22 June 2017
EMA/530965/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 31 of Directive 2001/83/EC

Symbioflor 2 (Escherichia coli bacteria (cells and autolysate)) and associated names

Procedure number: EMEA/H/A-31/1441

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

Symbioflor 2 (*Escherichia coli* bacteria (cells and autolysate)) and associated names (Symbioflor 2) is a probiotic containing living *Escherichia coli* bacteria, which exist in normal gut flora in humans. Symbioflor 2 is composed of 10 different isolates of *Escherichia coli* which are partly autolysed and partly presented as living bacteria. Symbioflor 2 is available in the European Union (EU) in Austria (AT), Germany (DE) and Hungary (HU) as a medicine not subject to prescription or over-the-counter (OTC). Symbioflor 2 has been marketed in Germany since 1954 and in Austria since 1975.

Symbioflor 2 is currently used for the indications:

- Regulation of the immune system, gastrointestinal disorders, irritable bowel syndrome (DE).
- Functional disturbances of the gastrointestinal tract and irritable bowel syndrome (Colon irritable) (AT).
- To regulate the immune system (immune-regulation): functional disturbances of the gastrointestinal system (HU).

The marketing authorisations were granted in Austria in 2000 (renewed on 12 February 2014) and in 2003 in Hungary (HU) respectively. In Germany, since Symbioflor 2 was placed on the market before the entry into force of the German Drug Law in 1978, Symbioflor 2 had to undergo the renewal procedure according to § 105 German Drug Law in order to achieve the conformity of the authorisation in Germany with the Union legislation.

In 2005, based on the evaluation of the available evidence at that time in the claimed indications ("functional gastrointestinal disorders'', "irritable bowel syndrome"), the application was refused by the German National Competent Authority on the ground that a positive benefit-risk had not been adequately established. Following the rejection of the application, the Marketing Authorisation Holder (MAH) requested to be granted a German National Marketing Authorisation on the basis that an authorisation had already been granted in another country of the European Union (Austria).

On 30 March 2016 Germany triggered a referral under Article 31 of Directive 2001/83/EC, and requested the CHMP to assess the benefit-risk balance of Symbioflor 2 in the claimed indications ("functional gastrointestinal disorders'', "irritable bowel syndrome") and to issue an opinion on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

The CHMP reviewed all available data from clinical studies, published literature, post-marketing experience, as well as the views of the ad hoc expert group on Symbioflor 2, including responses and communications submitted by the marketing authorisation holder (MAH) in writing on the efficacy and safety of Symbioflor 2 (Escherichia coli bacteria (cells and autolysate)) and associated names in their proposed indications. It should be noted that this report summarises the most relevant data.

It is noted that the CHMP is a scientific committee and that while it operates within the legal framework, it cannot discuss the specific merits of procedural and legal aspects of administrative procedures laid down in the legislation.

Table 1 Overview of key efficacy data submitted

Study id and design / reference	**Key objectives / endpoints**	**Population**	**Inclusion/ exclusion criteria**	**Treatment**	**Main efficacy results**
Therapeutic indication "Irritable bowel Syndrome"					
Clinical Study in patients with irritable bowel syndrome (S2 PAZ 9527-5-52)	"Differences in effects and tolerability between Symbioflor 2 and placebo"	Patients with irritable bowel diagnosed according to "Kruis criteria"	"Kruis clinical score" of >44; presence of abdominal pain, no relevant acute of chronic illness	Symbioflor 2: 1st week: 3x10 drops 2nd week: 3x20 drops Or matching placebo	1st analysis: PGA*: 63.6% vs. 39.4% (good or very good) 2nd analysis: 18.2% vs 4.67% and 18.9% vs. 6.67% for global symptom and pain response.
Efficacy and Tolerability of Symbioflor 2 in Children with Irritable Bowel Syndrome	Document the efficacy and tolerability of Symbioflor 2 in children.	Children with irritable bowel syndrome in the age groups of 4–11 years and 12–18 years	All children/adolescents had one of the four clinical types of irritable bowel syndrome as specified by the ROME III criteria	10 drops once a day (for the vast majority of patients)	PGA*: 83.3% (good or very good)
Therapeutic indication "Functional gastrointestinal disorders"					
No data submitted/available					

* Physician Global Assessment

2.2. Data on efficacy

2.2.1. Indication in the treatment of functional gastrointestinal disorders

"Functional gastrointestinal disorders" defines a heterogeneous group of individual diseases, ranging from functional oesophageal, gastric, intestinal, biliary, pancreatic to functional anorectal disorders, with a wide range of different underlying pathophysiologies and symptomatic entities that require different treatment modalities. Apart from data on irritable bowel syndrome (IBS), no controlled or uncontrolled clinical study or literature data are available to assess the efficacy and safety of Symbioflor 2 in the treatment of these diseases. The CHMP asked the MAH to submit data to support this broad indication. No data was provided. Given the heterogeneity of the disease and the absence of data, the CHMP was not able to conclude positively on the efficacy and safety of Symbioflor 2 in the treatment of "functional gastrointestinal disorders" and accepted the MAH proposal to delete the indication.

2.2.2. Indication in the treatment of irritable bowel syndrome

Two studies were submitted to support the indication in the treatment of irritable bowel syndrome, namely "*Clinical Study in patients with irritable bowel syndrome (S2 PAZ 9527-5-52)"* – hereafter referred to as Study S2 and "*Efficacy and Tolerability of Symbioflor 2 in Children with Irritable Bowel Syndrome".* These two studies are described and discussed in more detail below.

Study S2 was initially conducted as a placebo-controlled multi-centre trial in 19 different private practices in Germany between October 1988 and February 1989 and entitled "Schaffstein, W. and Burkard, I.: Symbioflor 2 – Eine therapeutische Alternative zur Behandlung des irritablen Kolons. Jatros Gastroenterol, 1993" (Study S2). The report submitted in this referral is a re-analysis, in 2005, entitled "Efficacy and tolerability of Symbioflor2: A randomised, multicentre, double-blind, placebo-controlled trial in 298 patients with irritable bowel syndrome treated continuously for 8 weeks with Symbioflor 2 (clinical phase IV). Supplementary Integrated Clinical Study Report Final PAZ 9527-5-S2".

2.2.2.1. Clinical Study in adult patients with irritable bowel syndrome (S2)

Patients in Study S2 were treated with either Symbioflor 2 or placebo. The dosage given was 3x10 drops per day during the first week, and 3x20 drops from weeks 2 to 8. The total treatment duration was 8 weeks.

Inclusion/Exclusion criteria

According to the protocol, patients to be included in the study could be either male or female adults, had been receiving medical treatment for this indication during the last year for the same disease, had abdominal pain (grade not specified) and had a clinical score ("Kruis score") of above 44. Exclusion criteria were the absence of abdominal pain, any organic disease of the gastrointestinal tract including conditions of the gallbladder and biliary tract, acute pancreatitis, ileus, or other severe acute or chronic illness.

Randomisation

Although not clearly described it is understood that block randomisation was used (blocks of 6 patients), which is acceptable.

Blinding (masking)

Bottles given to patients were identical in appearance, which is appropriate.

Endpoints and statistical methods

In the **Final Study Report of Study S2 (1989)**, "global evaluation" of efficacy by the Investigator at the end of the trial was chosen as the primary endpoint of the trial. The clinical outcome measures were measurements on ordinal scales (0 to 3 or 0-4) for the categories "general health", "spontaneous pain or on palpation", "sigmoid colon" (without specification on whether it was measured by pain or palpation), stool consistency, heartburn, belching, nausea, bloating, vomiting, borborygmus, flatulence, headaches, depression, loss of appetite, and sleep disorder. The stool frequency was also mentioned as an outcome measure (without specifying the interval for recording). In addition, the protocol mentions "global final assessment" and "tolerability of the investigational medicinal product" (both on a 0-4 scale) as additional outcome measures. The "global final assessment" and the tolerability assessment were evaluated at the last visit (day 56), whereas the other parameters were recorded during the weekly patient visits. It was not specified whether the assessment was to be done by the patient or by the investigator.

In the **re-evaluation report of Study S2 (2005)**, "patient-specific global assessment of the symptoms" and "patient specific assessment of abdominal discomfort/pain" were defined as (co-) primary outcome. The response criteria were defined as the complete absence of IBS symptoms as diagnosed at baseline visit. The response rate was measured at the end of the eight-week period (visit 9). Secondary endpoints, included abdominal pain (composite of "spontaneous pain: - lower abdomen", "spontaneous pain: - diffuse", "spontaneous pain on palpation:- gall bladder", "spontaneous pain on palpation: - colon"), abnormal defecation (composite of "stool consistency", "stool frequency", "sigmoid colon (i.e. palpable sigmoid colon), and abdominal distension (including the item "subjective symptoms – bloating").

The study report as well as the Statistical Analysis Plan (SAP) defined the populations to be analysed as the "efficacy data set" (all patients for which a complete dataset can be constructed using the Last Observation Carried Forward (LOCF) approach), the per-protocol data set (all patients for which a complete dataset is available), and the tolerability dataset, comprising all patients who have at least taken the study medication once.

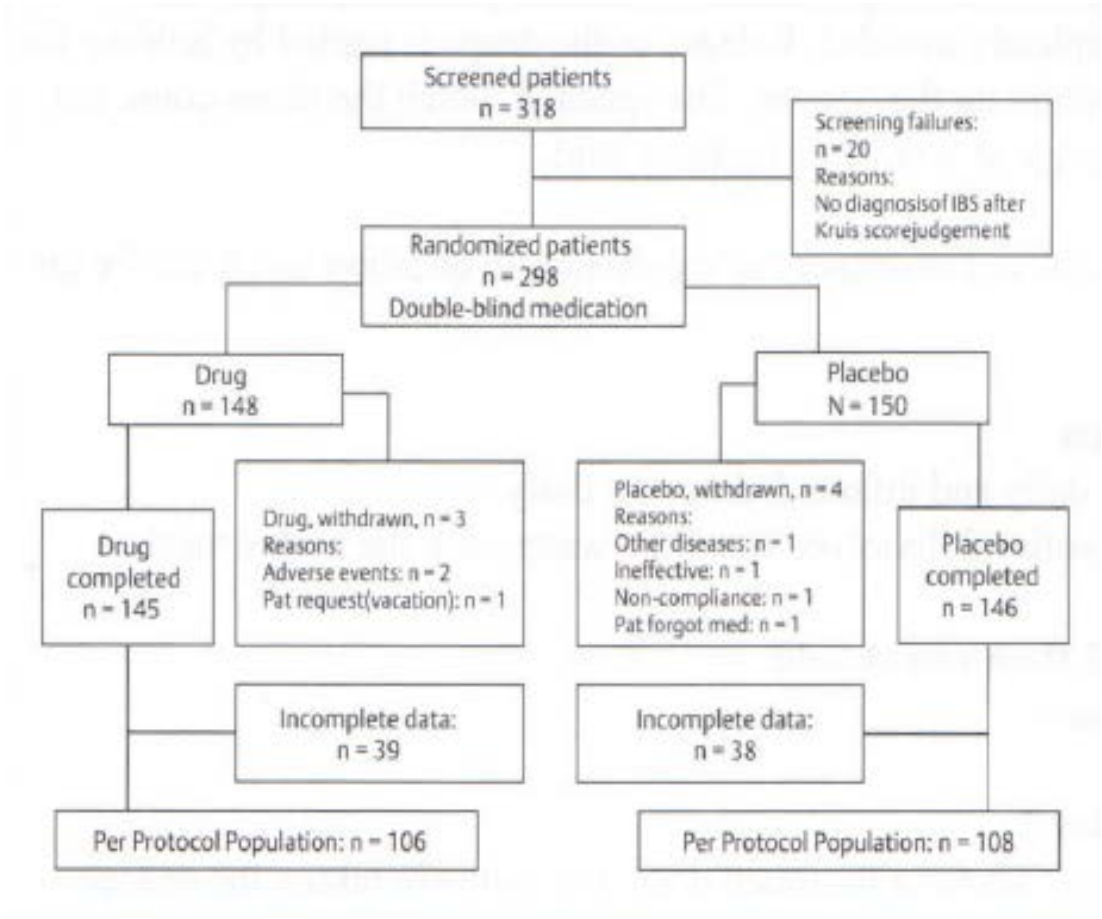
The null hypothesis was defined as no difference between the groups in the point estimates (mean or median). The observed frequencies for the two primary endpoints were tested using Fisher's exact test. The significance level was ($\alpha = 0.05$) for a two-sided interval.

For primary variables, the last measurable value should be transferred to the subsequent missing value (last-value-carried-forward) and so on up to Visit 9. Missing data from Visit 1 was supplemented with plausible values, but only if this could be justified medically. For all other variables, missing data were not to be estimated but be accepted as missing.

Discontinuations

The number of discontinuations is presented in Figure 1.

Figure 1: Participant flow study S2:



The number of discontinuation was low (7/298=2.3%).

Baseline data

Table 2 presents an overview of the demographic data for age, weight, height, body mass index (BMI).

Table 2: Overview of the demographic data of the patients (Efficacy data set; N=148 active; N=150 placebo).

Parameter	Age [years]	Weight [kg]	Height [cm]	BMI [ ]
Verum				
N of cases	148	148	148	148
Minimum	19	49	152	19.63
Maximum	74	101.1	189	34.17
Mean	48.71	69.86	168.55	24.51
95% CI upper	50.49	71.57	169.79	24.95
95% CI lower	46.93	68.15	167.32	24.07
Standard deviation	10.97	10.53	7.62	2.71
CV	0.23	0.15	0.05	0.11
Placebo				
N of cases	150	150	150	150
Minimum	18	44	146	18.07
Maximum	82	104.5	187	37.92
Mean	48.25	70.37	169.04	24.57
95% CI upper	50.35	72.08	170.27	25.05
95% CI lower	46.15	68.66	167.81	24.08
Standard deviation	13.02	10.60	7.60	3.01
CV	0.27	0.15	0.04	0.12
2 sample Student's t-test p	0.740128	0.581735	0.581729	0.678494

Baseline data were overall well balanced between treatment arms with regards to demographic parameters.

There were 41.9% men and 58.1% women in the Symbioflor 2 arm and 46.0% men and 54.0% women in the placebo arm respectively. The gender distribution in both treatment arms, while not identical, was overall well balanced and in line with the expected 1:2 distribution encountered in this disease in the overall population.

Symptoms at baseline by treatment arms are presented in table 3.

Table 3: Symptoms at baseline by treatment arms (Efficacy data set)

Parameter / Symptom	Treatment	Total	yes		no		No data		Missing	
		N	N	%	N	%	N	%	N	%
Have you come because of abdominal pain?	Verum	148	148	100.0%						
	Placebo	150	150	100.0%						
Do you have wind frequently?	Verum	148	146	98.6%	1	0.7%	1	0.7%		
	Placebo	150	147	98.0%	3	2.0%				
Do you often have diarrhoea or constipation?	Verum	148	146	98.6%	1	0.7%	1	0.7%		
	Placebo	150	150	100.0%						
Have you had your discomfort for more than one year?	Verum	148	126	85.1%	20	13.5%	2	1.4%		
	Placebo	150	127	84.7%	21	14.0%			2	1.3%
How would you describe your abdominal pain: burning?	Verum	148	47	31.8%	75	50.7%	26	17.6%		
	Placebo	150	26	17.3%	87	58.0%	37	24.7%		
cutting?	Verum	148	22	14.9%	100	67.6%	26	17.6%		
	Placebo	150	28	18.7%	84	56.0%	38	25.3%		
very severe?	Verum	148	33	22.3%	89	60.1%	26	17.6%		
	Placebo	150	21	14.0%	91	60.7%	38	25.3%		
terrible?	Verum	148	2	1.4%	119	80.4%	27	18.2%		
	Placebo	150	5	3.3%	108	72.0%	37	24.7%		
Sensation of pressure?	Verum	148	65	43.9%	58	39.2%	25	16.9%		
	Placebo	150	79	52.7%	43	28.7%	28	18.7%		
dull?	Verum	148	43	29.1%	80	54.1%	24	16.2%	1	0.7%
	Placebo	150	49	32.7%	73	48.7%	28	18.7%		
boring?	Verum	148	25	16.9%	97	65.5%	26	17.6%		
	Placebo	150	33	22.0%	88	58.7%	29	19.3%		
tolerable?	Verum	148	43	29.1%	80	54.1%	25	16.9%		
	Placebo	150	46	30.7%	75	50.0%	29	19.3%		
Are there any findings or information in the patient's history to indicate a diagnosis other than irritable bowel syndrome?	Verum	148			148	100.0%				
	Placebo	150			149	99.3%			1	0.7%
Erythrocyte sedimentation rate >20 mm/2 h?	Verum	148	23	15.5%	125	84.5%				
	Placebo	150	29	19.3%	120	80.0%			1	0.7%
Leuocyte count > 10,000/mL?	Verum	148			148	100.0%				
	Placebo	150			146	97.3%	2	1.3%	2	1.3%
Hb <12 g% in women or <14 g% in men?	Verum	148			146	98.6%			2	1.4%
	Placebo	150			148	98.7%	1	0.7%	1	0.7%
Has there been evidence of blood in the stool once before?	Verum	148			147	99.3%			1	0.7%
	Placebo	150			148	98.7%			2	1.3%

Overall, baseline characteristics were well balanced between treatment arms. ¾ of the patients had alternating bowel habits.

The distribution of the Kruis score values is shown in table 4.

Table 4: Frequencies of patients with various clinical scores by treatment arm:

Clinical score [points]	Frequencies N		
	Verum	Placebo	Total
87	79	76	155
84	1		1
83	2		2
74	16	20	36
73	25	23	48
71	12	12	24
66		1	1
60	3	6	9
58	2	1	3
57	5	8	13
53	1	2	3
44	2	1	3
Total	148	150	298

76.4% of patients taking Symbioflor 2 and 74.7% of patients taking placebo presented with alternating diarrhoea and constipation. In addition, respectively 22.3% of the patients in the Symbioflor 2 arm and 14% of the patients in the placebo arm rated their symptoms as being severe, and 1.4% and 3.3% as “terrible”, and only 29% and 30% as “tolerable”.

34% of the patients taking Symbioflor 2 and 39% in the placebo arm had one or more comorbidities. There were no relevant differences between the treatment arms. Most frequent concomitant diseases were diabetes mellitus, hypertension, coronary heart disease, bronchitis, and hyperuricaemia. There were also no notable differences between the treatment arms with regards to the number of patients with previous surgery and the time elapsed with complaints.

Outcomes and estimation

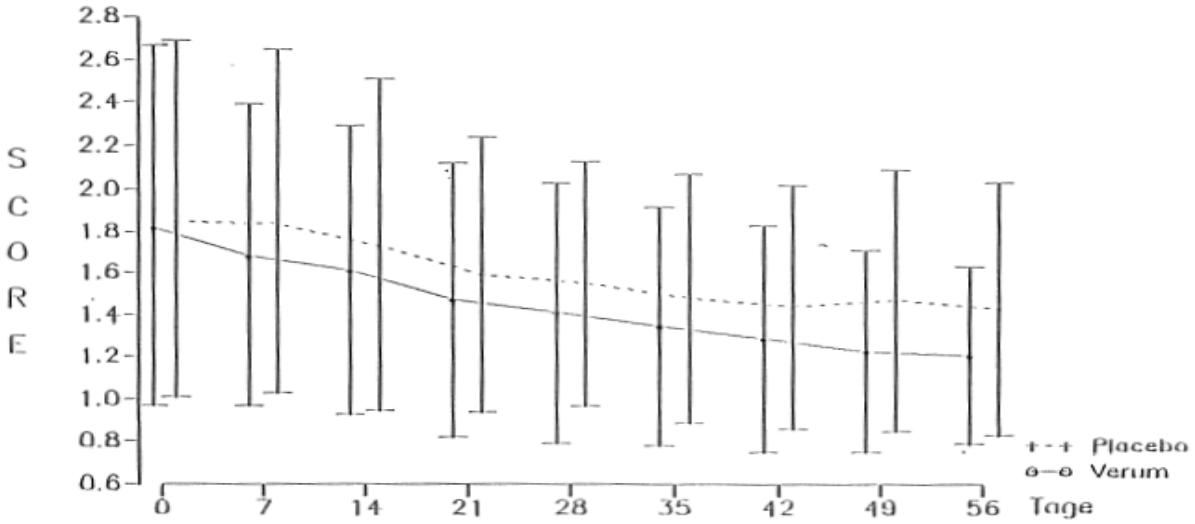
Final Study Report of Study S2 (1989)

The analysed parameters were reported numerically. No statistical analysis was included in this report.

General health

Changes in the means and standard deviations for the endpoint “general health” are presented in Figure 2.

Figure 2: Changes in the means and standard deviations – general health:

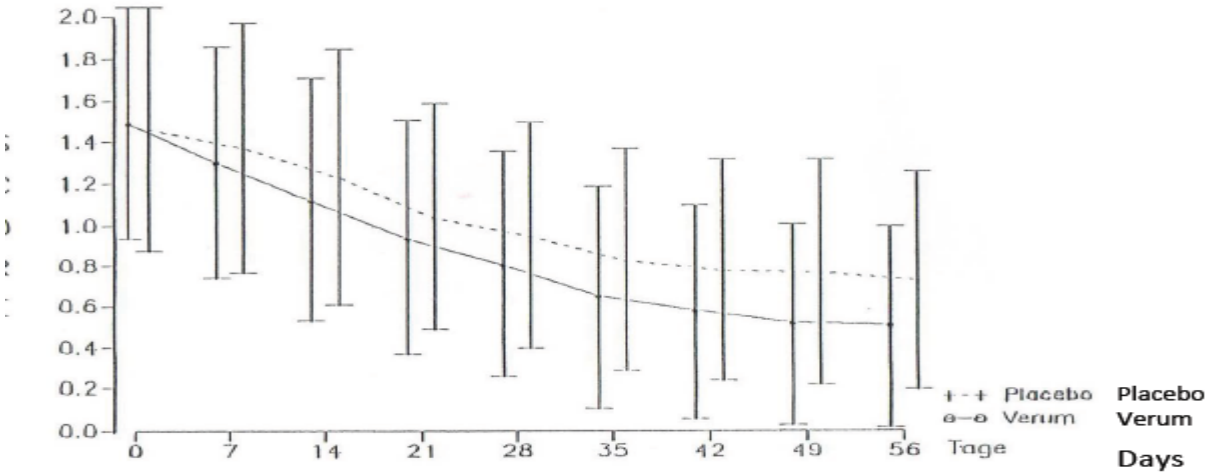


"General health" was comparable in both arms at the start of treatment, and in the range of fair to very poor for 55% of the patients in the Symbioflor 2 arm and for 58% in the placebo arm (mean score = 2). A marked improvement was observed in patients taking Symbioflor 2 over the course of the study compared to a slight improvement in the placebo arm. At the final evaluation on day 56, 80% of the cases were rated as good in the Symbioflor 2 arm compared to 63% in the placebo arm.

Pain

Mean pain scores are presented in figure 3.

Figure 3: Mean pain scores



"Pain" was a composite of the symptoms "upper abdomen pain", "lower abdomen pain", "pain before and after eating", and "diffuse pain". Frequency and severity of "spontaneous pain" and "pain during palpation" were initially comparable. In the course of the eight-week study and weekly evaluation, there was improvement in both the Symbioflor 2 and placebo arms for "upper abdominal pain" and "lower abdominal pain", "diffuse pain, before and after meals and during the night" and "palpation of the stomach, gall bladder region and colon". In the three groups, improvement was higher in the Symbioflor 2 arm than in the placebo arm.

Stools

At the start of the Study, stool consistency was rated “watery” or “mushy” in approximately 40% in the Symbioflor 2 arm and in 34% in the placebo arm and “normal” in 13% in the Symbioflor 2 arm and in 9% in the placebo arm. Over the course of treatment, stool normalisation was seen in 57% in the Symbioflor 2 arm and in 37% of the placebo arm. The stool frequency per day decreased from an average of 1.22 to 0.96 in the Symbioflor 2 arm and showed no change in the placebo arm (1.14).

Symptom parameters heartburn, belching, nausea, bloating, vomiting, borborygmus, flatulence, headache, depression, loss of appetite and sleep disorders, which had been rated using a five-point score, were comparable at the start of the study. As expected, flatulence, bloating and borborygmus were the highest. At the end of the study, there were higher improvements in the mean of all symptoms in the Symbioflor 2 arm than in the placebo arm. It was however unclear whether the numerical differences were sufficiently pronounced to reach statistical significance.

Re-evaluation report of Study S2 (2005)

Analysis of the co-primary endpoints

The first primary endpoint was “Patient-specific global assessment of the symptoms” after 8 weeks of continuous treatment (Visit 9). The response rate was 18.2% (n=27 out of 148 patients) in the Symbioflor 2 arm and 4.67% (n=7 of 150 patients) in the placebo arm (p=0.00397).

The second primary endpoint was “Patient-specific assessment of abdominal discomfort/pain” after 8 weeks of continuous treatment (visit 9). The response rate was 18.9% (n=28 out of 148 patients) in the Symbioflor 2 arm and 6.67% (n=10 of 150 patients) in the placebo arm (p=0.001649).

Table 5 present the results for the parameter “Spontaneous pain: lower abdomen”.

Table 5: Symptom score “Spontaneous pain: lower abdomen” after dichotomisation into the categories “symptom-free” and “symptoms of IBS” at Visit 1 (baseline) and Visit 9 (after 56 days of treatment with active or placebo).

Visit 1			
Treatment group	Frequency N		
	Symptom-free	Symptoms of IBS	Total
	+	-	
Verum	11	137	148
	7.43% (95% CI: 5.71–16.0%)		
Placebo	12	138	150
	8.00% (95% CI: 22.5–37.8%)		
Total	23	275	298
Statistics test		p-value	
Fisher’s exact test (two-sided)		1.000000	
Visit 9			
Treatment group	Frequency N		
	Symptom-free	Symptoms of IBS	Total
Verum	72	76	148
	48.6% (95% CI: 40.4 - 57.0 %)		
Placebo	51	99	150
	34.0% (95% CI: 26.5 - 42.2 %)		
Total	123	175	298
Statistics test		p-value	
Fisher’s exact test (two-sided)		0.013345	

Table 6 present the results for the parameter “Spontaneous pain: diffuse”.

Table 6: Symptom score “Spontaneous pain: diffuse” after dichotomisation into the categories “symptom-free” and “symptoms of IBS” at Visit 1 (baseline) and Visit 9 (after 56 days of treatment with active or placebo)

Visit 1			
Treatment group	Frequency N		
	Symptom-free	Symptoms of IBS	Total
	+	-	
Verum	29	119	148
	19.6% (95% CI: 13.5 – 26.9%)		
Placebo	26	124	150
	17.3% (95% CI: 11.6 – 24.4%)		
Total	55	243	298
Statistics test		p-value	
Fisher’s exact test (two-sided)		0.655848	
Visit 9			
Treatment group	Frequency N		
	Symptom-free	Symptoms of IBS	Total
Verum	74	74	148
	50.0% (95% CI: 41.7 – 58.3%)		
Placebo	56	94	150
	37.3% (95% CI: 29.6 – 45.6%)		
Total	130	168	298
Statistics test		p-value	
Fisher’s exact test (two-sided)		0.035331	

The analysis of the parameter “Pain on palpation: gall baldder” showed that 88.5% of the patients receiving Symbioflor 2 and 69.3% of the patients receiving placebo were symptom-free at the end of the treatment (p=0.000059).

The analysis of the parameter “Spontaneous pain on palpation: Colon” showed that 42.5% (95% CI: 34.5–51.0%) of the patients receiving Symbioflor 2 and 28.0% (95% CI: 21.0–35.9%) of the patients receiving placebo were symptom-free at the end of the study (p=0.000059). At the end of treatment, the frequencies for the grade “none” were n=63 for Symbioflor 2 and n=42 for placebo respectively.

The MAH also provided the p-value for the following parameters: “sigmoid colon: palpability” (p=0.000145); “bloating” (p=0.001160); “pain frequency” (p=0.000113), “overall well-being” (p=0.004963).

Table 7 and 8 present the results for the parameter “stool consistency”.

Table 7: “Stool consistency” after dichotomisation into the categories “symptom free” and “symptoms of IBS” at Visit 1 (baseline) and Visit 9 (after 56 days of treatment with active or placebo)

Visit 1			
Treatment group	Frequency N		
	Symptom-free	Symptoms of IBS	Total
	+	-	
Verum	19	129	148
	12.8% (95% CI: 7.90 – 19.3%)		
Placebo	14	136	150
	9.33% (95% CI: 5.19 – 15.2%)		
Total	33	265	298
Statistics test		p-value	
Fisher's exact test (two-sided)		0.361061	
Visit 9			
Treatment group	Frequency N		
	Symptom-free	Symptoms of IBS	Total
Verum	83	65	148
	56.1% (95% CI: 47.7 – 64.2%)		
Placebo	56	94	150
	37.3% (95% CI: 29.6 – 45.6%)		
Total	139	159	298
Statistics test		p-value	
Fisher's exact test (two-sided)		0.001671	

Table 8: Symptom 'stool frequency' after dichotomisation into the scores 'normal' and 'abnormal' according to the recommendation from the EMA [8] in visit 1 (before treatment) and in visit 9 (after 56 days on active or placebo).

Visit 1			
Treatment group	Frequency N		
	Symptom-free	Symptoms of IBS	Total
	+	-	
Verum	138	10	148
	93.2% (95% CI: 87.9–96.7%)		
Placebo	139	11	150
	92.7% (95% CI: 87.3–96.3%)		
Total	277	21	298
Statistics test		p-value	
Fisher's exact test (two-sided)		1.000000	
Visit 9			
Treatment group	Frequency N		
	Symptom-free	Symptoms of IBS	Total
Verum	147	1	148
	99.3% (95% CI: 96.2–100%)		
Placebo	144	6	150
	96.0% (95% CI: 91.5–98.5%)		
Total	139	159	298
Statistics test		p-value	
Fisher's exact test (two-sided)		0.120640	

The analysis of the parameter "Stool consistency" was statistically significant between treatment arms at visit 9 (p=0.001671) when analysed with the criteria "symptons free" vs "symmptoms of IBS" but was not statistically significant analyzed with the criteria "normal" vs "abnormal" (p=0120640) .

Table 9 presents the results for global assessment of efficacy by the Investigator at the end of the treatment period:

Table 9: Frequencies N and relative proportions of the sample of the scores for the 'global medical assessment of the efficacy of the investigational medicinal product' assessed after 8 weeks' treatment of IBS with either active or placebo. Randomised patients: N=148 active; N=150 placebo, n=1 (active, patient 246) and n=2 (placebo; patients 244 and 266) missing assessments due to termination of the study.

Score	Global medical assessment of the efficacy of the investigational medicinal product			
Frequencies	N	%	N	%
Treatment	Verum		Placebo	
1 = very good	43	29.1%	16	10.7%
1.5 = good – very good	-	-	1	0.7%
2 = good	50	33.8%	42	28.0%
3 = satisfactory	30	20.3%	46	30.7%
4 = unsatisfactory	24	16.2%	43	28.7%
Missing	1	0.7%	2	1.3%
Total	148	100.0%	150	100.0%

The χ2 test of independence was rejected with p=0.000121 (2 × 4 contingency table with consolidation of scores 1 and 1.5 for placebo; n=295. The results indicate that the score is distributed differently between placebo and verum. There were more favourable assessments for verum than for placebo. Conversely, there were more frequent assessments with the unfavourable scores 'satisfactory' and 'unsatisfactory' for the placebo.

Other symptoms:

Similarly, the following symptoms also showed statistical significance at visit 9 for "Pain on palpation – stomach", "pain after eating", "pain at night", "belching", "vomiting", "borborygmus", "flatulence", "headaches", "sleep disorder" and "depression".

The following symptoms did not show a statistically significant difference: "spontaneous pain – upper abdomen", "pain before eating", "heartburn", "nausea", and "loss of appetite".

Ancillary analyses

Centre effect

The MAH evaluated whether the frequencies of symptom-free patients with regards to the primary and secondary endpoints was well balanced between centres. Centres 2, 8, 10, 14, 15, 19 and 20 recruited less than 6 patients each. In order to enable a comparison with the 'large' centres, the frequencies for these centres were pooled to create a 'new' centre 100. In 5 centres the frequency of symptom-free patients (responders) was higher for Symbioflor 2 than for placebo (centres 6, 9, 12 and 13 and the pooled centre). In centre 7, the frequency of responders for placebo was the same as for Symbioflor 2.

The evaluation conducted for the primary endpoint is shown in the table below:

Table 70 **Patient-specific global assessment of the symptoms:** Frequencies N of symptom-free patients (responders) and patients with one or more typical IBS symptoms (non-responders) in visit 9.

Tab. 70 continued.

Treatment group	Patient-specific global assessment of the symptoms Visit 9: After treatment Frequencies N		
	Symptom-free	IBS symptom present	Total
Centre = 1			
Verum	0	5	5
Placebo	0	6	6
Total	0	11	11
Centre = 3			
Verum	0	6	6
Placebo	0	6	6
Total	0	12	12
Centre = 4			
Verum	0	6	6
Placebo	0	6	6
Total	0	12	12
Centre = 5			
Verum	0	27	27
Placebo	0	27	27
Total	0	54	54
Centre = 6			
Verum	14	10	24
Placebo	0	24	24
Total	14	34	48
Centre = 7			
Verum	7	5	12
Placebo	7	5	12
Total	14	10	24
Centre = 9			
Verum	3	3	6
Placebo	0	6	6
Total	3	9	12

There was significant heterogeneity between centres in 3 out of 6 symptom-score outcomes, as well as for the global physician's assessment of efficacy. The centre responsible for the most significant heterogeneity was centre 6. If centre 6 was excluded from the analyses, statistical significance was lost for both co-primary variables, as well as for the physician's global assessment endpoint.

Evaluation by gender

The evaluation by gender is shown in table 10 below:

Table 10: Response for the first (patient-specific global assessment of the symptoms) and the second primary (patient-specific assessment of abdominal discomfort /pain) endpoints for active and placebo reported separately by sex. Efficacy data set (N=148 active; N=150 placebo).

Patient-specific global assessment of the symptoms Frequencies N				
Sex = m				
	Symptom-free	IBS symptom	Total	
Verum	14	48	62	
Placebo	5	64	69	
Total	19	112	131	131
Sex = f				
	Symptom-free	IBS symptom	Total	
Verum	13	73	86	
Placebo	2	79	81	
Total	15	152	167	167
				298
Patient-specific assessment of abdominal discomfort / pain Frequencies N				
Sex = m				
	Symptom-free	IBS symptom	Total	
Verum	15	47	62	
Placebo	5	64	69	
Total	20	111	131	131
Sex = f				
	Symptom-free	IBS symptom	Total	
Verum	13	15	86	
Placebo	5	5	81	
Total	18	20	167	167
				298

Only marginal differences were seen between genders with a slightly higher response rate in males compared to females. A discrepancy was noted in the number of female patients with IBS symptoms in the second primary endpoint where it is stated 20 when the total should be 149 (the total of 167 minus the 18 responders).

Evaluation by Age

The evaluation by age is presented in table 11.

Table 11: Response for the first (patient-specific global assessment of the symptoms) and the second primary (patient-specific assessment of abdominal pain / discomfort) endpoints for active and placebo stratified by age. Efficacy data set (N=148 active; N=150 placebo).

Patient-specific global assessment of the symptoms Frequencies N				
Age group = < 40 years				
	Symptom-free	IBS symptoms	Total	
Verum	9	23	32	
Placebo	5	31	36	
Total	14	54	68	68
Age group = 40–59 years				
	Symptom-free	IBS symptoms	Total	
Verum	15	74	89	
Placebo	2	81	83	
Total	17	155	172	172
Age group = > 60 years				
	Symptom-free	IBS symptoms	Total	
Verum	3	24	27	
Placebo	0	31	31	
Total	3	55	58	58
				Total: 298
Patient-specific assessment of abdominal discomfort/pain Frequencies N				
Age group = < 40 years				
	Symptom-free	IBS symptoms	Total	
Verum	9	23	32	
Placebo	6	30	36	
Total	15	53	68	68
Age group = 40–59 years				
	Symptom-free	IBS symptoms	Total	
Verum	16	73	89	
Placebo	3	80	83	
Total	19	153	172	172
Age group = > 60 years				
	Symptom-free	IBS symptoms	Total	
Verum	3	24	27	
Placebo	1	30	31	
Total	4	54	58	58
				Total: 298

The response rate was 28.8% in the Symbioflor 2 arm and 13.9% in the placebo arm in the age group < 40 years, 16.9% and 2.4% in the age group 40–59 years and 11.0% and 0% in the age group > 60 years respectively. The response rates declined with the age of the patients. The rates between Symbioflor 2 (11%) and placebo (14.5%) didn't significantly vary between the age classes.

Per-protocol dataset:

The evaluations for the two primary endpoints per-protocol population are presented in tables 12&13.

Table 12: Exact Fisher's test for the first primary endpoint patient-specific global assessment of the symptoms in the per-protocol data set (without LVCF)

Treatment	Symptom-free	IBS symptoms	N
	+	-	
Verum	27 (18.6%)	118 (81.4%)	145 (100.0%)
Placebo	7 (4.76%)	140 (95.2%)	147 (100.0%)
N	34	258	292
Test statistic	Value	DF	Prob
Fisher's exact test (two-tailed)			0.000390 ***

Table 13: Exact Fisher's test for the second primary endpoint patient-specific assessment of abdominal discomfort / pain on the per-protocol data set (without LVCF)

Treatment	Symptom-free	IBS symptoms	N
	+	-	
Verum	28 (19.3%)	117 (80.7%)	145 (100.0%)
Placebo	10 (6.80%)	137 (93.2%)	147 (100.0%)
N	38	254	292
Test statistic	Value	DF	Prob
Fisher's exact test (two-tailed)			0.001622 **

Based on the responder definition for the general symptom score, 27/148 (18.2 %) patients in the Symbioflor 2 arm were free of symptoms at visit 9 (=last visit), and 7/150 (4.67%) in the placebo arm (p=0.000397). For the abdominal pain score, the response rate was 28/148 (18.9%) in the Symbioflor 2 arm and 10/150 (6.67%) in the placebo arm (p=0.001649). Symbioflor 2 was better than placebo in improving all but one individual IBS symptoms.

The primary endpoints were also evaluated for the per-protocol data set to assess if the missing observations had any effect on the study result. Results assessed as per the protocol data sets and the full population dataset were similar.

Meta-analyses

The MAH submitted several meta-analyses and reviews of the efficacy of prebiotics, probiotics, or synbiotics in the treatment of IBS as supportive evidence. All reviews state that the quality of some of the studies reviewed is rather limited. One meta-analysis (Ford, 2014) performed a literature search in MEDLINE, EMBASE databases and Cochrane Controlled Trials Register in order to identify randomized clinical trials recruiting adults with IBS. 43 randomised clinical trials were eligible for inclusion. This meta-analysis concluded that probiotics are effective therapies for IBS, in terms of both improvement in overall symptoms as a dichotomous measure and improvement in global symptom, abdominal pain, bloating, and flatulence scores. However, the only meta-analysis that included Symbioflor 2 (Enck, 2009, 2016) did not include any new data on Symbioflor 2 in addition to the data already presented in the re-evaluation of study S2.

2.2.2.2. Efficacy and safety in children and adolescents with Irritable Bowel Syndrome

The claim for the indication in the treatment of irritable bowel syndrome (IBS) is based on an observational non-interventional study in 203 children and adolescents conducted between 2007 and 2008 in Germany, as supportive data, entitled “Efficacy and tolerability of Symbioflor 2 in children with Irritable Bowel Syndrome”.

This study was conducted in 2 age groups (4–11 and 12–18 years) who had not previously received Symbioflor 2 for irritable bowel syndrome at approximately 14 paediatric private practices. Patients with known colon polyps, lactose intolerance, and coeliac disease were excluded from the study.

In line with the non-interventional nature of the observations, the number of visits and the time between visits as well as the nature and timing of visits were determined by the treating physicians on an individual basis. To assess the success of the treatment, it was advisable to conduct an interim examination around 2 weeks after the initial examination, followed by a final examination after about 3 months of treatment. The data to be recorded, including the recording of adverse events, at the initial visit, at one interim visit, and at the end of the observation period were clearly defined.

The study protocol stated that any biometric analysis was considered explorative in nature. There was no hypothesis to be tested formally.

Baseline characteristics

There were no significant differences among the four clinical types of irritable bowel syndrome with regards to the mean age ($p = 0.4318$), the mean weight ($p = 0.9256$, adjusted for age) and the mean height of the patients ($p = 0.5218$, adjusted for age).

The majority of patients were female is both age groups and for all clinical types. In the age group of 12–18 years, on average, one in four patients was male and in the age group of 4–11 years, one in three patients was male. The gender distribution did not vary significantly among the four clinical types of irritable bowel syndrome ($p = 0.2023$, adjusted for age).

Dosing of study medication, duration of treatment and concomitant medication

77.4% of children and adolescents received the dose of Symbioflor 2 recommended for children. This percentage was 95.2% in children between the ages of 4 and 11 years and 59.7% in adolescents.

Symbioflor 2 was administered at a constant dose in nearly 95% of the cases. Dose changes were rare except in two subgroups (12–18-year-old patients with the clinical type ‘pain + constipation’ (dose was increased in 20.7% of the cases) and 12–18-year-old patients with unspecified pain (dose was increased in 9.1% of the cases)).

Concomitant therapy had generally no or negligible impact on the treatment outcomes with Symbioflor 2.

The mean length of treatment with Symbioflor 2 in both age groups and for each clinical type of irritable bowel syndrome was 40–50 days except in the subgroup with ‘pain, unspecified’ in the age group of 12–18-year-old patients, which was treated for an average of only 34 days.

Outcomes and estimation

Stool frequency

At initial examination, the mean number of stools in the four groups: ‘pain + diarrhoea’, ‘pain + constipation’, ‘pain + alternating diarrhoea/constipation’ and ‘pain, unspecified’ were 3.35, 0.39, 1.90

and 1.28 respectively. At final examination, the data for the respective groups reflected a normalisation of the bowel movements (1.26/0.83/1.12/1.07). There were no significant differences among age groups (p = 0.8241).

Stool consistency

As expected, stool consistency varied greatly at initial examination among the four clinical types of IBS. The majority of patients reported 'liquid' consistency (66.0%) for the clinical type 'pain + diarrhoea', a 'hard/lumpy' consistency (92.9%) for the clinical type 'pain + constipation', 'alternating consistency' (57.1%) for the clinical type 'pain + alternating diarrhoea/constipation', and 'well-formed' consistency (53.6%) for the clinical type 'pain, unspecified'. At final examination, the majority of patients had normalised bowel movements and reported a 'well-formed' consistency (82.0%/83.9%/67.9%/85.5%) in all four groups. There were no significant differences among age groups (p = 0.1151).

Blood in mucus or stool

At initial examination, 26.6% of the patients reported having mucus in their stool and 3.0% of the patients reported having blood in their stool. At final examination, no patient reported having blood or mucous in their stool. There were no significant differences among age groups and the four clinical types of irritable bowel syndrome. No significance tests could be performed for the final examination due to the low number of data.

Abdominal pain

At initial examination 63.5% of the patients had frequent abdominal pain and 35.0% of the patients had occasional abdominal pain. At final examination, 6.4% of the patients had frequent abdominal pain and 32.5% of the patients had occasional abdominal pain. This effect was statistically significant (p < 0.0001). There were no significant differences among age groups and the four clinical types of irritable bowel syndrome (p = 0.5624).

Meteorism

At initial examination 42.9% of the patients had 'frequent' meteorism and 42.4% of the patients had 'occasional' meteorism. At final examination, 2.0% of the patients had 'frequent' meteorism and 25.6% of the patients had 'occasional' meteorism. This effect was statistically significant (p < 0.0001). There were no significant differences among age groups and the four clinical types of irritable bowel syndrome (p = 0.7936 and p = 0.1191 respectively).

Flatulence

At initial examination, 19.2% of the patients had 'frequent' and 46.3% of the patients had 'occasional' flatulence. At final examination, 0.0% of the patients had 'frequent' flatulence and 12.8% of the patients had 'occasional' flatulence. This effect was statistically significant (p < 0.0001). There were no significant differences among age groups and the four clinical types of irritable bowel syndrome (p = 0.5995).

Stool passage

The percentage of patients who mentioned 'straining' decreased from 45.8% at initial examination to 29.6% at final examination. At the same time, the percentage of patients who mentioned urgent need to defecate increased from 50.7% at initial examination to 66.5% at final examination. This effect was statistically significant (p = 0.0002). There were no significant differences among age groups and the four clinical types of irritable bowel syndrome (p = 0.6369).

Global assessment of efficacy by the physician and patients

The efficacy of the treatment was rated ‘very good’ or ‘good’ in the majority of cases (81.8%) for all age groups and every clinical type of irritable bowel syndrome. The lowest rating was obtained for the patients in the 12–18 year group with the clinical type ‘pain + alternating diarrhoea/constipation’, for whom the treatment was rated ‘very good’ or ‘good’ by 55.5% of the patients.

The global assessment of the efficacy of the treatment with Symbioflor 2 by the patients or their parents was qualitatively in line with that of the participating physicians. The efficacy of the treatment was rated ‘very good’ or ‘good’ in all age groups and for all clinical types of irritable bowel syndrome by 83.3% of the patients.

2.2.3. Analysis of efficacy

The MAH submitted several publications. These were meta-analyses and reviews of the efficacy of prebiotics, probiotics, or synbiotics in the treatment of IBS as supportive evidence. Individual strains of probiotics may have different effects, and thus, benefits observed clinically with one species or with a combination of species cannot be generalized to another. In addition, there are limitations to the systematic reviews and meta-analyses presented, which arise from the nature of the studies available for synthesis. Notably, there was evidence of heterogeneity between the clinical trials included in those meta-analyses and bias in the different studies was not assessed. However, the only meta-analysis that included Symbioflor 2 (Enck, 2009, 2016) did not include any new data on Symbioflor 2 in addition to the data already presented in the re-evaluation of study S2 and therefore no further discussion was warranted.

2.2.3.1 Indication in the treatment of functional gastrointestinal disorders

Apart from data on IBS, no data were submitted in support of the indication gastro-intestinal disorders.

2.2.3.2 Indication in the treatment of irritable bowel syndrome in adults

Inclusion/Exclusion criteria

Study S2 included male and female patients diagnosed with IBS based on the “Kruis criteria”. The choice of the Kruis criteria, a partially validated tool to identify patients with IBS, was acceptable for the diagnosis of IBS at the time the study was conducted. It is however noteworthy that the “Kruis criteria” do not allow distinguishing patients by subtype of IBS because the Kruis criteria diagnoses “irregularities” of bowel movements but do not capture specific abnormality of stools and/or defaecation. It also not possible to conclude the population was a population with mild disease because, although study participants were patients from primary care, and had a balanced gender distribution, the criteria for disease severity were not defined.

The treatment duration of 8 weeks used in Study S2 was acceptable, although there was no run-in period, which is usually required in order to assess the pattern of symptoms experienced by the patients and exclude those patients with the most inconsistent pattern.

Endpoints

“Global evaluation” of efficacy by the Investigator at the end of the trial was chosen as the primary endpoint of the trial. The endpoints used in the trial were partly relying on physical examination by the treating physician, without recording the symptoms experienced by the patients on a daily basis. The recording of symptoms was done on a weekly basis, whereas the global assessments were only

conducted at the end of the treatment. The choice of this endpoint is questionable given the endpoint was only assessed at a single point in time at the end of the study and could be regarded as subjective as it reflects the impressions of the investigator regarding the overall well-being of the patients and is subject to what the patient recalls over the totality of the treatment period. In this type of disease, a patient-related or –reported outcome would have been regarded to be more clearly indicative of the overall well-being of the patient. In addition, neither the primary outcome measure, the primary hypothesis to be tested in the trial, the sample size nor the statistical methods to be applied were specified in the protocol despite the fact that the principles of statistical methodology were already then well established. It cannot be excluded that significant bias confounded the results and the study should therefore only be regarded as exploratory.

The definition of "global assessment" in Study S2 also differs from the one defined in the guideline (CPMP/EWP/785/97, 2003) in place at the time of the re-evaluation of Study S2. It was in fact limited to the inclusion of symptom evaluation of abdominal pain, abnormal defaecation, and abdominal distension. Potential influences of somatisation, depression and other extra-intestinal "manifestations" of IBS were not included. "Abdominal pain" was quantified by patients at the time of study visits and consisted of scores which included not only "spontaneous pain" but also "palpation related pain". The latter is acceptable in the context of functional disease, in which it is required to record the spontaneous symptomatology on a continuous basis. The MAH explained that this practice was recommended by scientific guidelines (World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians (WONCA)) and German Society of Digestive and Metabolic Diseases (DGVS, 2011)) in force at the time. The DGVS guideline does not, however, include such recommendation. The WONCA guideline was not provided.

"Abnormal defecation" consisted of "stool consistency", "stool frequency", and "palpable sigmoid colon". It is, however, unclear whether the "palpability" of the sigmoid is in any way related to the subjective well-being of a patient. Moreover, "stool frequency" was only defined post-hoc with a score of 0 for normal (where normal was defined with a weekly frequency of 3/week up to 3/day) and 1 for abnormal (all other categories). It was left to the investigator to interpret whether the daily stool frequency of 3/day was meant as a maximum daily stool frequency during the last week, an average over the week or the stool frequency the day before the corresponding visit. Abdominal pain/discomfort included not only the spontaneous pain categories and bloating (which is considered adequate), but also stool frequency and stool consistency, which are not necessarily related to pain but also measures defaecation related outcomes. Finally, the planned assessment was not based on the evaluation of response over time, but on the occurrence of "freedom from symptoms" at a single point in time and therefore did not take into account fluctuations (waning and flares) characterising IBS.

Statistical methods

Regarding the statistical analysis methods, the Fisher's exact test could have been considered appropriate if it had been pre-specified in advance. However, the statistical analysis methods were not pre-specified before the actual conduct of the trial but only before the re-evaluation of Study S2. It was therefore not possible to control the Type-1 error. The re-evaluation was conducted in full knowledge of the study results and it can therefore not be excluded that significant bias has confounded the results.

The application and validity of the missing data imputation also remains unclear, for example, in case of single missing data. E.g., stool frequency per day was missing in some cases even if the weekly stool frequency was greater than 3 (see e.g. sample CRF provided from Patient 228, visit 3). It remains unclear whether this could have affected the primary endpoint.

Baseline characteristics

Overall, baseline characteristics were well balanced between treatment arms. 3/4 of the patients had alternating bowel habits. Because the selection criteria differ, it was however unclear whether these baseline characteristics define an "IBS-M" ("mixed type" comprising both bowel movements with BSSF 1 and 6) according to Rome IV population.

Regarding the severity of the disease and although the number of discontinuation was low, it was not possible to conclude whether this was an indicator of the good tolerability of the compound and/or the overall good health status of the patient (e.g. patients with disease of mild severity).

It was also noteworthy that 76.4% of patients taking Symbioflor 2 and 74.7% of patients taking placebo presented with alternating diarrhoea and constipation. It therefore appears that the patients suffered from a relatively high level of episodes, although this finding was not necessarily reflective of the severity of the disease (14 points being scored solely by the presence of alternating bowel habits).

Finally, respectively 22.3% of the patients in the Symbioflor 2 arm and 14% of the patients in the placebo arm rated their symptoms as being severe, and 1.4% and 3.3% as "terrible", and only 29% and 30% as "tolerable". Again this finding may not be reflective of the severity of the disease, as this could be also interpreted as more than two-thirds of patients were suffering from "intolerable" symptoms.

Outcomes and estimation

The evaluation made in the initial report in 1989 showed that Symbioflor 2 had better outcomes than placebo on most of the evaluated endpoints. Overall, the graphical evaluations presented by the MAH indicated that the decrease in symptom score was more important in the Symbioflor 2 than in the placebo arm. The superiority of the Symbioflor 2 arm over placebo was however not consistent across all the parameters assessed. In addition, the decision to pool the pain scores and the "other symptoms" was been made post-hoc. Statistical evaluations having not been included a priori into the initial study report (1989), any conclusion with regards to the statistical significance and the strength of the statistical significance and the magnitude of the effect would therefore be speculative.

The re-evaluation of this trial was conducted in 2005 re-defining the endpoints, combining parameters of a patient-centred assessment of spontaneous symptoms with endpoints based on physical examination by the physician. The newly defined primary endpoints in this re-evaluation were designed evaluated with adequate statistical methodology and were strict with regards to treatment success, because only patients completely free of symptoms were counted as "responders". The analyses showed statistical significant superiority of the active treatment over placebo in almost all endpoints evaluated. The findings were consistent across age and gender subgroups.

Several possible deficiencies were, however, noted during the assessment of the data presented by the MAH. The most notable are presented below:

Conduct of the study

Centres 5 and 6 recruited respectively 54 and 48 patients. Centre 5 recruited (visit 1) 10 patients every Monday or Thursday between 10 October 1988, and 26 October 1988 (The last 4 patients were recruited on 2 November 1988). Centre 6 recruited 42 of the 48 patients within one week, recruiting between 6 and 10 patients a day. For both centres all subsequent 8 study visits occurred according to the study plan on the same day every week for all patients with only one exception for one patient in centre 6. In centre 5, the study visits for 10 patients (3 patients at study visit 3 and 7 patients at study

visit 4) occurred as scheduled in the study plan on the 16th November, 1988, which was a public holiday in this region of Germany.

The MAH stated that upon investigation by the German national competent authority (BfArM), "one large centre of the study was inspected by the competent supervisory authority on 24th August, 2004, without any objection". The inspection report was however not presented by the MAH and it was subsequently clarified that the inspection did not concern study S2 but another study with the same Investigator.

It cannot be verified any longer if these possible deficiencies may constitute a breach in the conduct of the trial and what impact these data may have on the results as the source data are no longer available. Although most of the differences related to the safety evaluation and Good Clinical Practices were not in place at the time of the conduct of the study, these findings cast further doubt on the robustness of the presented data and contribute to the uncertainty of the magnitude of the benefit of Symbioflor 2 in IBS.

2.2.3.3 Indication in the treatment of irritable bowel syndrome in children and adolescent

The study "Efficacy and tolerability of Symbioflor 2 in children with Irritable Bowel Syndrome" was conducted in 2008 as a non-interventional, uncontrolled observational study. The confirmation of the diagnosis of IBS according to the Rome III criteria by the investigator was an inclusion criteria. Non-interventional studies document efficacy and safety of a medicinal product prescribed as part of normal clinical practice. A control arm is normally not involved. There is no intervention in the medical treatments. In particular, the treating physician would not undertake any measures that would not also have been applied outside the study due to the medical needs of the individual patients with the medicinal product used here.

The observational study in children reported mainly global evaluations of efficacy (and safety). Overall, the results indicated a very high treatment success rate based on the ratings from both the physicians and the patients. The individual symptoms of irritable bowel syndrome (number of stools, stool consistency, blood or mucus in the stool, abdominal pain, meteorism, flatulence, stool passage) diminished over the course of treatment with Symbioflor 2. There were no significant differences between the age groups. Additionally, both the treating doctors and the patients/parents rated the efficacy of Symbioflor 2 positively.

2.2.4 Discussion on efficacy

The MAH has presented in support of the proposed indications one controlled clinical study conducted in adult patients with IBS conducted in 1988-89. The MAH also presented as supportive documentation of efficacy, an observational, uncontrolled study of children and adolescents conducted in children with IBS in the primary care setting in 2008-2009. No controlled or uncontrolled clinical study or literature data was available to assess the efficacy and safety of Symbioflor 2 in the treatment of functional gastrointestinal disease. Regarding the efficacy of Symbioflor 2 in adults with IBS, although both the first and the second evaluation of the clinical trial may have shown beneficial effects of the treatment with Symbioflor 2 there is not enough data to actually conclude whether Symbioflor 2 is efficacious or not in IBS.

In effect, the MAH conducted only one pivotal study for the support of Symbioflor's efficacy. In order to obtain the approval for a medicinal product, it is expected that the clinical development programme will provide sufficient evidence of efficacy and safety. In addition, where the MAH chose to submit one

single pivotal study in support of the efficacy in adults, the demonstration should be both robust and of a magnitude that is statistically and clinically convincing and meaningful.

Although a guideline for the conduct and evaluation of a clinical study was not in force at the time of the study in 1988, the basic principles were already broadly applicable. The study protocol did neither clearly define a primary endpoint nor an evaluation strategy. The primary endpoint “global evaluation of efficacy”, the statistical evaluation were defined post-hoc and the efficacy results were only descriptive. It is therefore not possible to draw firm conclusion on the efficacy of Symbioflor 2.

Instead of taking this study as a pilot study in order to design and conduct a confirmatory trial, the MAH then decided, in 2005, in contradiction with the guideline in place at the time, to re-evaluate the same study with a new set of endpoints, despite the fact that a post-hoc definition of primary endpoints in full knowledge of all results cannot be accepted as confirmatory evidence from a scientific and statistical point of view.

Among several methodological uncertainties, it is notably unclear whether measuring the endpoints on a weekly basis and not recording them as they occurred biased the results. The endpoints were based on the provocation of symptoms by the examining physician, hence did not reflect the patient well-being adequately. Quality of life was also not recorded.

In addition, there was a significant heterogeneity between centres in 3 out of 6 symptom-score outcomes, as well as for the global physician’s assessment of efficacy that can hardly be explained by chance alone. Not only several centres did not have responders, the overall results were driven by one or two centres. The centre responsible for the most significant heterogeneity was centre 6. If centre 6 was excluded from the analyses, statistical significance was lost for both co-primary variables, as well as for the physician’s global assessment endpoint. Coincidentally, possible deficiencies were also identified in the conduct of the trial. Whether the trial was conducted in line of the rules applicable at the time indeed cannot be verified any longer because the source data are no longer available. These findings, however, add to the uncertainty of the magnitude of the benefit of Symbioflor 2 in IBS.

With regards to the efficacy of Symbioflor 2 in children and adolescents with IBS, despite the encouraging results seen in this study, the value of an observational, uncontrolled study is limited and cannot be regarded as adequately supporting the efficacy of the compound in this age group and should be interpreted with caution. The data were neither controlled for spontaneous fluctuations of symptoms nor for a placebo response, which are known and effective factors contributing to the manifestation of symptoms in IBS (Martens, 2010). In addition, patient selection was not standardized, and only patients considered “suitable for Symbioflor treatment” by the Investigators were included, which might have introduced bias in the study. In addition no data were available for children below the age of 4. Finally, no data to substantiate the extrapolation of efficacy from adults to children were provided. Proof of the efficacy of Symbioflor 2 in children and adolescent would have required a prospective, double-blinded, randomized and placebo-controlled trial as per the guideline CPMP/EWP/785/97 in force at the time of the conduct of the study.

In conclusion, remaining uncertainties should be addressed in the form of a post-authorisation efficacy study conducted to confirm the efficacy of Symbioflor 2 in this indication. It should be a well-designed and adequately powered multi-centre double blind randomised placebo controlled post approval efficacy study allowing for relevant subpopulation analyses to confirm the efficacy of Symbioflor 2 in the treatment of IBS in general versus subtypes of the disease such as IBS C and IBS D, gender, disease severity and address the sustainability of efficacy. Before conducting the study it is strongly encouraged that the MAH seeks scientific advice on the protocol of the study.

2.3. Data on safety

2.3.1 Safety data from Study S2

Table 14 presents adverse events reported in Study S2 by System Organ Class (SOC).

Based on discrepancies noted during the referral procedure, corrected numbers were provided by the MAH.

Table 14: Reported Adverse events of "Symbioflor 2" vs placebo in Study S2 by SOC

Adverse event	Study medication				rel. incidence >=2
	Symbioflor 2		Placebo		
	number	incidence in %	number	incidence in %	
Cardiac disorders	**1**		**0**		
Tachycardia	1	0.7	0	0.0	
Gastrointestinal disorders	**18**		**12**		
Abdominal pain	5	3.4	1	0.7	5.1
Diarrhoea	5	3.4	4	2.7	1.3
Dysgeusia	2	1.4	2	1.3	1.0
Vomiting	2	1.4	0	0.0	
Nausea	1	0.7	3	2.0	0.3
Flatulence	1	0.7	1	0.7	1.
Eructation	1	0.7	1	0.7	1.0
Gastroenteritis	1	0.7	0	0.0	
General disorders and administration site conditions	**14**		**17**		
Fatigue	13	8.8	17	11.3	0.
Hot flush	1	0.7	0	0.0	
Nervous system disorder	**5**		**4**		
Headache	3	2.0	2	1.3	1.5
Dizziness	2	1.4	2	1.3	1.0
Skin and subcutaneous tissue disorders	**12**		**11**		
Urticaria	3	2.0	1	0.7	3.0
Erythema	2	1.4	2	1.3	1.0
Rash	1	0.7	2	1.3	0.5
Pruritus	6	4.1	6	4.0	1.0
Total	**50**		**44**		

In the clinical development program, there were respectively 50 adverse drug reactions reported in the Symbioflor 2 arm, and 44 in the placebo arm for Study S2 in 79 patients for a treatment duration of up to 8 weeks.

The MAH also presented the summaries of adverse events grouped by organ class as well as the frequencies of adverse events grouped by treatment and organ system as well as the classification of the causal relationship with the investigational medicinal products.

In another evaluation, the Investigators rated the tolerability of the treatment according to a 4-point scale at the end of the treatment. Although this method of assessing the overall safety profile is usually not acceptable, the results did not show relevant differences between active treatment and placebo.

2.3.2. Safety data from the observational study in children and adolescents

In order to document tolerability in this trial, the treating physicians were to document any adverse events that occurred and rate the tolerability of the treatment at the end of the observational study on a five-point scale ('very good', 'good', 'satisfactory', 'adequate', 'unsatisfactory') both by patients and treating physicians.

No adverse events were documented during the trial. With two exceptions ('satisfactory') from a total 203 cases the Symbioflor 2's tolerability was rated as 'very good' or "good" in 98.6% of the cases. There were no ratings of 'adequate' or 'unsatisfactory'. There were no relevant differences between the age groups.

The analysis of tolerability ratings by patients/parents was qualitatively in line with doctors' ratings. With two exceptions (1 × 'satisfactory', 1 × 'adequate') from a total of 203 cases, the tolerability of Symbioflor 2 was rated as 'very good' or 'good' in 98.5% of the cases.

2.3.3 Post marketing safety data

The MAH could not produce any adverse event reports that were received before the year 2006, although procedures for the handling of post-marketing adverse event data according to the legal requirements had been in force since 1986.

A pharmacovigilance system was put in place by the MAH in 2006. Adverse reactions were mainly related to the gastrointestinal tract, namely abdominal pain, diarrhoea, flatulence ad nausea, as well as to the skin with urticaria being the most frequent event reported for this SOC. This was in line with the adverse event (AE) profile observed in the clinical trial population.

2.3.4 Discussion on safety

The adverse events, retrieved from the MAH database on about 150 patients receiving Symbioflor 2 for a period of 8 weeks in Study S2, were generally benign in nature, and mostly restricted to the gastrointestinal tract (such as abdominal pain and nausea) or related to the occurrence of skin efflorescences. There were no serious events or deaths during the study and no clinically meaningful laboratory findings and impact on vital signs. Reporting in special population was too low to draw meaningful conclusions. No evaluation was made related to drug-drug interactions and other interactions were not evaluated. Discontinuations in 2 patients did not raise particular concern. The observational study conducted in children aged 4-18 years did not report any adverse events. However, as no adverse event was actually reported during the trial, the safety in patients younger than 18 years old appears not to have been documented with appropriate quality. The results have therefore to be taken with caution.

This relatively benign safety profile is confirmed by post-marketing data. Despite substantial exposure, a very low number of spontaneous reports have been reported over a period of 15 years. These reports, mainly related to the gastrointestinal tract and the skin (including potentially immune mediated events), confirm the safety profile established in clinical trials.

The number of patients included in controlled clinical trials receiving active study medication was very limited. Less frequent events might therefore have been missed. Treatment duration was limited to less than 8 weeks. The safety in children was assessed in an uncontrolled, observational study. In addition, no adverse events were recorded. Although the reporting of a significant number of adverse events would have been expected due to the underlying disease regardless of the safety profile of

Symbioflor 2, this study therefore failed to contribute to further establishing the safety profile of Symbioflor 2.

There were also no adverse events reported before 2006 and it remains uncertain whether this number is the result of the overall very low number of events or deficiencies in the reporting system.

Indirect risks associated with the intake of a potentially inefficacious medication for IBS with regards to continued impairment of quality of life and potential consequences regarding work- and health-care-seeking -related behaviour need also to be considered. There is, in addition, a theoretical, small risk of further invasive diagnostics and/or inappropriate surgical procedures consequential to potentially ineffective treatment, which entails a risk of delaying the opportunity for a patient to access an effective medicine with a possible impairment of the patient's quality of life and the persistence of the symptoms as a result.

In conclusion, although the reporting might have been suboptimal and uncertainties remain with regards to the nature and frequency of the adverse events occurring with Symbioflor 2 in order to fully characterize its safety profile and notably its long term safety profile, the analysis of the safety data did not raise particular concerns and, considering the long presence on the market of Symbioflor 2 with limited adverse drug reactions reporting, the safety profile of Symbioflor 2 is generally expected to be benign.

3. Expert consultation

An expert group meeting was held on 13 January 2017. The experts explained that the knowledge on probiotics has evolved over time in particular into the direction of more individualized treatment adapted to specific subtypes of the disease and particular patient symptom profiles. The experts acknowledged that there is no treatment in IBS effective in all patients but a treatment algorithm should be followed to putting the treatment with the best evidence of therapeutic benefit first to spare patients unnecessary burden. The experts reiterated that no treatment is effective in IBS in every patient but emphasized that the repertoire of drugs to be chosen from needs to have at least a sensible margin of efficacy to avoid unsuccessful treatment approaches producing unnecessary harm to the patient by symptom continuation.

4. Benefit-risk balance

Two reports in support of the claimed indication in the treatment of irritable bowel syndrome (IBS) were submitted in the context of this referral procedure:

- A 2005 re-analysis of a 1988 study "Efficacy and tolerability of Symbioflor2: A randomised, multicentre, double-blind, placebo-controlled trial in 298 patients with irritable bowel syndrome treated continuously for 8 weeks with Symbioflor 2 (clinical phase IV). Supplementary Integrated Clinical Study Report Final PAZ 9527-5-S2", of the study conducted in 1988 in Germany entitled "Schaffstein, W. and Burkard, I.: Symbioflor 2 - Eine therapeutische Alternative zur Behandlung des irritablen Kolons. Jatros Gastroenterol, 1993" (Study S2)", and
- An observational non-interventional study in 203 children and adolescents conducted between 2007 and 2008 in Germany "Efficacy and tolerability of Symbioflor 2 in children with Irritable Bowel Syndrome".

No study was submitted to support the indication in the treatment of functional gastrointestinal disorders.

In addition, an ad-hoc expert group was convened on 13 January 2017, where the CHMP requested feedback from experts in the treatment of IBS on specific questions regarding the therapeutic role of Symbioflor 2.

Indication in the treatment of functional gastrointestinal disorders

"Functional gastrointestinal disorders" defines a heterogeneous group of individual diseases, ranging from functional oesophageal, gastric, intestinal, biliary, pancreatic to functional anorectal disorders, with a wide range of different underlying pathophysiologies and symptomatic entities that require different treatment modalities. Apart from data on IBS, no controlled or uncontrolled clinical study or literature data are available to assess the efficacy and safety of Symbioflor 2 in the treatment of these diseases. Given the heterogeneity of the disease and the absence of data, the CHMP asked the MAH to submit evidence to support this indication. The MAH did not provide such data and decided to withdraw this indication. The CHMP acknowledged the deletion of the indication "functional gastrointestinal disorders" during this procedure.

Indication in the treatment of irritable bowel syndrome

Benefits

IBS is a highly prevalent disease and a chronic condition that needs to be managed on a long term basis. It is not life threatening but can significantly impact the quality of life of patients. Whereas it cannot generally be stated that probiotics are efficacious or not efficacious in the treatment of IBS, it appears that specific probiotic species or strains could potentially be efficacious for specific symptoms of the disease. Which species and strains are most beneficial has to be determined individually case by case, and the mechanism of action of probiotics remains speculative.

The evaluations presented in the Study Report of Study S2 (1989), based on a primary endpoint of "global evaluation" of efficacy by the investigator at the end of the trial, showed that Symbioflor 2 administered over an 8-week period had better outcomes than placebo on most of the evaluated endpoints. Overall, the evaluations presented by the MAH indicated that the decrease in symptom score was more important in the Symbioflor 2 than in the placebo arm.

In the re-evaluation report of Study S2 (2005), the endpoints were redefined, combining parameters of a patient-centred assessment of spontaneous symptoms with endpoints based on physical examination by the physician. The newly defined primary endpoints in this re-evaluation were evaluated with adequate statistical methodology and were strict with regards to treatment success, because only patients completely free of symptoms were counted as "responders". The analyses showed statistical significant superiority of the active treatment over placebo in almost all endpoints evaluated. The findings were consistent across age and gender subgroups.

The CHMP also noted that results of the observational study in children older than 4 years with IBS suggested a possible efficacy of Symbioflor 2.

Uncertainties about benefits

Although Study S2 was conducted before requirements of the current IBS guideline "Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome" (CPMP/EWP/785/97) or the previous CHMP point to consider on IBS came into force, the original protocol of Study S2 neither defined a primary endpoint nor planned for a statistical analysis. The evaluation of the results was descriptive and thus did not allow establishing whether the differences in efficacy between Symbioflor 2 and placebo were statistically different and clinically meaningful. Additional bias might have been introduced by various other deficiencies encountered in the conduct of Study S2, including the fact that

the endpoint was solely based on the rating by the investigator on a weekly basis rather than self-assessed by the patient closer to the administration of Symbioflor 2. In the absence of a run-in phase and specific inclusion criteria, there was also insufficient assurance that the patient population indeed suffered from IBS. In addition, the CHMP was of the opinion that the adequacy of a global evaluation criterion defined by the MAH for the assessment of the efficacy of Symbioflor 2 in the treatment of IBS was questionable in comparison to the specific, better measurable and less subjective evaluation of changes in stool related abnormalities and pain.

Although the results of Study S2 point at a possible efficacy of Symbioflor 2 in the treatment of IBS, a large unexplained heterogeneity was observed among centres in terms of treatment effect and response rate. While several centres did not report any responder, the overall results were driven by one centre. When excluding centre number 6, a statistically significant centre effect was seen and the statistical significance was lost for both co-primary variables, as well as for the physician's global assessment endpoint. In addition, some facts in the conduct of the study cast doubt over the integrity of the data: for instance, for centres number 5 and number 6, the visits for all but one patient occurred in accordance with the study plan at the exact interval for the whole duration of the study, one of the dates being a public holiday. Source data are, however, no longer available.

In 2005, rather than conducting a new study in line with the "Note for guidance on statistical principles for clinical trials" (CPMP/ICH/363/96) then in force, the MAH decided to perform a post-hoc re-evaluation of Study S2, i.e. establishing the definition of the primary hypothesis, the corresponding evaluation plan and the statistical analysis methods in full knowledge of the results. Such a re-analysis in full knowledge of the results carries the risk of introducing bias that can compromise the integrity of a study.

The CHMP therefore concluded that the possibility that significant bias had compromised the validity of the results of this study could not be ruled out. In addition, the CHMP noted that data generated in study S2 have not established the long term efficacy of Symbioflor 2 beyond 8 weeks of treatment.

Finally, the value of an observational study in children and adolescents for substantiating the efficacy of the product in this patient population is limited. Data were not controlled and did thus not account for the contribution of spontaneous fluctuations of IBS symptoms or for a placebo response in the assessment of the benefit-risk of Symbioflor 2. Proof of the efficacy of Symbioflor 2 in this patient population would have required a prospective, double-blinded, randomized and placebo-controlled trial as per the guideline CPMP/EWP/785/97 in force at the time of the conduct of the Study. The CHMP concluded that this study cannot be regarded as adequately supporting an indication for Symbioflor 2 in this age group. In the absence of relevant data submitted by the MAH and in view of the uncertainties about proof of efficacy in Study S2, the CHMP concluded that these results cannot be extrapolated from adults to children or to adolescents. The SmPC was amended to reflect that efficacy in children has not been established.

In summary, in the absence of valid statistical evaluation and given the risk of bias and the paucity of elements contributing to support the robustness and the strength of the results (the evidence being based on a single pivotal trial), the CHMP was not able to confidently draw a conclusion with regards to the efficacy of Symbioflor 2 in IBS or a sub-type of IBS. On this basis and considering the absence of new data since the initial marketing authorisation, the CHMP considered changes to the product information to include the information of this review necessary. Furthermore, the CHMP requested that the MAH conduct a well-designed and adequately powered multi-centre, double blind, randomised, placebo controlled post approval efficacy study allowing for relevant subpopulation analyses to assess the efficacy of Symbioflor 2 in the treatment of IBS in general versus subtypes of the disease such as

IBS C and IBS D, gender, disease severity and address the sustainability of efficacy to confirm the efficacy of Symbioflor 2 in IBS.

Risks

In the clinical development program, there were respectively 50 adverse drug reactions reported in the Symbioflor 2 group, and 44 in the placebo group for Study S2 in 79 patients. The adverse events were generally benign in nature, and mostly restricted to the gastrointestinal tract (such as abdominal pain and nausea) or related to the occurrence of skin efflorescences. This relatively benign safety profile was confirmed by post-marketing data.

No adverse events were reported in the observational study conducted in children and adolescents. The CHMP was of the opinion that a significant number of adverse events would have been expected to be reported in this study due to the underlying disease regardless of the safety profile of Symbioflor 2. This study therefore cannot be considered to contribute to further establishing the safety profile of Symbioflor 2.

Uncertainties about risks

The CHMP noted that in the clinical development program no data were available for treatment beyond 8 weeks. From post-marketing experience, only 18 adverse reactions have been reported to Eudravigilance for Symbioflor 2, covering both the treatment of IBS and other functional gastrointestinal disorders despite significant exposure over several decades of marketing and the pharmacovigilance system put in place by the MAH since the early 2000. Finally, the CHMP noted that the total number of reports was low, and as per the Weber effect, a decline in reporting of adverse events is likely over time. It is therefore unlikely that post-marketing data will provide significant further information on the safety profile of Symbioflor 2 in the treatment of IBS. In general, the CHMP was of the opinion that, although the reporting might have been suboptimal and uncertainties remain with regards to the nature and frequency of the adverse events occurring with Symbioflor 2 in order to fully characterize its safety profile and notably its long term safety profile, the analysis of the safety data did not raise particular concerns. However, indirect risks associated with the intake of a potentially inefficacious medication for IBS with regards to continued impairment of quality of life and potential consequences regarding work- and health-care-seeking -related behaviour need to be considered.

The CHMP agreed with the MAH's proposal to amend the product information to include the information of this review and concluded that, considering its long presence on the market with limited adverse drug reactions reporting, the safety profile of Symbioflor 2 is generally expected to be benign.

Grounds for CHMP opinion

Whereas,

- The CHMP considered the procedure under Article 31 of Directive 2001/83/EC for Symbioflor 2 (*Escherichia coli* bacteria (cells and autolysate)) and associated names (Symbioflor 2);
- The CHMP reviewed all available data from clinical studies, published literature, post-marketing experience, including responses and communications submitted by the MAH in writing, on the efficacy and safety of Symbioflor 2 in their proposed indications and sought as well views of the ad hoc expert group on Symbioflor 2;
- The CHMP considered that "functional gastrointestinal disorders" is a heterogeneous group of individual diseases with a wide range of different underlying pathophysiologies and symptoms that require different treatment modalities. The CHMP acknowledged the MAH's proposal to delete this indication as, in the absence of any data to support the treatment of functional gastrointestinal disorders, a positive benefit-risk balance of Symbioflor 2 could not be established;
- The CHMP was of the opinion that, although the results of Study S2 seemed to suggest possible efficacy of Symbioflor 2 in IBS in adult patients, the possibility that significant bias had been introduced compromising the validity of the results could not be ruled out. In addition, in the absence of valid statistical evaluations and given the paucity of elements contributing to support the robustness and the strength of the results, the CHMP was, neither able to draw reliable conclusions with regards to the efficacy of Symbioflor 2, nor to establish whether Symbioflor 2 is efficacious in IBS in general or any sub-type of IBS. However, the CHMP concluded that there were no new elements to motivate a change in the established benefit risk balance since the initial marketing authorisation for Symbioflor 2 in adult patients for the treatment of IBS.
- The CHMP also noted that results of the observational study in children older than 4 years with IBS suggested a possible efficacy of Symbioflor 2. Data, however, were not controlled. The value of an observational study for substantiating the efficacy of the product in this patient population is limited and therefore the CHMP concluded that this study could not be regarded as adequately supporting the efficacy of Symbioflor 2 in this age group. In the absence of relevant data submitted by the MAH to support the paediatric use and in view of the uncertainties about the benefit-risk in Study S2 conducted in adult patients only, the CHMP concluded that extrapolation of the results from adults to children or adolescents was not justified. In this regards, the SmPC is amended to reflect that efficacy in children has not been established;
- Acknowledging the limitations of the established efficacy profile of Symbioflor 2, the CHMP requested the MAH to conduct a well-designed and adequately powered multi-centre, double blind, randomised, placebo controlled post approval efficacy study allowing for relevant subpopulation analyses to confirm the efficacy of Symbioflor 2 in the treatment of IBS in general versus subtypes of the disease such as IBS C and IBS D, gender, disease severity and address the sustainability of efficacy to confirm the efficacy of Symbioflor 2 in IBS;
- Considering available safety data from the clinical trial and post-marketing experience with Symbioflor 2, the CHMP came to the conclusion that the demonstrated risks were overall low.

CHMP opinion

Based on the review of all available data in the framework of this Article 31 procedure, the CHMP concludes that there are no new elements since the granting of the marketing authorisation for

Symbioflor 2 (*Escherichia coli* bacteria (cells and autolysate)) and associated names, and therefore the previous conclusion of the national competent authorities on a positive benefit-risk balance remains unchanged. The CHMP recommends amendments to the product information and in view of the limitations of the currently available efficacy data for Symbioflor2 in the treatment of irritable bowel syndrome (IBS), the CHMP is of the view that a post-authorisation efficacy study should be conducted. Therefore, the CHMP recommends a variation to the terms of the marketing authorisation.

4.1.1. Amendments to the product information

The CHMP considered that amendments to sections 4.1 4.2, 4.3, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC were necessary to include the information of this review and harmonize the product information in the countries where Symbioflor 2 is approved.

In particular, in section 4.1, the indication in functional gastrointestinal disorders was deleted and the indication restricted to the treatment of patients with irritable bowel syndrome.

Section 4.2 was revised to reflect that the efficacy and safety in children has not been established and that the Efficacy and safety of Symbioflor 2 beyond 8 weeks have not been studied.

Section 4.4 was updated to reflect that if other, longer-lasting or unexplained gastrointestinal symptoms occur, treatment should be discontinued.

Section 4.8 was revised to reflect updated adverse events figures.

The results of the clinical studies were revised in section 5.1.

The Package Leaflet was amended accordingly.

5. Condition(s) to the marketing authorisations

Conditions Symbioflor 2 (*Escherichia coli* bacteria (cells and autolysate)) and associated names	**Date**
In order to address the uncertainties with regards to the efficacy and safety of Symbioflor 2 (*Escherichia coli* bacteria (cells and autolysate)) and associated names in the treatment of irritable bowel syndrome in adult patients, the MAH should conduct and submit the results of a well-designed and adequately powered multi-centre double blind randomised placebo controlled post approval efficacy study allowing for relevant subpopulation analyses, in accordance with an agreed protocol to assess the efficacy of Symbioflor 2 in the treatment of IBS in general versus subtypes of the disease such as IBS C and IBS D, both gender, disease severity and address the sustainability of efficacy The final study report should be submitted to the relevant National Competent Authorities.	Submission of the final study results by March 2022.

Attachment 1 - Amendments to the product information as recommended by the CHMP

The existing product information shall be amended (insertion, replacement or deletion of the text, as appropriate) to reflect the agreed wording as provided below]

Summary of product characteristics

4.1 Therapeutic indications

The wording of the indication should be deleted and the text below should be inserted in its place:

Irritable bowel syndrome

4.2 Posology and method of administration

The text below should be inserted by replacing the existing text of this section:

Posology

Adults:

At the beginning of the treatment: 10 drops three-times daily.

After one week, the dose is increased to 20 drops three-times daily.

If signs of gastrointestinal symptoms like flatulence, diarrhoea, abdominal pain or abdominal discomfort worsen or occur more frequently at the beginning of the treatment, Symbioflor *E. coli* should be taken diluted in water, or the dose should be reduced or the number of drops should be increased more slowly.

Paediatric population:
The efficacy and safety in children and adolescents have not been established. Available data are described in sections 4.8 and 5.1.

Method of administration

The drops are taken orally during the meals. If necessary, they can be diluted in water (see above).

Duration of treatment

Duration of use of 8 weeks is recommended.

If symptoms worsen during treatment or persist after 8 weeks of treatment, the patient should seek medical advice.

Efficacy and safety beyond 8 weeks have not been studied.

4.3 Contraindications

The text below should be inserted by replacing the existing text of this section:

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Severe organic diseases of the gastrointestinal tract such as acute cholecystitis, acute pancreatitis, ileus, as well as cachexia and marasmus.

4.4 Special warnings and precautions for use

The text below should be inserted by replacing the existing text of this section:

Prior to a diagnosis of ‚irritable bowel syndrome', organic causes of the gastrointestinal disorders must be excluded.

During acute febrile diseases, Symbioflor *E. coli* should be temporarily discontinued.

Symbioflor *E. coli* should not be taken during a treatment with antibiotics or within 5 days after the end of such a treatment (see also section 4.5).

If symptoms are more severe, e.g. acute diarrhoea with high fever or with blood in stool or the diarrhoea lasts longer than 2 days, or if other, longer-lasting or unexplained gastrointestinal symptoms occur, treatment should be discontinued and a doctor should be consulted.

4.8 Undesirable effects

The text below should be inserted by replacing the existing text of this section:

Summary of safety profile

The most common undesirable effects observed in the clinical trial, predominantly observed within the first 4 weeks of treatment, were abdominal pain and urticaria. These reactions usually disappear within a few days even if treatment is continued.

Tabulated list of adverse reactions

The evaluation of undesirable effects is based on the following frequencies:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
not known (cannot be estimated from the available

data) The following undesirable effects may occur:

Immune system disorders Common:
urticaria

Gastrointestinal disorders

Common: abdominal pain (including upper abdominal pain and abdominal discomfort).

Not known: flatulence, nausea, diarrhoea.

Gastrointestinal symptoms

If gastrointestinal symptoms (like abdominal pain, flatulence or diarrhoea) worsen or occur more frequently at the beginning of the treatment, please refer to section 4.2 for measures to be taken to reduce or avoid these symptoms.

Paediatric population

In a non-interventional study with 203 children aged 4-18 years no undesirable effects were reported. Only limited experience of adverse reactions in children from pharmacovigilance data is available. However, based on these limited data the safety profile for children and adolescents is considered to be comparable to that of adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system (details see below). *[To be filled in nationally]*

4.9 Overdose

The text below should be inserted by replacing the existing text of this section**:**

In a non-interventional post-marketing high-dose safety study in healthy volunteers, two of five subjects experienced side effects. Only non-serious and already known side effects as described in section 4.8 were reported upon administration of single doses up to 20 times higher than the recommended daily dose.

5.1 Pharmacodynamic properties

The text below should be inserted by replacing the existing text of this section:

Pharmacotherapeutic group: Other immunostimulants, Antidiarrheal microorganisms ATC code: L03AX, A07FA

Mechanism of action

Escherichia coli, the active substance in Symbioflor *E. coli*, is a living bacterium that is present in the healthy intestinal flora of humans.

An in-vitro study carried out using polymerase chain reaction (PCR) to investigate the effects of Symbioflor *E. coli* on epithelial cells (SW 480) from the human intestinal mucosa showed an up-regulation of the cytokines IL-1β, TNF-α, GM-CSF and the chemokine IL-8.

The qualitative effect on the gene expression in the mucosal epithelial cells, the key control elements of immune function in the human intestine, is similar to that exerted by the natural, physiological intestinal flora.

In a human whole-blood culture model, Symbioflor *E. coli* exerts strong modulating effects on the physiologically induced synthesis and release of cytokines and chemokines. Overall, there is a shift in

activity in favour of Th1 helper cells, accompanied by inhibition of the Th2 helper cells. If and to what extend these results are applicable for the use in patients is not yet known.

Clinical efficacy and safety

A clinical trial including 298 patients with irritable bowel syndrome recruited in primary care centres showed a good or very good treatment success on Symbioflor E. coli in 62.9 % of the patients and in 39.4 % of the patients treated with placebo based on the investigator's global assessment of efficacy on a 4-point rating scale

Efficacy was confirmed when using two post-hoc defined patient assessed endpoints, i.e. patient's assessment of symptoms and abdominal discomfort/pain comprising each of 8 or respectively 5 IBS relevant symptoms. The number of patients free of all the assessed IBS relevant symptoms after the treatment period of 8 weeks was significantly higher for Symbioflor *E. coli* treatment compared to placebo

Overall, Symbioflor *E. coli* was well tolerated in the clinical trial with no significant differences in the tolerability compared to placebo regarding vital functions, body weight and all laboratory parameters tested. Only non-serious adverse events were recorded with a slightly higher frequency for Symbioflor *E. coli*. The investigator's global assessment of tolerability was predominantly good to very good and balanced between Symbioflor *E. coli* and placebo.

In a non-interventional study with 203 children aged 4 – 18 years, that were diagnosed for having IBS based on the ROM III criteria for children, the overall assessment of efficacy for all 4 IBS subtypes was very good to good in more than 80 % of the children for both, the physician's and the patient/parent's assessment. In the group of children aged 12 – 18 years with the IBS subtype "pain + alternating diarrhoea and constipation" the physician's and patient/parent's assessment of efficacy was lowest (55 % or 66 %, respectively).

The overall assessment of tolerability was good to very good in more than 98 % of the children for both, the physician's and the patient/parent's assessment (see also section 4.8).

5.2 Pharmacokinetic properties

The text below should be inserted by replacing the existing text of this section:

E. coli bacteria are not absorbed but act locally at the intestinal immune system.

In an in-vitro gastric exposure model mimicking the human stomach and ileus under fasting conditions 1 ml (less than a single dose) of Symbioflor *E. coli* was tested for the survivability of the *E. coli* production strain. In this model enough bacteria of the *E. coli* strain survived the acid stomach passage so that their number increased again when they reached the small intestine conditions. When the same volume was tested in the SHIME model (Simulation of the Human Intestinal Microbial Ecosystem) under conditions simulating food intake fewer bacteria were killed in the stomach while their numbers were relatively stable in the conditions simulating the upper gastrointestinal tract.

The high dose study (see section 4.9) demonstrated that the specific *E. coli* strain cultivates the human gut at least for days but also for up to months after a single dose.

The *E. coli* bacteria are excreted via the faeces.

Package leaflet

Section 2 What you need to know before you take Symbioflor E. coli

The text below should be inserted by replacing the existing text of this section**:**

Do not take Symbioflor *E. coli*:
- if you are allergic to *Escherichia coli* bacteria or any of the other ingredients of this medicine (listed in section 6).

- if you have severe organic diseases of the gastrointestinal tract such as acute inflammation of the gallbladder or pancreas, or intestinal obstruction.

- if you have very severe abnormal weight loss or extreme weight loss due to malnutrition (cachexia, marasmus).

Warnings and precautions

Talk to your doctor or pharmacist before taking Symbioflor *E. coli*.

Prior to a diagnosis of 'irritable bowel syndrome', your doctor should exclude organic causes of the gastrointestinal disorders.

Do not take Symbioflor *E. coli* during acute illnesses with fever. Please interrupt treatment, temporarily.

Do not take Symbioflor *E. coli* during a treatment with antibiotics or within 5 days after the end of such a treatment (see also section 4.5).

Consult a doctor and stop treatment if symptoms are more severe, e.g. acute diarrhoea with high fever or blood in stool, or the diarrhoea lasts longer than 2 days, or other, longer-lasting or unexplained gastrointestinal symptoms occur.

Other medicines and Symbioflor *E. coli*

Tell your doctor or pharmacist if you are taking/using, have recently taken/used or might take/use any other medicines.

Antibiotics may inhibit the *Escherichia coli* bacteria and thus reduce the efficacy of this medicine.

Symbioflor *E. coli* with food and drink
Take the drops during meals (see section 3 How to take Symbioflor *E. coli*)

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Although there are no known harmful effects of Symbioflor *E. coli* on the unborn child, the drops should be used during pregnancy and when breast-feeding only after a careful benefit-risk assessment by the doctor.

Driving and using machines

Symbioflor *E. coli* has no or negligible influence on the ability to drive or use machines.

Section 3 How to take Symbioflor *E. coli*

The text below should be inserted by replacing the existing text of this section:

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is:

Adults take 10 drops orally three-times daily during meals at the beginning of treatment. After one week, increase the dose to 20 drops three-times daily.

If signs of gastrointestinal symptoms like flatulence, diarrhoea, abdominal pain or abdominal discomfort worsen or occur more frequently at the beginning of treatment, Symbioflor *E. coli* should be taken diluted in water, or the dose should be reduced or the number of drops should be increased more slowly.

Duration of use of 8 weeks is recommended.

If symptoms worsen during treatment or persist after 8 weeks of treatment, seek medical advice.

Use in children and adolescents

No recommendation on a posology can be made as the efficacy and safety in children and adolescents have not been established.

Shake Symbioflor *E. coli* well before use. This will cause slight turbidity.

Symbioflor *E. coli* contains no preservatives and is therefore susceptible to contamination in the event of improper use. This can be prevented by opening the bottle for a short time only when using this product, and by dispensing the drops carefully. Do not touch the dropper. Because of the high surface tension of Symbioflor *E. coli*, problems with starting and stopping release of the drops of solution cannot be completely avoided. Release of the drops is started by holding the bottle at an angle and tapping lightly on the bottom. The speed at which the drops come out can be changed by varying the angle at which the bottle is held.

If you take more Symbioflor *E. coli* than you should

No countermeasures are necessary.

If you forget to take Symbioflor *E. coli*

Do not take a double dose to make up for a forgotten dose, but continue taking the dosage prescribed.

If you stop taking Symbioflor *E. coli*

No special measures are indicated. If appropriate, speak to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

Section 4 Possible side effects

The text below should be inserted by replacing the existing text of this section:

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following undesirable effects may occur:

Common (may affect up to 1 in 10 patients):

- Abdominal pain (including upper abdominal pain and abdominal discomfort)
- Hives

These reactions usually occur within the first 4 weeks of treatment and disappear within a few days even if treatment is continued.

Not known (cannot be estimated from the available data):

- Flatulence
- Nausea
- Diarrhoea

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system: *[to be filled in nationally]*

By reporting side effects, you can help provide more information on the safety of this medicine.

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