Clin Drug Investig (2014) 34:783–793
DOI 10.1007/s40261-014-0233-y

ORIGINAL RESEARCH ARTICLE

Quality of Life in Patients with Irritable Bowel Syndrome (IBS), Assessed Using the IBS–Quality of Life (IBS-QOL) Measure After 4 and 8 Weeks of Treatment with Mebeverine Hydrochloride or Pinaverium Bromide: Results of an International Prospective Observational Cohort Study in Poland, Egypt, Mexico and China

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Published online: 26 September 2014

Abstract

Background and Objective Irritable Bowel Syndrome (IBS) has a substantial impact on health-related quality of life (HR-QoL) but high-quality data pre- and post-treatment using the IBS–Quality of Life (IBS-QOL) measure are limited. The objective of this study was to evaluate the changes from baseline of the IBS-QOL scores, symptom scores and health economic data in IBS patients, after 4 and 8 weeks of treatment with mebeverine hydrochloride or pinaverium bromide.

Methods This was a prospective observational cohort study in patients with IBS, diagnosed using the Rome III criteria in four countries (Poland, Egypt, Mexico and China).

Results A total of 607 patients were enrolled. At baseline, the IBS-QOL total scores were 52.0 in Poland, 48.9 in Egypt, 51.9 in Mexico, 76.4 in China and 56.4 overall. Increases in IBS-QOL total score were statistically significant at Weeks 4 and 8 overall and in each country (overall: 11.8 at Week 4, 24.3 at Week 8; $p < 0.001$).

ClinicalTrials.gov identifier: NCT01678781.

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Improvements were shown in all IBS-QOL subscales and scores. Symptoms and health economic outcomes were improved. Furthermore, the favourable safety profile of these treatments was confirmed in this study.

Conclusions This study demonstrated that IBS patients have a substantially reduced HR-QoL and that treatment with mebeverine hydrochloride or pinaverium bromide improved HR-QoL.

Key Points

We performed a prospective, observational cohort study in patients with Irritable Bowel Syndrome (IBS), diagnosed using the Rome III criteria in four countries (Poland, Egypt, Mexico and China) assessing quality of life pre- and post-treatment (at 4 and 8 weeks) using the IBS-QOL measure.

Treatment with mebeverine hydrochloride in Poland, Egypt and Mexico, and pinaverium bromide in China confirmed treatment effectiveness in terms of improvement in all IBS-QOL subscales and scores. Results were statistically significant and exceeded the minimal important response (≥10.2) for the IBS-QOL total score (change from baseline at Week 4). At Week 8, the increase in the IBS-QOL total score was 24.3, greatly exceeding the meaningful clinical response (considered to be an increase of at least 14).

The favourable safety profile of treatment with either mebeverine hydrochloride or pinaverium bromide was confirmed in this study.

1 Introduction

Irritable Bowel Syndrome (IBS) has a substantial impact on health-related quality of life (HR-QoL) [1, 2]. The impact of IBS on quality of life (QOL) is often underestimated in patients as they do not appear to be disabled in any obvious way and there is no apparent impact on life expectancy [3]. QoL in IBS patients has been documented to be even lower than QoL of diabetes mellitus, dialysis-dependent end-stage renal disease or gastroesophageal reflux patients [4]. As there are limited data available pre- and post-treatment and specifically with mebeverine hydrochloride and pinaverium bromide [5, 6], this study was initiated to obtain QoL data in different regions of the world, using these treatments within a single study and using the IBS–Quality of Life (IBS-QOL) measure [7].

Mebeverine hydrochloride (Duspatal®, Duspatalin®, Colofac®, Colotal®, Mebeverin(e-i-a)®, Colospa®, Rudakol®, Boots IBS relief®, Fomac®, Mebecon®) is a musculotropic antispasmodic with a direct effect on the smooth muscle of the gastrointestinal tract, relieving spasm without affecting normal gut motility. Pinaverium bromide (Dicetel®, Eldicet®) is an antispasmodic that selectively acts on the gastrointestinal tract, by inhibiting the influx of calcium into intestinal smooth muscle cells. Both antispasmodics are indicated for the treatment of IBS. Mebeverine hydrochloride is a sodium channel antagonist and pinaverium bromide is a gastrointestinal-selective calcium channel antagonist. Both antispasmodics are available in different dosages. In a pharmacokinetic study, the Duspatalin® 200 mg twice-daily formulation has been compared with the 135 mg tablet three times daily and has demonstrated optimal relative bioavailability (103 % for single and 97 % for multiple doses) [8].

The IBS-QOL measure is a specific tool developed and validated to assess impairment of QoL in IBS [7, 9]. The IBS-QOL measure consists of 34 IBS-specific items and a 5-point Likert scale (1 = not at all, 2 = slightly, 3 = moderately, 4 = quite a bit, 5 = extremely or a great deal). The sum of the items is transformed into a score (potential range 34–100; 100 = maximum QoL). The IBS-QOL measure contains eight IBS-QOL subscales: dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual concerns and relationships. With regards to interpretation of results, apart from reaching statistical significance, a minimal important response (MIR) for the IBS-QOL measure is an increase of 10.2 and meaningful clinical response (MCR) is an increase of at least 14 [10].

2 Subjects and Methods

2.1 Study Design

The study was performed from July 2012 to August 2013 and took place in Poland, China, Egypt and Mexico. IBS patients were diagnosed according to Rome III diagnostic criteria. Patients were aged ≥18 years, prescribed

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mebeverine hydrochloride or pinaverium bromide according to the local label, and provided informed consent and written authorisation that their data could be used for analysis. The study of either mebeverine hydrochloride or pinaverium bromide depended on which of the medications were marketed in the countries. The total observational period was 8 weeks, per the US FDA guidance recommendation [11]. QoL was assessed after 4 and 8 weeks of treatment as the measure uses a recall period of the previous month (30 days).

Exclusion criteria were (i) general and specific contraindications to the treatment according to the local label; (ii) being currently treated/having been treated with mebeverine hydrochloride or pinaverium bromide within 4 weeks prior to study entry; (iii) pregnancy/lactation; (iv) other conditions precluding participation (investigator judgment); and (vii) previous enrolment in present study.

The study was approved by local independent ethics committees (IECs) in China and Mexico and by a central IEC in Poland. There was no requirement for IEC approval in Egypt. The study was registered or approved by regulatory authorities as applicable, and published on ClinicalTrials.gov on 13 July 2012 (NCT01678781).

Treatments were taken in accordance with both local marketing authorisation and the prescribing information—Poland: Duspatalin retard® 200 mg twice daily; Egypt: Duspatalin® 135 mg three times daily; Mexico: Duspatalin® 200 mg twice daily; and China: Dicetel® 50 mg three times daily. The Duspatalin retard® 200 mg capsule formulation is a prolonged-release formulation, which explains why a twice-daily regimen is sufficient; whereas the 135 mg tablet is an immediate-release formulation, requiring a three-times-daily treatment regimen.

IBS-QOL questionnaires were completed electronically by the patient at each visit using an electronic patient-reported outcome (ePRO) instrument.

Other symptom assessments were entered directly into the electronic case report form (eCRF).

2.2 Statistical Analysis

There were two patient samples defined for the study analyses: a safety analysis set (SAS), consisting of all patients who have received at least one dose of study medication, and a full analysis set (FAS), consisting of all patients in the SAS who had any post-baseline QoL data. Demographic and safety analyses were carried out using the SAS and efficacy analysis was carried out on the FAS.

Table 1 details the primary and secondary objectives of effectiveness, assessed after 4 and 8 weeks of treatment.

Table 1 Primary and secondary objectives

Primary objective
Change from baseline in IBS-QOL total score
Secondary objectives
Changes from baseline in the 8 IBS-QOL subscales (scores)
Change from baseline in IBS-QOL total and subscale scores within patient subgroups (IBS-C, IBS-D, IBS-M, sex and age)
Change from baseline in IBS symptom score:
abdominal pain (none/mild/moderate/severe/incapacitating)
stool frequency (mean number per day during last week prior to visit)
straining (present/absent)
urgency (present/absent)
feeling of incomplete defecation (present/absent)
passage of mucus (present/absent)
bloating or feeling of abdominal distension (present/absent)
Change from baseline in gastrointestinal symptoms (number of occurrences during last week prior to visit):
heartburn
early satiety
postprandial fullness
nausea
vomiting
Health economic data[a]
Evaluate the safety of mebeverine hydrochloride/pinaverium bromide by country and overall

IBS irritable bowel syndrome, *IBS-C* IBS with constipation, *IBS-D* IBS with diarrhoea, *IBS-M* IBS-mixed (constipation and diarrhoea), *IBS-QOL* IBS–Quality of Life

[a] After 8 weeks of treatment only

The required per-country sample size was 119 patients, securing a comparison-wise statistical power of 95 %. This sample size was based on the following assumptions: a mean baseline IBS-QOL total score of 60; an MIR from baseline >10; and a standard deviation of the change scores of 30 [10]. To allow for dropouts, and given that this number was an approximation, a per-country sample size of 133 patients resulted.

Statistical analysis of changes from baseline in total scores and subscores was performed using the Wilcoxon signed–rank test. A p value <0.05 was considered statistically significant.

3 Results

3.1 Disposition and Demographics

All patients ($n = 607$) received at least one dose of study drug and were included in the SAS. A total of 596/607 patients (98.2 %) had post-baseline QoL data—the FAS. Per country, the FAS consisted of: Poland—133 patients, 99.3 %; Egypt—208 patients, 99.5 %; Mexico—120 patients, 99.2 %; and China—135 patients, 94.4 %.

Figure 1 shows patient disposition and Table 2 summarises the demographic data.

Patients in Poland, Egypt and Mexico received treatment with mebeverine hydrochloride and patients in China received treatment with pinaverium bromide. Overall, 464/607 patients (76.4 %) received mebeverine and 143/607 patients (23.6 %) received pinaverium.

A total of 259 (42.7 %) patients reported taking concomitant medication at the start of or during the study. Concomitant medication was indicated for both IBS and other conditions.

With regards to IBS subgroups, the IBS with constipation (IBS-C) subgroup was far more prevalent in Mexico and the IBS with diarrhoea (IBS-D) subgroup was far more prevalent in China.

3.2 Primary Objective

3.2.1 Change from Baseline in Irritable Bowel Syndrome (IBS)–Quality of Life (IBS-QOL) Total Score

Table 3 provides an overview of the mean IBS-QOL total score at baseline, after 4 and 8 weeks, as well as the statistical analyses of the primary objective of the change from baseline in IBS QOL total score at Weeks 4 and 8 (FAS).

At baseline, the IBS-QOL mean total scores were similar and ranged from 48.9 to 52.0 but China had a significantly higher score of 76.4. Statistical analysis of the primary objective of IBS-QOL total score showed a statistically significant increase from baseline at Week 4 and 8, in each country and overall. The mean increase from baseline was greater at Week 8 (overall 24.3; range by country 10.4–31.8) than Week 4 (overall 11.8; range by country 7.7–14.9). For each country the increase at Week 8 was greater than at Week 4.

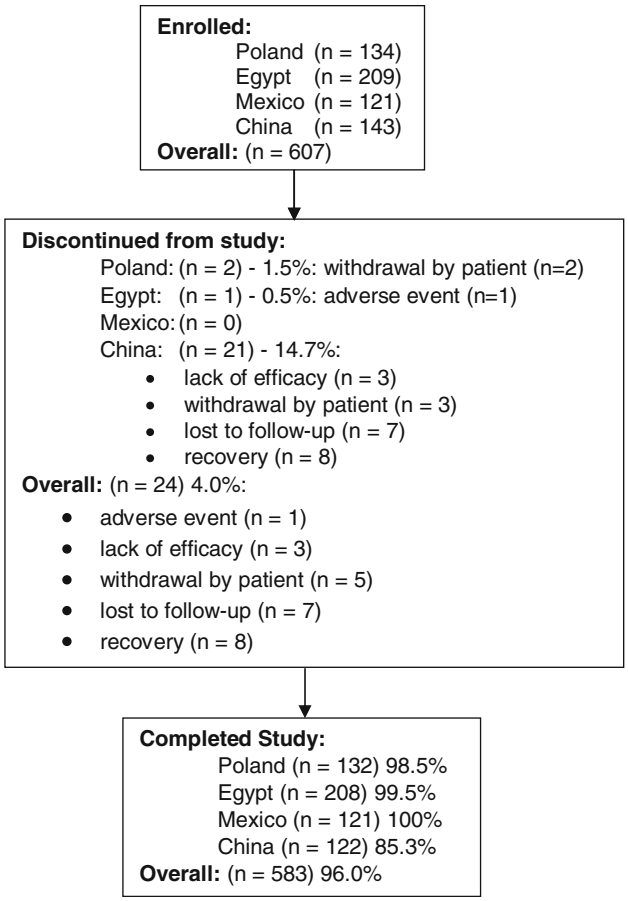


Fig. 1 Patient disposition (all patients)

3.3 Secondary Objectives

3.3.1 Change from Baseline in IBS-QOL Subscales

Figure 2 displays and Table 4 summarises the results regarding the IBS subscales (per country and overall, respectively).

There was a statistically significant increase from baseline in IBS-QOL for all subscales at Week 4 and 8, overall. Also, for each country, there was a statistically significant increase at Week 4 and 8, with the exception of interference with activity and social reaction in Mexico at Week 4 only. At Week 4, the increases for subscales for health worry, dysphoria, food avoidance and body image exceeded the MIR, whereas for social reaction and

Table 2 Summary of demographic data by country and overall (safety analysis set)

Characteristic	Poland ($n = 134$)	Egypt ($n = 209$)	Mexico ($n = 121$)	China ($n = 143$)	Overall ($n = 607$)
Sex [*n* (%)]					
Male	47 (35.1)	99 (47.4)	25 (20.7)	74 (51.7)	245 (40.4)
Female	87 (64.9)	110 (52.6)	96 (79.3)	69 (48.3)	362 (59.6)
Race [*n* (%)]					
Asian	0	0	0	143	143 (23.6)
Black	0	3 (1.4)	0	(100.0)	3 (0.5)
White	134 (100.0)	0	15 (12.5)	0	149 (24.6)
Other	0	206 (98.6)	105 (87.5)	0	311 (51.3)
Unknown	0	0	1	0	1
Age (*n*)	134	209	120	143	606
Mean (SD) [years]	43.8 (14.30)	37.2 (10.76)	44.4 (15.36)	43.6 (13.94)	41.6 (13.68)
Minimum, maximum (years)	20, 74	19, 75	19, 78	20, 80	19, 80
Age group [*n* (%)]					
18–30 years	26 (19.4)	69 (33.0)	26 (21.7)	27 (18.9)	148 (24.4)
31–40 years	36 (26.9)	58 (27.8)	30 (25.0)	42 (29.4)	166 (27.4)
41–65 years	63 (47.0)	81 (38.8)	49 (40.8)	66 (46.2)	259 (42.7)
>65 years	9 (6.7)	1 (0.5)	15 (12.5)	8 (5.6)	33 (5.4)
Out of range/missing age	0	0	1	0	1
Subgroup of IBS [*n* (%)]					
IBS-C	21 (15.7)	55 (26.3)	77 (64.2)	20 (14.0)	173 (28.5)
IBS-D	70 (52.2)	62 (29.7)	23 (19.2)	97 (67.8)	252 (41.6)
IBS-M	43 (32.1)	92 (44.0)	20 (16.7)	26 (18.2)	181 (29.9)
Unknown	0	0	1	0	1

Percentages are based on the number of patients with non-missing data in the respective group

IBS irritable bowel syndrome, *IBS-C* IBS with constipation, *IBS-D* IBS with diarrhoea, *IBS-M* IBS—mixed (constipation and diarrhoea), *SD* standard deviation

Table 3 Statistical analyses of the primary objective of the change from baseline in the Irritable Bowel Syndrome–Quality of Life (IBS-QOL) total score at Weeks 4 and 8

Visit	IBS-QOL total score[a]				
	Poland	Egypt	Mexico	China	Overall
Week 0 (baseline)	52.0 (18.32) ($n = 133$)	48.9 (18.58) ($n = 206$)	51.9 (18.62) ($n = 120$)	76.4 (14.18) ($n = 134$)	56.4 (20.68) ($n = 593$)
Week 4	65.4 (17.28) ($n = 132$)	63.7 (15.18) ($n = 208$)	60.2 (16.56) ($n = 111$)	83.7 (12.03) ($n = 129$)	67.8 (17.57) ($n = 580$)
Week 8	75.1 (18.09) ($n = 132$)	78.0 (12.36) ($n = 205$)	83.8 (13.65) ($n = 119$)	87.1 (11.25) ($n = 129$)	80.5 (14.58) ($n = 580$)
Change from baseline to Week 4	13.4 (15.94)* ($n = 132$)	14.9 (18.70)* ($n = 206$)	8.9 (23.45)** ($n = 111$)	7.7 (11.03)* ($n = 128$)	11.8 (17.98)* ($n = 577$)
Change from baseline to Week 8	23.3 (20.44)* ($n = 132$)	29.4 (19.18)* ($n = 203$)	31.8 (20.89)* ($n = 119$)	10.4 (11.98)* ($n = 130$)	24.3 (20.13)* ($n = 584$)

Data are presented as mean (standard deviation)

IBS-QOL Irritable Bowel Syndrome-Quality of Life, *QoL* quality of life, $^{*}p < 0.001$, $^{**}p = 0.001$

[a] Scale: 100 = best possible QOL, 0 = worst possible QoL

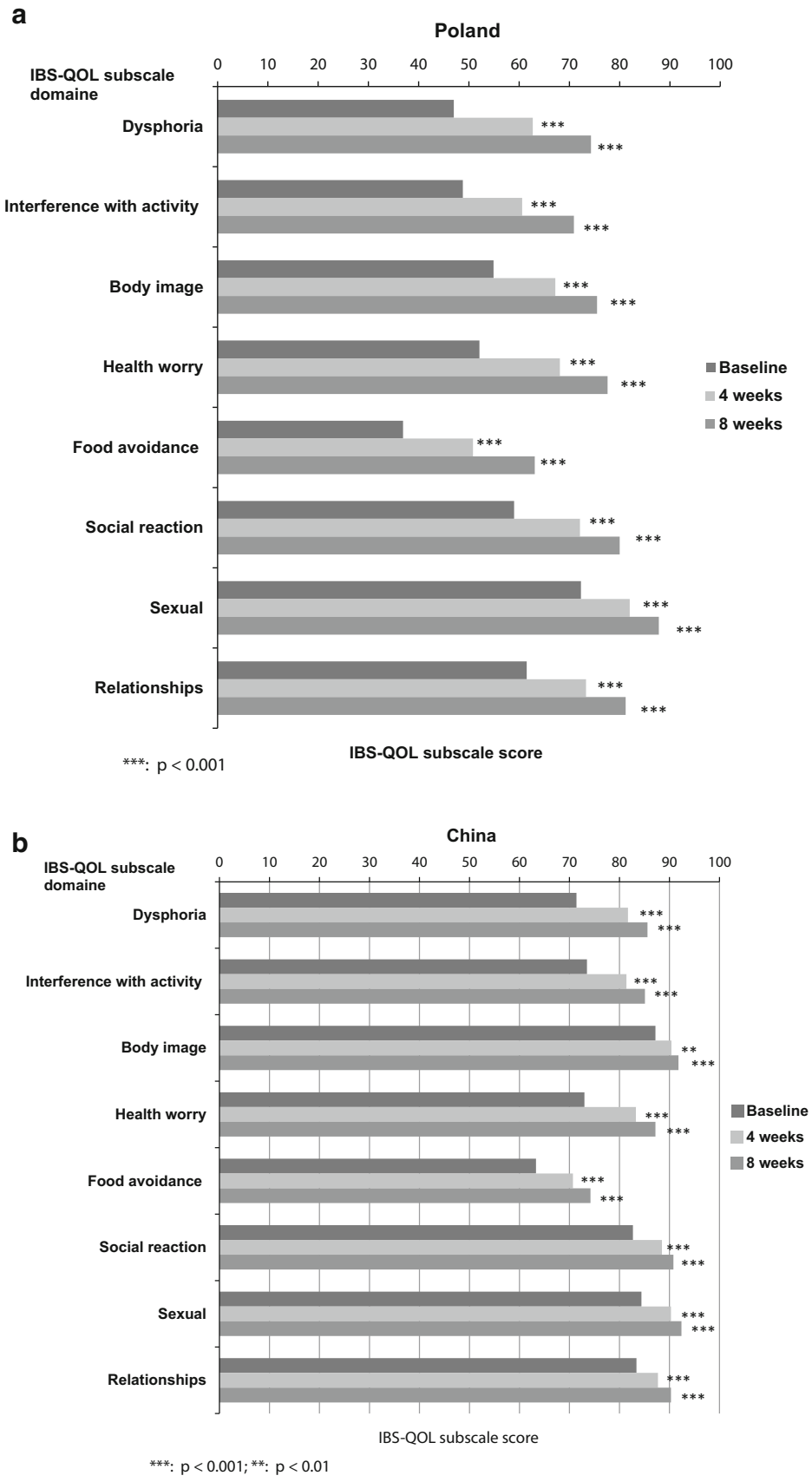
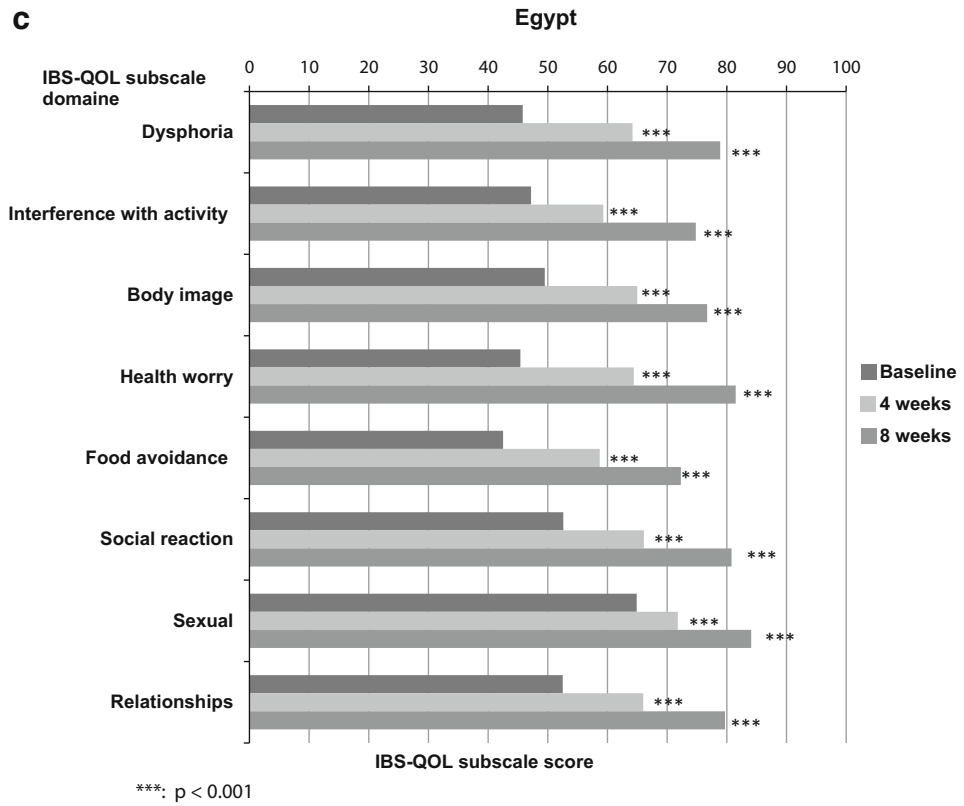


Fig. 2 Change from baseline, in Irritable Bowel Syndrome–Quality of Life (IBS-QOL) subscale scores at Weeks 4 and 8 in Poland (**a**), China (**b**), Egypt (**c**) and Mexico (**d**)

Fig. 2 continued



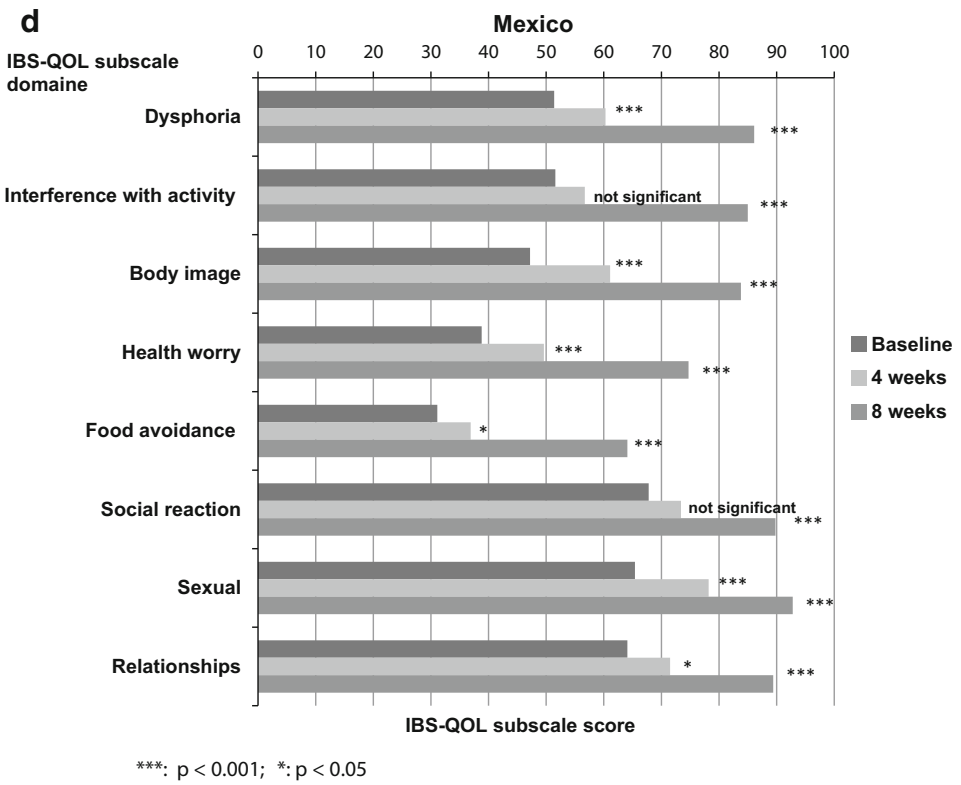


Table 4 Statistical analyses of the secondary endpoint of the change from baseline, overall, in Irritable Bowel Syndrome–Quality of Life subscale scores at Weeks 4 and 8

Visit	IBS-QOL subscale score[a]							
	Dysphoria	Interference with activity	Body image	Health worry	Food avoidance	Social reaction	Sexual	Relationships
Week 0 (baseline)	53.0 (23.56) ($n = 595$)	54.4 (21.93) ($n = 595$)	58.8 (24.87) ($n = 596$)	51.8 (24.97) ($n = 596$)	43.7 (25.55) ($n = 596$)	63.9 (24.92) ($n = 596$)	71.0 (27.97) ($n = 594$)	63.8 (25.14) ($n = 596$)
Week 4	67.0 (19.57) ($n = 580$)	64.0 (20.17) ($n = 580$)	70.4 (19.78) ($n = 580$)	66.6 (22.3) ($n = 580$)	55.4 (24.31) ($n = 580$)	73.8 (19.32) ($n = 580$)	79.5 (21.13) ($n = 580$)	73.5 (19.41) ($n = 580$)
Week 8	80.8 (16.39) ($n = 587$)	78.3 (16.51) ($n = 587$)	81.3 (16.89) ($n = 587$)	80.5 (17.24) ($n = 587$)	69.0 (21.13) ($n = 587$)	84.7 (16.32) ($n = 587$)	88.5 (16.92) ($n = 586$)	84.4 (16.25) ($n = 587$)
Change from baseline to Week 4	14.4 (20.66)* ($n = 579$)	10.0 (21.14)* ($n = 579$)	11.7 (20.68)* ($n = 580$)	15.1 (22.35)* ($n = 580$)	12.1 (23.35)* ($n = 580$)	10.1 (21.10)* ($n = 580$)	8.4 (24.56)* ($n = 578$)	10.0 (22.43)* ($n = 580$)
Change from baseline to Week 8	27.9 (23.79)* ($n = 586$)	24.0 (21.72)* ($n = 586$)	22.6 (23.39)* ($n = 587$)	28.9 (25.03)* ($n = 587$)	25.4 (26.16)* ($n = 587$)	21.0 (22.59)* ($n = 587$)	17.4 (26.57)* ($n = 585$)	20.7 (23.82)* ($n = 587$)

Data are presented as mean (standard deviation)

IBS-QOL Irritable Bowel Syndrome–Quality Of Life, *QoL* quality of life, * $p < 0.001$

[a] Scale: 100 = best possible QoL, 0 = worst possible QoL

Table 5 Irritable bowel syndrome symptom scores for abdominal pain/discomfort at baseline and after 4 and 8 weeks of treatment with mebeverine hydrochloride or pinaverium bromide by country and overall

Visit	Mean abdominal pain/discomfort: IBS symptom scores[a]				
	Poland ($n = 133$)	Egypt ($n = 208$)	Mexico ($n = 120$)	China ($n = 135$)	Overall ($n = 596$)
Week 0 (baseline)	2.0 (0.63) ($n = 133$)	2.0 (0.66) ($n = 208$)	2.3 (0.83) ($n = 120$)	1.5 (0.68) ($n = 135$)	2.0 (0.74) ($n = 596$)
Change from baseline to Week 4	−0.9 (0.73) ($n = 133$)	−0.9 (0.77) ($n = 208$)	−1.4 (1.02) ($n = 111$)	−0.7 (0.81) ($n = 130$)	−0.9 (0.86) ($n = 582$)
Change from baseline to Week 8	−1.3 (0.80) ($n = 132$)	−1.4 (0.78) ($n = 208$)	−1.9 (1.08) ($n = 120$)	−1.0 (0.87) ($n = 131$)	−1.3 (0.92) ($n = 591$)

Data are presented as mean (standard deviation)

IBS irritable bowel syndrome

[a] Scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = incapacitating

interference with activity and relationships, the increases were just below the MIR at 10.0 or 10.1. For sexual concerns, the increase was lower at 8.4. For each subscale, overall and in each country, the mean increase at Week 8 was greater than at Week 4.

Patients in Poland, Egypt and Mexico had similar mean baseline scores for the subscales and responses in Poland and Egypt at Week 4 were comparable, whereas in Mexico all mean responses, with the exception of 'body image' and 'sexual', were lower. By Week 8, the mean response for patients in Poland, Egypt and Mexico was similar. In China, the patients had higher baseline subscale scores and response at Week 4 and Week 8 was less than in the other countries, which was most apparent for 'body image' and 'relationships'.

3.4 Analysis of IBS Subgroups

There was a mean increase from baseline in IBS-QOL total and subscales for all IBS subgroups at Weeks 4 and 8. For each total score and subscale, overall and in each country, the increase at Week 8 was greater than at Week 4. The response in patients with IBS-D at both Week 4 and 8 was lower than for patients with IBS-C and irritable bowel syndrome—mixed (constipation and diarrhoea) (IBS-M), suggesting that patients with IBS-D respond less well to treatment than those with IBS-C and IBS-M. Lower responses were seen for the IBS subgroups in Mexico at Week 4 (as for all IBS patients combined), with the response for IBS-C patients and particularly IBS-D patients being lower there than those patient subgroups in Poland

and Egypt. In China, the IBS-QOL total score for each IBS subgroup showed a higher baseline and response was lower at Weeks 4 and 8. Evaluation of the subscales showed responses for IBS-D patients being consistently lower than for IBS-C and IBS-M patients.

3.5 Analysis by Sex and Age

There was no notable difference according to sex regarding the increase in IBS-QOL total scores at Week 4 and 8. Females had slightly lower mean baseline IBS-QOL total scores and showed a greater mean increase from baseline than males at Week 8 in all countries with the exception of Egypt. There was no apparent difference in response with increasing age.

3.6 IBS and Gastrointestinal Symptom Scores

Table 5 summarises the IBS symptom scores for abdominal pain and discomfort.

There was a mean decrease in abdominal discomfort/pain at Week 4 and a further decrease at Week 8 in all countries (overall: −0.9 at Week 4 compared with −1.3 at Week 8).

Analysis of IBS-C and IBS-D subgroups showed improvements for both stool frequency and stool form. Overall for IBS-C, there was a mean increase from baseline of 0.4 per day for stool frequency at Weeks 4 and 8 and a mean increase in stool form of 0.6 (Week 4) and 0.7 (Week 8). Overall for IBS-D, there was a mean decrease at Weeks 4 and 8 (−0.9 and −1.2 per day, respectively) for stool frequency and for stool form of −1.4 (Week 4) and −1.6 (Week 8).

Overall, patients showed consistent improvement across the IBS symptoms of straining, urgency, feeling of incomplete defecation, passage of mucus and bloating/feeling of abdominal distension. These symptoms were present in 41.6–79.9 % of patients at baseline; they showed an improvement in 26.1–36.6 % of patients at Week 4 and in 37.2–47.4 % of patients at Week 8. For the IBS subgroups, 87.2 % of IBS-C patients experienced bloating or a feeling of abdominal distension at baseline and showed a notable improvement from Week 4 to Week 8 (26.3 to 55.9 % of patients) and for IBS-D patients, 75.2 % of patients had a feeling of urgency at baseline, which showed the most improvement compared to other IBS symptoms at both Week 4 and Week 8 (47.7 and 59.3 % of patients, respectively). Bloating/abdominal distension is a symptom that is typically reported in the Asian population, and described in Asian consensus guidelines as being one of the most predominant symptoms of IBS. However, within the Rome III diagnostic criteria, there is no mention of bloating; therefore, it is of interest to have data on improvement of symptoms of bloating/abdominal distension with treatment on top of data regarding the QoL.

There was a mean decrease from baseline for all gastrointestinal symptoms (number of occurrences during the last week prior to visit): heartburn (−0.5), early satiety (−0.7), postprandial fullness (−0.8), nausea (−0.5) and vomiting (−0.2) at Week 4. For heartburn, early satiety and postprandial fullness, there was a greater decrease from baseline at Week 8 (means of −0.7, −1.0 and −1.2, respectively), whereas for nausea and vomiting there was no further change at Week 8 versus Week 4.

3.7 Health Economic Data

The health economic data showed that no patients spent any days in hospital due to their IBS in the 8-week treatment period, compared to a mean of 0.2 days (patients in Egypt, Mexico and China only) in the 8-week period prior to baseline. For the patients currently employed, a mean of 0.1 days (patients in Poland, Egypt and China only) was missed from work during the 8 weeks of treatment due to IBS, compared with a mean of 1.2 days (patients in all countries) in the 8-week period prior to baseline.

3.8 Safety

Treatment was well-tolerated. The incidence of adverse events (AEs) was low (3.3 % of patients), the most frequently reported being headache (three patients) and pharyngitis and upper respiratory tract infection (in two patients each). Twenty patients reported a total of 21 AEs. Two AEs considered possibly drug-related were abdominal distension (moderate severity) and somnolence (mild severity), both of which were non-serious and ongoing at the end of the study period; both occurred with mebeverine. The other 19 AEs were considered unrelated to study treatment. A serious AE of mild haemorrhoids (requiring hospitalization for surgery) was not considered drug-related by the investigator (in China). A pregnancy was reported after the start of the study, which is currently ongoing (in Egypt).

4 Discussion

The IBS-QOL [7] questionnaire was developed by Patrick and Drossman [7] in the 1990s and further validation has confirmed the responsiveness of the scale [1, 10, 2]. A systematic review has appraised the IBS-QOL measure as the best of five IBS-specific QoL scores available and assessed to establish changes in HR-QoL [12].

This study (596 IBS patients, 59.6 % females, assessed using the Rome III criteria) shows a mean, overall IBS-

QOL total score at baseline of 56.4, indicative of moderate/severe disease and is consistent with an international survey of patients with IBS published by Drossman et al. in 2009, where patients also met Rome III criteria for IBS in 90.8 % of the cases (1,966 patients; 83 % female, 91 % Caucasian, 78 % USA/Canada) [2] and where the overall mean at baseline was 51.1.

In this study, the impairment at baseline was similar in Egypt, Mexico and Poland (mean IBS-QOL total scores of 48.9–52.0), but lower in China at 76.4 (indicative of mild/moderate disease). Of note, there are no general practitioners in China and patients consult specialist care immediately, which potentially explains severity of disease being less in China at baseline; thereby leaving a smaller relative room for improvement. Previous studies have shown different mean baseline IBS-QOL total scores, using different diagnostic criteria, a different male/female ratio, different IBS subtyping distribution and different geographical locations: 70.3 (30 Japanese patients, percentage females/males not stated, Rome II diagnosis) [3]; 66.3 (1,555 patients in Canada, 85.1 % females, physician diagnosed) [13]; and 64.3 (value adjusted for age, education, race, marital status) (317 patients in Canada, 100 % females, Rome I diagnosis) [10]. These differences may reflect known cross-cultural differences across countries (e.g. race, food or lifestyle) and variation in diagnosis and sex of patients. In this study, all patients were diagnosed according to the Rome III criteria, so the diagnosis of IBS (Rome III) is not a contributory factor to the higher baseline seen in China.

For the IBS-QOL, Drossman et al. [10] reported an MIR to be an increase of 10.2 and an MCR to be an increase $\geq$14. In this study, the overall change from baseline in IBS-QOL total score at Week 4 of 11.8 achieved the MIR and by Week 8 the improvement of 24.3 greatly exceeded the MCR.

In this study, the greatest impairment at baseline (determined as scores <55) was observed for the subscale of food avoidance (43.7), health worry (51.8), dysphoria (53.0) and interference with activity (54.4). These findings were similar to the previously mentioned international survey results [2], where the greatest impairments of similar magnitude were shown for food avoidance, dysphoria and interference with activity, but not health worry. In Japanese patients [3], food avoidance, dysphoria and interference with activity also showed the greatest impairment. Studies in Canada showed the greatest baseline impairment in food avoidance, health worry and body image [13], and for food avoidance, interference with activities and dysphoria [10].

The greatest improvements in IBS-QOL in this study, after 8 weeks of treatment, were observed for the subscales of food avoidance, health worry, dysphoria and interference with activity; with these subscales having the lowest pre-treatment scores, they have a greater potential for improvement. Similar findings to this study have been previously reported [2], with the exception of social reaction also having a greater improvement and replacing food avoidance. The remaining subscales of body image, social reaction, sexual concerns and relationships in this study all showed clinically meaningful responses at 8 weeks (range 17.4–28.9).

Randomised placebo-controlled trials conducted in patients with IBS tend to be characterised by a relatively high placebo response. Considering the fact that a placebo effect generally tends to occur early in treatment and is less likely to persist, and the IBS-QOL scores increasing up to Week 8, this does not appear to have significantly impacted the outcome of the study; albeit a certain degree of placebo response cannot be completely excluded. Patel et al. [14] have demonstrated that fulfilment of the Rome criteria for study entry and an increased number of office visits are significantly associated with a lower placebo response rate. By requiring patients to fulfil the Rome III criteria, and by having three visits within the 8-week treatment period, a proactive effort was made to contribute to a lower placebo response rate.

Abdominal pain is one of the main symptoms associated with IBS and a responder has been defined in several studies in IBS patients [15] as demonstrating a 50 % decrease in symptom severity. For the IBS symptoms of abdominal pain and discomfort in this study, a mean decrease of >50 % in symptom severity was seen in all countries, and overall, at Week 8.

This study provides further relevant information on the IBS-QOL measure as a means to determine adequate treatment response. For the clinician, the study attests to the value of the IBS-QOL as a 'barometer' of the patient's clinical course, more than any biological measure. It provides information on the patient's perception of ill health, and how it is modified for better or worse in response to treatment, and can therefore be used as a yardstick of treatment progress, including when a particular intervention would be considered optimal.

The limitations of this study are in regard to both the study being observational in design and also to how the findings can be related to other populations. An observational study represents a 'less perfect' experiment than an efficacy trial and there can be issues relating to data quality and completeness, as well as the non-randomised design. The aim of this study, however, was to provide high-quality data by gathering it electronically, and statistical analysis showed significant increases from baseline in IBS-QOL total score at Weeks 4 and 8 for all countries and overall, which could be quantified in terms of a high MCR at Week 8. The findings, however, may not be applicable to

men or women with milder or more severe disease, or with other functional gastrointestinal symptoms. The study does provide new information regarding the impact of IBS on HR-QoL and the magnitude of improvement in response to treatment with mebeverine hydrochloride or pinaverium bromide, showing the effectiveness of these treatments in a real-life setting. Many patients in this observational study received treatment for IBS and then in addition received mebeverine hydrochloride or pinaverium bromide, reflective of the real-life setting (where often a combination of medications is given to address the symptoms of the individual patient and IBS subtype) and showing the added value of additional treatment.

5 Conclusion

Treatment of patients with IBS with mebeverine hydrochloride in Poland, Egypt and Mexico and pinaverium bromide in China confirmed the effectiveness of the study medication in terms of the improvement in IBS-QOL total scores and subscales. Results were statistically significant and exceeded the MIR ($\geq$10.2) for the IBS-QOL measure, from baseline, with the changes being greater at Week 8 than Week 4. At Week 8, the increase in the IBS-QOL total score was 24.3, greatly exceeding the MCR (considered to be an increase of at least 14) [10].

An improvement in IBS and gastrointestinal symptoms was also shown for the patients overall and for each subgroup (IBS-C, IBS-D and IBS-M). There was also an improvement in the health economic data for the patients, with a reduction during the treatment period in both the number of days spent in hospital and the number of days missed from work. Furthermore, the favourable safety profile of these treatments was confirmed in this study.

Acknowledgments We acknowledge Janet Ward, Chiltern International, Slough, UK for medical writing assistance and contributing to clinical study report preparation.

Investigators that have also contributed to the recruitment of patients: Duowu Zhou (Shanghai, China), Huahong Wang (Beijing, China), Tomasz Arlukowic (Olsztyn, Poland), Jacek Romatowski (Bialystok, Poland), Marek Karczewski (Bydgoszcz, Poland).

Funding The research was sponsored by Abbott Products Operations, AG, Allschwil, Switzerland.

Conflict of interest Dr. Afifi has lectured for AstraZeneca and Sanofi Aventis. Dr. El-Khayat has provided lectures and has been involved in clinical research for: BMS, MSD, AstraZeneca, Abbott and Gilead. Gwendolyn Janssen-van Solingen is an employee of Abbott Products Operations AG in the position of Global Medical Director Gastroenterology portfolio.

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