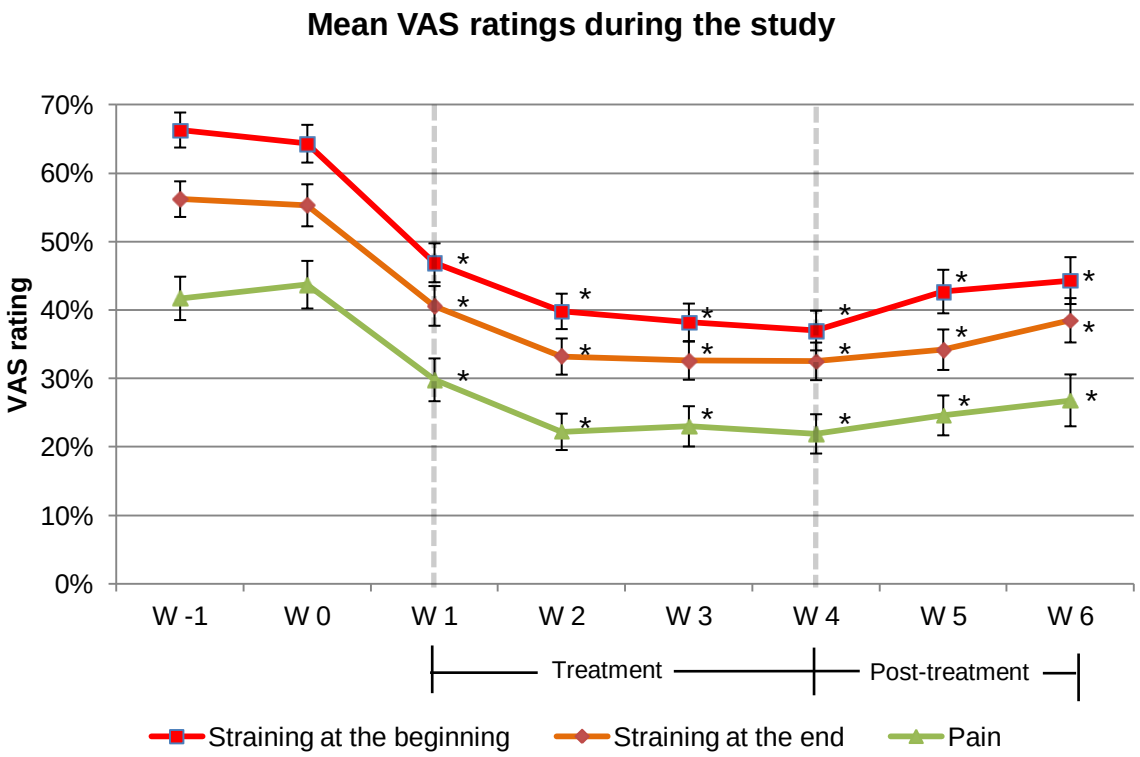

Figure 2. Mean VAS rating (%) for straining (at beginning and end of defecation) and feeling of pain during defecation. * = $p < 0.001$ compared to Week 0 (W 0) of respective parameter (non-parametric Wilcoxon test).

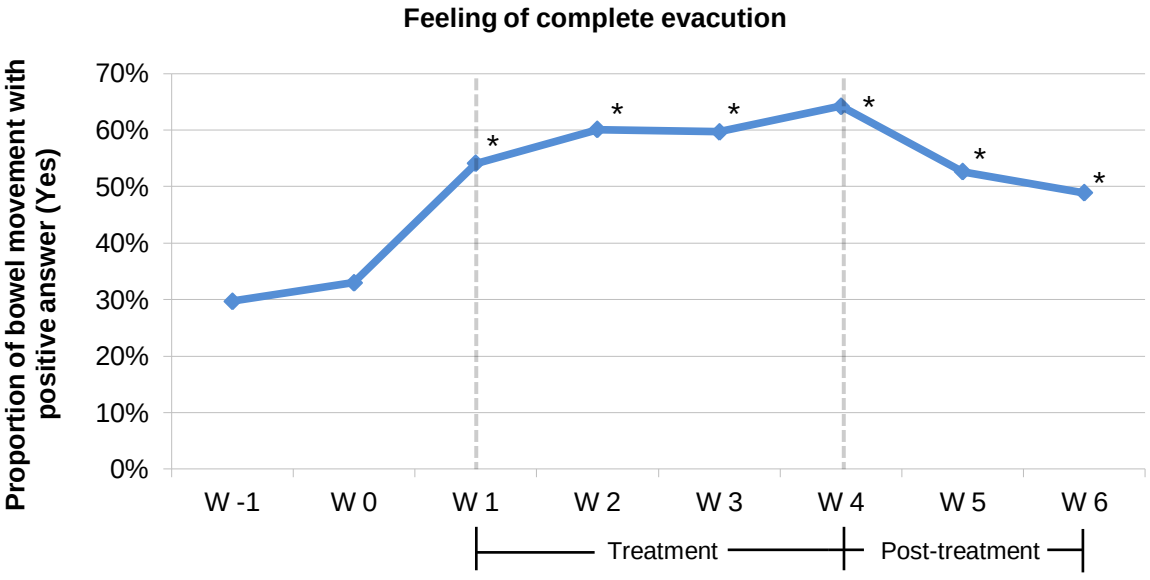

Figure 3. Bowel movements with feeling of complete evacuation. * = $p \leq 0.001$ compared to Week 0 (W 0) (non-parametric Wilcoxon test).

of complete evacuation. The proportion of positive answer ('yes') increased from 33% (CI: 26.0 to 40.5%) at Week 0 to 64.2% (CI: 58.4 to 69.7%) at Week 4, the improvement is statistically significant ($p < 0.001$) (Figure 3). Post-treatment, the proportion of bowel movement with the feeling of complete evacuation was also maintained at Week 6 at a statistically higher level compared to Week 0 ($p \leq 0.001$).

Time from first dose of IQP-PO-101 to first defecation

The time between intake of first dose of IQP-PO-101 and first bowel movement was documented. 27 out of 50 subjects (54%) had at least one bowel movement at Day 1. For these 27 subjects, the time between intake of first dose of IP and the first bowel movement was 5.02 (SD 3.47) hour on average, with a median of 4 h 45 min. Another 4 subjects reported the time to first bowel movement on Day 2, from 18 to 21.3 h after ingestion. In total, 62% of subjects reported first defecation within the first 24 h after consumption of IQP-PO-101.

Global evaluation of efficacy

The investigator rated the efficacy as “good” or “very good” for 90.0% of the subjects (45 of 50; CI: 78.1 to 96.7%), while 88.0% of subjects (44 of 50; CI: 75.6 to 95.5%) rated the efficacy as “good” or “very good”. There was no statistically significant difference in the global evaluation of efficacy between the investigator and the subjects ($p = 1.000$).

Safety and tolerability

Overall, 5 subjects (10%) documented 5 adverse events which included flatulence, abdominal discomfort, anal fissure and bleeding hemorrohoids. 2 incidences of flatulence and 1 incidence of abdominal discomfort were considered likely to be associated with the use of investigational product. There were no significant abnormalities or changes in the vital signs, blood counts and laboratory parameters. The investigators and the subjects both rated the safety as “good” or “very good” for 49 subjects (98%, CI: 89.3 to 99.9%).

DISCUSSION

Dietary fibre from psyllium husk has been reported to increase the water content in the colonic contents, thereby resulting in increased fecal volume and weight. Additionally, the fibrous gel formed by psyllium is not fermented in the colon – unlike other dietaty fibres that are frequently used in gastrointestinal disorders (Eswaran et al., 2013).

Thus psyllium husk fibres are able to provide lubrication that facilitate propulsion of colonic content and improve bowel regularity (Marlett et al., 2000). Addition of chia seed that is rich in insoluble fibre was shown to complement the swelling and bulking effect of psyllium *in vitro* but clinical evaluation of the combination’s efficacy is lacking. This was therefore the objective of the present trial.

In this open label study, results show that IQP-PO-101, a proprietary composition of psyllium and chia seed is able to induce overall improvement of unpleasant symptoms in subjects with mild to moderate constipation, as positive and significant changes were observed in both objective and subjective endpoints.

Consumption of IQP-PO-101 was able to normalize bowel movement frequency in constipated subjects. The increase in bowel movement frequency from 3.56 times per week at baseline to 6 times or more per week during the treatment phase was statistically significant. The onset of this bowel regulatory effect was reported to be as early as 5 h. Besides regularizing the bowel movement to almost daily frequency, significant improvement in stool consistency was also observed, where the occurrence of hard stools decreased from 70% at baseline to below 35% at end of treatment phase. Additionally, a large proportion of the subjects reported reduced straining (88%) and pain (82%) during defecations. Feeling of incomplete defecation often associated with constipation was also improved as reported by the subjects. Notably, the positive effects achieved by IQP-PO-101 in Week 1 were maintained throughout the treatment period even though treatment dosage was reduced by half from Week 2 to Week 4. This suggests that bowel regularity may be maintained with continued use of IQP-PO-101 at lower dose on a longer term. During the two-week post treatment, subjects were still able to maintain a statistically significant increase in stool number per week and improvement in other associated symptoms (as compared to Week 0). These observations indicate that IQP-PO-101 is able to maintain its bowel regularity effect up to a minimum of 2 weeks after treatment is discontinued.

The treatment with IQP-PO-101 is generally safe (as indicated by normal laboratory findings) and well tolerated, with mild gastrointestinal effects, such as abdominal discomfort and flatulence reported.

The present study included both men and women, in a broad range of age (23 to 65 years) and BMI (18.2 to 43.6 kg/m^2), thus making the results generalizable across all demographic groups. Limitation remains that long-term benefits, that is, a continuous treatment beyond 4 weeks, were not observed in this study. Another limitation lies with the non-placebo controlled, non-blinded study design. The large effect size observed in the main efficacy endpoints, and the decline in readings during the post treatment period at Week 5 and Week 6 towards baseline values, suggest that the improvements observed were more likely due to the treatment and not a placebo effect, nor observational bias.

The results reported here suggest an improvement compared to previous findings: A meta analysis on the effects of dietary fibre on constipation evaluated 5 relevant randomized controlled studies - in all of them dietary fibre was shown to have significant advantage over placebo in stool frequency, however, there were no

obvious improvements in stool consistency, treatment success, laxative use and painful defecation (Yang et al., 2012). Accordingly, the combination psyllium and chia seed may be superior to other dietary fibre formulations by also improving stool consistency and alleviating defecation strain.

CONCLUSION

Overall, the administration of IQP-PO-101 has shown to result in significant improvement in subjects' bowel regularity with mild side effects.

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