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Clinical Study Synopsis for Public Disclosure

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Report date: 01 DEC 2009	**Trial No. / U No.:** 122.56/U09-2368-01	**Date of trial:** 14 September 2007 – 02 June 2009	**Date of revision:** Not applicable

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Title of trial:	A randomised, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of 4 weeks treatment with bisacodyl (Dulcolax®) tablets 10 mg administered orally, once daily, in patients with functional constipation
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study, cf. Appendix 16.1.4
Publication (reference):	Planned
Clinical phase:	IIIb
Objectives:	To compare the efficacy and safety of 4 weeks treatment with bisacodyl (Dulcolax®) tablets to placebo in patients with functional constipation
Methodology:	Randomised, double-blind, placebo-controlled, parallel group design
No. of patients:	
planned:	450 screened patients 360 entered patients 240 bisacodyl (Dulcolax®) 120 placebo (2:1 randomisation)
actual:	Enrolled: 736 treatment bisacodyl: entered: 247, treated: 247, analysed (for primary endpoint): 239 (FAS) treatment placebo: entered: 121, treated: 121, analysed (for primary endpoint): 117 (FAS)
Diagnosis and main criteria for inclusion:	Male and female patients, aged 18 and above, with functional constipation as defined by the Rome III diagnostic criteria

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Test product:	Bisacodyl (Dulcolax®)
dose:	10 mg (2 x 5 mg tablets) once daily, in the evening
mode of admin.:	Oral
labelled batch no.:	PR07/30053
batch no.:	718221A (=B071002728)
Reference therapy:	Placebo
dose:	2 tablets matching for bisacodyl (Dulcolax®) tablets
mode of admin.:	Oral
labelled batch no.:	PR07/30053
batch no.:	07009 (=B071002727)
Rescue medication:	Bisacodyl suppositories [Dulcolax®]
dose:	10 mg
mode of admin.:	Rectal
labelled batch no.:	731721 A
batch no.:	731721 A
Duration of treatment:	4-week double-blind treatment phase (preceded by a 2-week baseline period without treatment)
Criteria for evaluation:	
Efficacy:	Primary: • Mean number of complete spontaneous bowel movements (CSBMs) per week, during the 4 week treatment phase of the trial Secondary: • Number of CSBMs per week at each weekly time point during the treatment phase • Number of spontaneous bowel movements (SBMs) per week

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- Time to first SBM following intake of first dose of study medication
- Number of patients who have an increase of ≥ 1 CSBM per week compared with the last 7 days of the baseline period
- Number of patients who have ≥ 1 CSBM a day
- Number of patients who have ≥ 3 CSBMs per week
- Number of premature withdrawals
- Number of patients who have used rescue medication
- Changes from baseline in the scores for:
  - Degree of straining
  - Stool quality
  - Sensation of incomplete evacuation
  - Sensation of anorectal obstruction/blockade
  - Whether or not a manual manoeuvre was required
- Patients overall satisfaction with bowel habits and bothersomeness of:
  - Constipation
  - Abdominal bloating
  - Abdominal discomfort
- Overall assessment of efficacy by both the patient and the Investigator
- Quality of life

Safety:	Adverse events (AEs), vital signs, laboratory values (serum chemistry & electrolytes), overall assessment of tolerability by both the patient and the Investigator

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Statistical methods: Descriptive statistics; analysis of covariance for the mean number of Complete Spontaneous Bowel Movements (CSBMs) per week and the change from baseline in the scores for constipation symptoms; Kaplan-Meier estimator and log-rank test for time to first Spontaneous Bowel Movement (SBM); Cochran-Mantel-Haenszel test for overall satisfaction with bowel habits; Wilcoxon rank test for assessment of efficacy and tolerability; Fisher exact test for other frequency data; contingency table of incidence, severity and causal relationship of adverse events

SUMMARY – CONCLUSIONS:

Efficacy/clinical pharmacology results:

Primary endpoint

The primary endpoint of this study was the mean number of CSBMs per week during the 4 weeks treatment phase of the trial. The mean number of CSBMs/week increased in the bisacodyl group from 1.1 (SE=0.08) to 5.2 (SE=0.24) and in the placebo group from 1.1 (SE=0.10) to 2.0 (SE=0.16) during this time interval. The adjusted (for centre effects and baseline) means after 4 weeks of treatment were 5.2 (SE=0.27) in the bisacodyl group and 1.9 (SE=0.34) in the placebo group, yielding a difference between both treatment groups of 3.3 (SE=0.36) which was highly statistically significant in favour of bisacodyl ($p < 0.0001$). Therefore, clear superiority of bisacodyl in comparison with placebo could be demonstrated in this study with regard to the primary endpoint.

Secondary endpoints

The number of CSBMs was also analysed for each of the weeks 1, 2, 3 and 4 during the randomised treatment period. The adjusted means for the number of CSBMs for each of the weeks 1 to 4 ranged from 4.3 (SE=0.35) to 6.3 (SE=0.32) in the bisacodyl group, whereas they ranged from 1.4 (SE=0.41) to 2.0 (SE=0.40) in the placebo group. The comparisons between the treatment groups for each week resulted in highly statistically significant differences in favour of bisacodyl ($p < 0.0001$).

The time course of the adjusted means for the number of CSBMs over the 4 weeks treatment period showed a distinct increase from week -1 to week 1 (from 1.1 to 6.3 CSBMs/week) in the bisacodyl group which decreased by week 2 (to 4.9 CSBMs/week), and thereafter remained more or less constant (4.6 CSBMs/week at week 3, 4.3 CSBMs/week at week 4).

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The adjusted mean number of SBMs/week over the 4 weeks treatment period was 10.0 (SE=0.33) in the bisacodyl group and 5.1 (SE=0.41) in the placebo group. The adjusted mean difference of 4.9 (SE=0.43) was highly significant in favour of bisacodyl ($p < 0.0001$). The adjusted means for the weekly number of SBMs ranged from 7.8 (SE=0.36) to 12.1 (SE=0.37) in the bisacodyl group compared to a range from 4.0 (SE=0.42) to 5.3 (SE=0.46) in the placebo group. The treatment comparisons for each week resulted in highly statistically significant differences in favour of bisacodyl ($p < 0.0001$).

Patients treated with bisacodyl had their first SBM much earlier than those treated with placebo. After 12 hours following the study medication (SM) intake, 50% of the patients in the bisacodyl group had their first SBM, whereas in the placebo group the percentage of 50% was achieved after 19 hours. The difference between the treatment groups was statistically significant in favour of bisacodyl ($p < 0.0001$).

The percentage of patients, who had an increase of at least 1 CSBM per week over the 4 weeks treatment period compared with baseline (which means the last 7 days of the baseline period), was 82.0% in the bisacodyl group versus 40.2% in the placebo group, i.e. the probability of an increase in the number of CSBMs/week compared to baseline is doubled in the bisacodyl group compared to placebo. This difference was highly statistically significant ($p < 0.0001$). Taking into consideration the single weeks 1 to 4, the percentages ranged from 61.9% to 85.4% in the bisacodyl group and from 36.8% to 48.7% in the placebo group. The treatment comparisons for each week resulted in high differences in favour of bisacodyl ($p < 0.0001$).

The percentage of patients reaching a mean number of at least 1 CSBM a day over the 4 weeks treatment period was 29.3% in the bisacodyl group, whereas it was 1.7% in the placebo group ($p < 0.0001$).

The percentage of patients reaching a mean number of at least 3 CSBMs per week over the 4 weeks treatment period was 67.4% in the bisacodyl group versus 27.4% in the placebo group ($p < 0.0001$).

During the 4 weeks treatment period, 21.3% of the patients treated with bisacodyl discontinued the study prematurely, whereas the percentage in the placebo group was 8.5% ($p=0.0025$).

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The percentage of patients using rescue medication (RM) at least once during the 4 weeks treatment period was higher in the placebo group (17.9%) than in the bisacodyl group (3.3%). When measured weekly, between 0.4% and 2.5% of the patients treated with bisacodyl used RM, the percentages in the placebo group ranged between 1.7% and 10.3%.

The change from baseline to each of the weeks 1, 2, 3 and 4 in the mean score per week for the constipation symptom 'Degree of straining' was higher for the bisacodyl group compared to the placebo group in favour of bisacodyl ($p < 0.0001$). The same applied for the symptoms 'Stool quality' ($p < 0.0001$) and the 'Number of anorectal obstructions' ($p < 0.0001$) at each week. Also, the 'Number of manual manoeuvres' decreased more in patients treated with bisacodyl than in the placebo group ($p < 0.0001$ in week 1-3 and $p=0.0018$ in week 4) as well as the 'Number of incomplete evacuations' (p varied between 0.0002 and 0.0127). The results show that all symptoms of constipation were highly improved by bisacodyl treatment at each week assessed.

The percentage of patients with an improved overall satisfaction with their bowel habits compared to baseline ranged from 68.3% to 78.5% in the bisacodyl group, whereas the corresponding percentage in the placebo group ranged from 36.9% to 42.3% across the 4 weeks. The treatment differences were high in favour of bisacodyl ($p < 0.0001$). The percentage of patients with a reduced bothersomeness with their constipation compared to baseline ranged from 71.4% to 75.5% in the bisacodyl group, whereas the corresponding percentage in the placebo group ranged from 30.6% to 37.5% across the 4 weeks. The treatment differences were highly in favour of bisacodyl ($p < 0.0001$). The percentage of patients with a reduced bothersomeness with abdominal bloating compared to baseline ranged from 60.7% to 67.0% in the bisacodyl group, whereas the corresponding percentage in the placebo group ranged from 25.5% to 29.5% across the 4 weeks. The treatment differences were highly in favour of bisacodyl ($p < 0.0001$). The percentage of patients with a reduced bothersomeness with abdominal discomfort compared to baseline ranged from 41.5% to 55.4% in the bisacodyl group, whereas the corresponding percentage in the placebo group ranged from 26.1% to 33.0% across the 4 weeks. The treatment differences were in favour of bisacodyl at weeks 2 to 4 (p ranged between 0.0001 and 0.0005) but not at week 1 ($p=0.6773$). Taken together, the patients' satisfaction with their bowel habits and bothersomeness of the mentioned constipation-related

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symptoms was statistically proven to be improved in bisacodyl-treated patients in nearly each week assessed.

The final global efficacy was assessed by means of a 4-point VRS (good, satisfactory, not satisfactory, bad) by both the Investigator and the patient after the 4 weeks treatment period. The Investigators rated the efficacy as 'good' in 65.3% and as 'satisfactory' in 24.7% of all patients treated with bisacodyl and in only 22.2% as 'good' and as 'satisfactory' in 31.6% of all patients allocated to placebo. The difference was highly in favour of bisacodyl ($p < 0.0001$). The corresponding assessment by the patients was 'good' in 55.2% and 'satisfactory' in 24.3% in the bisacodyl group and as 'good' in 19.7% and as 'satisfactory' in 29.9% of the placebo-treated patients. The difference was again highly in favour of bisacodyl ($p < 0.0001$).

The analysis of the Quality of Life (QoL) questionnaire 36-Item Short Form Health Survey™ (SF-36v2™) showed significant improvements in favour of bisacodyl for the change from baseline in the SF-36v2™ dimensions 'Vitality' ($p=0.0130$) and 'Mental health' ($p=0.0273$). There were no significant improvements of the other dimensions (p ranged between 0.1290 and 0.7980) in either treatment group. Thus, the improvement of the clinical constipation symptoms was not reflected in all of the dimensions of this global QoL assessment.

In the assessment of QoL by the constipation-related Patient Assessment of Constipation© Quality of Life questionnaire (PAC−QoL©), the overall score as well as the single scores were significantly improved in favour of bisacodyl ($p < 0.0001$) for all scales except psychosocial discomfort where $p=0.0070$) as measured as the change from baseline. The observed improvement in the PAC−QoL© score in bisacodyl-treated patients compared to the patients of the placebo group shows that the treatment of constipation with bisacodyl resulted in a subsequent improvement in the patients' everyday functioning and well-being.

Nearly all of the analysed efficacy endpoints of this study showed highly significant differences in favour of the bisacodyl treatment: there was a clinically relevant increase in the mean number of CSBMs in the analysed time periods as well as in the mean number of SBMs per week. More patients of the bisacodyl group had an increase of at least 1 CSBM per week, reached a mean number of at least 1 CSBM a day and a mean number of at least 3 CSBMs per week. The time to the first SBM was clearly reduced compared to placebo. The number of

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patients using RM at least once was remarkably smaller in the bisacodyl group. All symptoms of constipation analysed were improved by the bisacodyl treatment at nearly each week assessed. The patients' satisfaction with their bowel habits and bothersomeness of constipation-related symptoms was improved in bisacodyl-treated patients in nearly each week assessed. Also, the constipation-related QoL was improved in favour of bisacodyl. In addition, the global assessment of efficacy by both the Investigator and the patient clearly supports these findings.

The difference of approximately 3 in the adjusted means of the number of CSBMs over 4 weeks between the treatment groups does not only show statistical significance, but is also supporting the clinical relevance of this study result. As for the whole treatment period, there is a difference of more than 3 in the adjusted means of the number of CSBMs for each week, a magnitude of clinical relevance. For the adjusted mean number of SBMs/week over the 4 weeks treatment period as well as for the adjusted means for the weekly number of SBMs, the same applied as for the CSBMs. The difference of at least 3 furthermore confirms the clinical relevance of the observations made in the course of this clinical study.

With regard to an increase of at least 1 CSBM per week, the chance of success was approximately doubled for the patients in the bisacodyl group in comparison to placebo. The chance of success for reaching a mean number of at least 1 CSBM a day and for reaching a mean number of at least 3 CSBMs per week was approximately a 17-fold and a 2.5-fold, respectively. The change from baseline for the different constipation symptoms (besides 'Number of incomplete evacuations' and 'Number of manual manoeuvres') was improved by approximately 1 category or more.

Referring to the overall satisfaction with the bowel habits and bothersomeness of constipation, abdominal bloating and abdominal discomfort, the percentage of patients with an improvement in these was more than 10% higher in the bisacodyl group compared to the placebo group which can be regarded as clinically significant.

In the QoL assessment by the SF-36v2™, the differences between the treatment groups of 4.3 ('Vitality') and 3.5 ('Mental Health') on a scale from 0 to 100 seem to be too small to show a clear clinical relevance. For the dimensions 'Physical discomfort', 'Satisfaction' and for the 'Overall score' of the PAC-

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	QoL© however, there was an improvement of approximately 1 category on the scale from 0 to 4 in the bisacodyl group, and this change is clinically relevant.
Safety results:	No patient died during the course of the study. In the Treated Set (TS) (n=368), 2 (1.7%) of 121 placebo-treated patients experienced 3 Serious Adverse Events (SAEs) ('Fall', 'Tibia fracture' and 'Pregnancy'). In the group of patients treated with bisacodyl, 1 patient (0.4%) of 247 suffered from 1 SAE ('Chest pain'). All SAEs were assessed as non-related to the intake of SM, and 'recovery' was reported as the outcome. Other significant AEs according to ICH E3 occurred in 7 patients (5.8%) of the placebo group and in 139 patients (56.3%) of the bisacodyl group. There were 6 patients (5.0%) in the placebo group and 44 patients (17.8%) in the bisacodyl group with AEs leading to discontinuation of the SM. Of these, 3 patients (2.5%) in the placebo group discontinued due to AEs assessed as 'related' by the Investigator. In the bisacodyl group, 39 patients (15.8%) discontinued due to AEs assessed as 'related' by the Investigator. In total, the number of patients in the placebo group affected by any AEs was 45 (37.2%) and by severe AEs was 2 (1.7%). 178 patients (72.1%) suffered from any AEs and 16 patients (6.5%) from severe AEs in the group of patients treated with bisacodyl. In the causality assessment to SM, 10 patients (8.3%) with AEs defined as drug-related by the Investigator were reported in the placebo group and 157 patients (63.6%) in the bisacodyl group. The higher number of bisacodyl-treated patients who suffered from AEs may be due to an individually too high dosage of bisacodyl (Dulcolax®) of 2 tablets once daily at the beginning of the study. As a dose reduction (to 1 tablet) was permitted (the mean total dose of SM decreased from 56.4 mg at week 1 to 44.9 mg at week 4), the number of patients with Investigator-defined drug-related AEs per week after the first week decreased until the end of the treatment (from 56.9% at week 1 to 4.7% at week 4). The most frequent AE symptom by Preferred Term (PT) was diarrhoea, which occurred in 2 patients (1.7%) treated with placebo and in 132 patients (53.4%) treated with bisacodyl. Diarrhoea was assessed as 'mild' in both placebo-treated patients. The AE diarrhoea in bisacodyl-treated patients was assessed as 'mild' in 45 patients (18.2%), as 'moderate' in 78 patients (31.6%) and 'severe' in 9 patients (3.6%). Other AEs occurring with a frequency of > 5% in one or other

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of the treatment groups were 'Abdominal pain' (placebo: 3 patients (2.5%), bisacodyl: 61 patients (24.7%)), 'Abdominal pain upper' (placebo: 3 patients (2.5%), bisacodyl: 19 patients (7.7%)) and 'Headache' (placebo: 7 patients (5.8%), bisacodyl: 8 patients (3.2%)).

All reported AEs in the course of this study, beside diarrhoea, abdominal pain and abdominal pain upper were observed with a similar frequency in both treatment groups. Due to the possibility to reduce the number of SM tablets per day to meet the patient's individual needs, the percentage of patients with Investigator-defined drug-related AEs decreased substantially after week 1 (placebo: 5.1%, bisacodyl: 56.9%) to a lower level in both treatment groups at week 4 (placebo: 0.0%, bisacodyl: 4.7%).

At baseline, there were no abnormal and potentially clinically relevant laboratory values classified as important protocol violations. Serum electrolyte levels were comparable between both treatment groups. A possibly clinically significant decrease was only observed for sodium in 1 bisacodyl-treated patient (0.4%) and a possibly clinically significant increase of the gamma glutamyl transferase (GGT) concentration was observed for 2 placebo-treated patients (1.8%).

In vital signs assessed at the end of the treatment, none of the parameters assessed showed systematically or relevant changes during the course of the study.

For the placebo group, the tolerability was assessed as 'good' in 75 cases (64.1%) by the Investigator and in 38 cases (32.5%) by the patient. For the bisacodyl group, the tolerability was assessed as 'good' in 85 cases (35.6%) by the Investigator and in 125 cases (52.3%) by the patient. The tolerability as assessed by the patient was significantly better in the bisacodyl group than in the placebo group ($p=0.0058$). This was in spite of the fact that the incidence of diarrhoea was higher in the bisacodyl group (53.4%) than in the placebo group (1.7%). This result by the patient was not reflected by the Investigator however, where the tolerability was assessed significantly better in the placebo-treated patients than in the bisacodyl group ($p<0.0001$). An explanation for this result may be the way in which the Investigators interpreted the question about tolerability - and suggests that they considered this to mean "a treatment without side effects". Unsurprisingly, in the eyes of the Investigators, the placebo treatment largely met this interpretation, whereas for bisacodyl the same did not apply given that patients often had loose bowel motions or diarrhoea. It would

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	seem that tolerability is completely different to efficacy; especially from the Investigators point of view. In conclusion, the bisacodyl treatment proved to be generally well tolerated and the safety data were in line with the so far known safety profile of the substance.
Conclusions:	In conclusion, during the treatment period of 4 weeks the bisacodyl treatment significantly increased the number of CSBMs, reduced the severity of symptoms and improved the disease-related QoL with respect to the PAC-QoL© score in patients with functional constipation. The treatment with bisacodyl proved to be generally well tolerated and effective. The dosage can be selected within the dose recommendation according to the SPC, dependent on the individual tolerability of a patient with regard to the occurrence of diarrhoea. Overall, superiority of bisacodyl in comparison with placebo could be shown with regard to the primary endpoint as well as the secondary efficacy endpoints. In the data presented, bisacodyl is demonstrated as an effective treatment of functional constipation. Safety data were in line with the so far known safety profile of the substance. The hitherto available information on the efficacy and safety of stimulant (contact) laxatives for the management of chronic constipation was considered insufficient for a positive categorisation by evidence-based medicine reviews [P05-10329, P05-08337]. For this reason, this study assessed the effects of bisacodyl treatment with regard to efficacy and safety, time of onset and QoL improvement. This placebo-controlled trial generated data according to the most recent requirements (Rome III diagnostic criteria/GCP), making use of an eDiary which is highly recommended by the FDA. Using a randomised, double-blind, placebo-controlled design, this study confirmed the results of the study data gained by Kienzle-Horn et al. [P07-03176] on the efficacy and safety of bisacodyl over a 4 week treatment period.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement the results for patient disposition and secondary endpoints. Note that not all endpoints defined in the trial protocol are presented in this synopsis because their number was too large to allow meaningful presentation in this format.

Results for	**presented in**
Patient Disposition	Table 15.1.1: 1
Number of CSBMs at each of weeks 1,2,3,4	Table 15.2.2.1: 2
Number of SBMs at each of weeks 1,2,3,4	Table 15.2.2.3: 2
Number of patients with an increase of $\geq$ 1CSBM compared with baseline at each of weeks 1,2,3,4	Table 15.2.2.6: 1
Numbers of patients using rescue medication at each of weeks 1,2,3,4	Table 15.2.2.12: 1
Change from baseline in mean score per week for constipation symptoms at each of weeks 1,2,3,4	Table 15.2.2.13: 2
Change from baseline in mean patients' satisfaction score at each of weeks 1,2,3,4	Table 15.2.2.14: 2
Assessment of final global efficacy by the investigator at 4 weeks	Table 15.2.2.15: 1
Assessment of final global efficacy by the patient at 4 weeks	Table 15.2.2.15: 2
Change from baseline in SF 36 dimensions-QoL at 4 weeks	Table 15.2.2.16: 2
Change from baseline in PAC-QoL scale scores at 4 weeks	Table 15.2.2.17: 2

Table 15.1.1: 1 Disposition of patients

	Placebo		BIS		Total	
	N	(%)	N	(%)	N	(%)
Enrolled					736	
Not entered/randomised					368	
Entered/randomised	121		247		368	
Not treated	0		0		0	
Treated*	121	(100.0)	247	(100.0)	368	(100.0)
Not prematurely discontinued from trial medication	106	(87.6)	191	(77.3)	297	(80.7)
No information about discontinuation of trial medication	0	(0.0)	0	(0.0)	0	(0.0)
Prematurely discontinued from trial medication	15	(12.4)	56	(22.7)	71	(19.3)
Adverse event	6	(5.0)	44	(17.8)	50	(13.6)
Worsening of disease under study	3	(2.5)	3	(1.2)	6	(1.6)
Worsening of other pre-existing disease	0	(0.0)	1	(0.4)	1	(0.3)
Other adverse event	3	(2.5)	40	(16.2)	43	(11.7)
Non compliant with protocol	4	(3.3)	10	(4.0)	14	(3.8)
Lost to follow-up	0	(0.0)	0	(0.0)	0	(0.0)
Consent withdrawn	3	(2.5)	1	(0.4)	4	(1.1)
Other	2	(1.7)	1	(0.4)	3	(0.8)

* All patients treated based on eCRF information (even though they might not be treated based on eDiary information) are included here and in the safety analyses

Table 15.2.2.1: 2 Adjusted mean (SE) and ANCOVA results for the number of CSBMs at each week - FAS

	Placebo	BIS
Week 1		
Number of patients	117	239
Baseline		
Mean (SE)	1.1 (0.10)	1.1 (0.08)
Mean over treatment period		
Mean (SE)	2.0 (0.20)	6.3 (0.28)
Adjusted* mean (SE)	2.0 (0.40)	6.3 (0.32)
Comparison vs Placebo		
Adjusted* mean (SE)		4.3 (0.42)
95% Confidence interval		(3.5 , 5.2)
p-value		<.0001
Week 2		
Number of patients	115	229
Baseline		
Mean (SE)	1.1 (0.10)	1.1 (0.08)
Mean over treatment period		
Mean (SE)	1.6 (0.17)	5.1 (0.29)
Adjusted* mean (SE)	1.4 (0.41)	4.9 (0.33)
Comparison vs Placebo		
Adjusted* mean (SE)		3.5 (0.43)
95% Confidence interval		(2.7 , 4.3)
p-value		<.0001
Week 3		
Number of patients	113	213
Baseline		
Mean (SE)	1.1 (0.10)	1.0 (0.09)
Mean over treatment period		
Mean (SE)	2.0 (0.19)	4.7 (0.27)
Adjusted* mean (SE)	1.8 (0.38)	4.6 (0.32)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.1 pgmef\ef_csbm4.sas 11SEP2009

Table 15.2.2.1: 2 Adjusted mean (SE) and ANCOVA results for the number of CSBMs at each week - FAS

	Placebo	BIS
Comparison vs Placebo		
Adjusted* mean (SE)		2.8 (0.39)
95% Confidence interval		(2.0 , 3.6)
p-value		<.0001
Week 4		
Number of patients	105	196
Baseline		
Mean (SE)	1.1 (0.11)	1.0 (0.09)
Mean over treatment period		
Mean (SE)	2.1 (0.21)	4.5 (0.29)
Adjusted* mean (SE)	1.7 (0.42)	4.3 (0.35)
Comparison vs Placebo		
Adjusted* mean (SE)		2.6 (0.43)
95% Confidence interval		(1.8 , 3.4)
p-value		<.0001

* Adjusted for centre effects and baseline value

Table 15.2.2.3: 2 Adjusted mean (SE) and ANCOVA results for the number of SBMs at each week - FAS

	Placebo	BIS
Week 1		
Number of patients	117	239
Baseline		
Mean (SE)	4.3 (0.23)	4.6 (0.25)
Mean over treatment period		
Mean (SE)	4.9 (0.22)	11.7 (0.34)
Adjusted* mean (SE)	5.3 (0.46)	12.1 (0.37)
Comparison vs Placebo		
Adjusted* mean (SE)		6.7 (0.49)
95% Confidence interval		(5.8 , 7.7)
p-value		<.0001
Week 2		
Number of patients	115	229
Baseline		
Mean (SE)	4.3 (0.23)	4.5 (0.26)
Mean over treatment period		
Mean (SE)	4.7 (0.25)	9.5 (0.31)
Adjusted* mean (SE)	4.9 (0.44)	9.6 (0.36)
Comparison vs Placebo		
Adjusted* mean (SE)		4.7 (0.46)
95% Confidence interval		(3.8 , 5.6)
p-value		<.0001
Week 3		
Number of patients	113	213
Baseline		
Mean (SE)	4.3 (0.24)	4.5 (0.28)
Mean over treatment period		
Mean (SE)	4.9 (0.28)	8.7 (0.30)
Adjusted* mean (SE)	4.8 (0.44)	8.6 (0.36)

Source data: Appendix 16.1.9.2, Statdoc 6.2.3.1 pgmef\ef_sbm4.sas 11SEP2009

Table 15.2.2.3: 2 Adjusted mean (SE) and ANCOVA results for the number of SBMs at each week - FAS

	Placebo	BIS
Comparison vs Placebo		
Adjusted* mean (SE)		3.8 (0.45)
95% Confidence interval		(2.9 , 4.7)
p-value		<.0001
Week 4		
Number of patients	105	196
Baseline		
Mean (SE)	4.3 (0.25)	4.4 (0.29)
Mean over treatment period		
Mean (SE)	4.5 (0.25)	8.3 (0.31)
Adjusted* mean (SE)	4.0 (0.42)	7.8 (0.36)
Comparison vs Placebo		
Adjusted* mean (SE)		3.7 (0.43)
95% Confidence interval		(2.9 , 4.6)
p-value		<.0001

* Adjusted for centre effects and baseline value

Table 15.2.2.6: 1 Frequency distribution and treatment comparisons for the number of patients with increase of >=1 CSBM compared to baseline at each week - FAS

	Placebo	BIS
Number of patients	117 (100.0)	239 (100.0)
Increase of >=1 CSBM in week 1 [N (%)]		
No	60 (51.3)	35 (14.6)
95% Confidence interval [%]*	(41.9 , 60.6)	(10.4 , 19.8)
Yes	57 (48.7)	204 (85.4)
95% Confidence interval [%]*	(39.4 , 58.1)	(80.2 , 89.6)
Comparison vs Placebo		
Estimate		1.75
95% Confidence interval*		(1.44 , 2.13)
p-value**		<.0001
Increase of >=1 CSBM in week 2 [N (%)]		
No	72 (61.5)	51 (21.3)
95% Confidence interval [%]*	(53.1 , 71.5)	(17.1 , 28.2)
Yes	43 (36.8)	178 (74.5)
95% Confidence interval [%]*	(28.5 , 46.9)	(71.8 , 82.9)
Comparison vs Placebo		
Estimate		2.08
95% Confidence interval*		(1.62 , 2.66)
p-value**		<.0001
Increase of >=1 CSBM in week 3 [N (%)]		
No	62 (53.0)	50 (20.9)
95% Confidence interval [%]*	(45.2 , 64.2)	(18.0 , 29.7)
Yes	51 (43.6)	163 (68.2)
95% Confidence interval [%]*	(35.8 , 54.8)	(70.3 , 82.0)
Comparison vs Placebo		
Estimate		1.70
95% Confidence interval*		(1.37 , 2.11)
p-value**		<.0001
Increase of >=1 CSBM in week 4 [N (%)]		
No	53 (45.3)	48 (20.1)
95% Confidence interval [%]*	(40.5 , 60.4)	(18.6 , 31.1)
Yes	52 (44.4)	148 (61.9)
95% Confidence interval [%]*	(39.6 , 59.5)	(68.9 , 81.4)
Comparison vs Placebo		

Table 15.2.2.6: 1 Frequency distribution and treatment comparisons for the number of patients with increase of >=1 CSBM compared to baseline at each week - FAS

	Placebo	BIS
Estimate		1.52
95% Confidence interval*		(1.24 , 1.88)
p-value**		<.0001

* exact 95% CI by Clopper and Pearson
** Fisher exact test

Table 15.2.2.12: 1 Frequency distribution and treatment comparison for the number of patients using rescue medication at each week - FAS

	Placebo	BIS
Number of patients	117 (100.0)	239 (100.0)
Use of rescue medication in week 1 [N (%)]		
No	115 (98.3)	238 (99.6)
95% Confidence interval [%]*	(94.0 , 99.8)	(97.7 , 100)
Yes	2 (1.7)	1 (0.4)
95% Confidence interval [%]*	(0.2 , 6.0)	(0.0 , 2.3)
Comparison vs Placebo		
Estimate		0.24
95% Confidence interval*		(0.02 , 2.67)
p-value**		0.2524
Use of rescue medication in week 2 [N (%)]		
No	105 (89.7)	225 (94.1)
95% Confidence interval [%]*	(84.6 , 95.8)	(95.6 , 99.5)
Yes	10 (8.5)	4 (1.7)
95% Confidence interval [%]*	(4.2 , 15.4)	(0.5 , 4.4)
Comparison vs Placebo		
Estimate		0.20
95% Confidence interval*		(0.06 , 0.63)
p-value**		0.0035
Use of rescue medication in week 3 [N (%)]		
No	104 (88.9)	212 (88.7)
95% Confidence interval [%]*	(85.4 , 96.3)	(97.4 , 100)
Yes	9 (7.7)	1 (0.4)
95% Confidence interval [%]*	(3.7 , 14.6)	(0.0 , 2.6)
Comparison vs Placebo		
Estimate		0.06
95% Confidence interval*		(0.01 , 0.46)
p-value**		0.0004
Use of rescue medication in week 4 [N (%)]		
No	93 (79.5)	190 (79.5)
95% Confidence interval [%]*	(80.9 , 94.0)	(93.5 , 98.9)
Yes	12 (10.3)	6 (2.5)
95% Confidence interval [%]*	(6.0 , 19.1)	(1.1 , 6.5)
Comparison vs Placebo		

Table 15.2.2.12: 1 Frequency distribution and treatment comparison for the number of patients using rescue medication at each week - FAS

	Placebo	BIS
Estimate		0.27
95% Confidence interval*		(0.10 , 0.69)
p-value**		0.0086

* exact 95% CI by Clopper and Pearson
** Fisher exact test

Table 15.2.2.13: 2 Adjusted mean (SE) and ANCOVA results for the change from baseline in the mean score/week for constipation symptoms at each week - FAS

	Placebo	BIS
Number of patients	117 (100.0)	239 (100.0)
Degree of straining		
Baseline		
Mean (SE)	2.0 (0.08)	1.9 (0.05)
Week 1		
Number of patients	105	222
Mean (SE)	1.8 (0.08)	0.7 (0.05)
Adjusted* mean (SE)	1.7 (0.08)	0.7 (0.07)
Change from baseline		
Mean (SE)	-0.2 (0.07)	-1.3 (0.06)
Adjusted* mean (SE)	-0.3 (0.08)	-1.3 (0.07)
Comparison vs Placebo		
Adjusted* mean (SE)		-1.0 (0.08)
95% Confidence interval		(-1.2 , -0.9)
p-value		<.0001
Week 2		
Number of patients	105	204
Mean (SE)	1.8 (0.09)	0.7 (0.05)
Adjusted* mean (SE)	1.9 (0.09)	0.8 (0.08)
Change from baseline		
Mean (SE)	-0.2 (0.09)	-1.2 (0.06)
Adjusted* mean (SE)	-0.1 (0.09)	-1.1 (0.08)
Comparison vs Placebo		
Adjusted* mean (SE)		-1.0 (0.09)
95% Confidence interval		(-1.2 , -0.8)

* Adjusted for centre effects and baseline value

Table 15.2.2.13: 2 Adjusted mean (SE) and ANCOVA results for the change from baseline in the mean score/week for constipation symptoms at each week - FAS

	Placebo	BIS
p-value		<.0001
Week 3		
Number of patients	100	190
Mean (SE)	1.7 (0.08)	0.7 (0.05)
Adjusted* mean (SE)	1.7 (0.09)	0.7 (0.08)
Change from baseline		
Mean (SE)	-0.3 (0.09)	-1.2 (0.07)
Adjusted* mean (SE)	-0.3 (0.09)	-1.3 (0.07)
Comparison vs Placebo		
Adjusted* mean (SE)		-1.0 (0.10)
95% Confidence interval		(-1.1 , -0.8)
p-value		<.0001
Week 4		
Number of patients	96	178
Mean (SE)	1.6 (0.09)	0.8 (0.06)
Adjusted* mean (SE)	1.6 (0.10)	0.8 (0.08)
Change from baseline		
Mean (SE)	-0.5 (0.10)	-1.2 (0.08)
Adjusted* mean (SE)	-0.5 (0.10)	-1.2 (0.08)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.7 (0.10)
95% Confidence interval		(-0.9 , -0.5)
p-value		<.0001
Stool quality		
Baseline		

* Adjusted for centre effects and baseline value

Table 15.2.2.13: 2 Adjusted mean (SE) and ANCOVA results for the change from baseline in the mean score/week for constipation symptoms at each week - FAS

	Placebo	BIS
Mean (SE)	2.5 (0.11)	2.6 (0.08)
Week 1		
Number of patients	105	222
Mean (SE)	2.9 (0.12)	5.4 (0.08)
Adjusted* mean (SE)	3.0 (0.13)	5.5 (0.10)
Change from baseline		
Mean (SE)	0.3 (0.11)	2.9 (0.10)
Adjusted* mean (SE)	0.4 (0.13)	3.0 (0.11)
Comparison vs Placebo		
Adjusted* mean (SE)		2.6 (0.14)
95% Confidence interval		(2.4 , 2.9)
p-value		<.0001
Week 2		
Number of patients	105	204
Mean (SE)	2.9 (0.13)	5.3 (0.08)
Adjusted* mean (SE)	2.8 (0.14)	5.2 (0.12)
Change from baseline		
Mean (SE)	0.4 (0.12)	2.7 (0.11)
Adjusted* mean (SE)	0.2 (0.15)	2.7 (0.12)
Comparison vs Placebo		
Adjusted* mean (SE)		2.4 (0.14)
95% Confidence interval		(2.1 , 2.7)
p-value		<.0001
Week 3		
Number of patients	100	190

* Adjusted for centre effects and baseline value

Table 15.2.2.13: 2 Adjusted mean (SE) and ANCOVA results for the change from baseline in the mean score/week for constipation symptoms at each week - FAS

	Placebo	BIS
Mean (SE)	2.9 (0.12)	5.1 (0.09)
Adjusted* mean (SE)	3.0 (0.14)	5.2 (0.12)
Change from baseline		
Mean (SE)	0.5 (0.11)	2.6 (0.12)
Adjusted* mean (SE)	0.5 (0.14)	2.8 (0.12)
Comparison vs Placebo		
Adjusted* mean (SE)		2.3 (0.15)
95% Confidence interval		(2.0 , 2.5)
p-value		<.0001
Week 4		
Number of patients	96	178
Mean (SE)	3.0 (0.13)	4.9 (0.10)
Adjusted* mean (SE)	3.1 (0.16)	5.0 (0.13)
Change from baseline		
Mean (SE)	0.6 (0.11)	2.5 (0.12)
Adjusted* mean (SE)	0.6 (0.16)	2.6 (0.13)
Comparison vs Placebo		
Adjusted* mean (SE)		2.0 (0.16)
95% Confidence interval		(1.7 , 2.3)
p-value		<.0001
Number of incomplete evacuations		
Baseline		
Mean (SE)	0.7 (0.03)	0.7 (0.02)
Week 1		
Number of patients	115	232

* Adjusted for centre effects and baseline value

Table 15.2.2.13: 2 Adjusted mean (SE) and ANCOVA results for the change from baseline in the mean score/week for constipation symptoms at each week - FAS

	Placebo	BIS
Mean (SE)	0.7 (0.04)	0.5 (0.03)
Adjusted* mean (SE)	0.7 (0.05)	0.5 (0.04)
Change from baseline		
Mean (SE)	-0.1 (0.04)	-0.2 (0.03)
Adjusted* mean (SE)	-0.0 (0.05)	-0.2 (0.04)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.2 (0.05)
95% Confidence interval		(-0.3 , -0.1)
p-value		0.0002
Week 2		
Number of patients	113	220
Mean (SE)	0.7 (0.04)	0.5 (0.03)
Adjusted* mean (SE)	0.7 (0.06)	0.5 (0.05)
Change from baseline		
Mean (SE)	-0.1 (0.04)	-0.2 (0.04)
Adjusted* mean (SE)	-0.0 (0.05)	-0.2 (0.04)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.2 (0.05)
95% Confidence interval		(-0.3 , -0.1)
p-value		0.0003
Week 3		
Number of patients	107	201
Mean (SE)	0.7 (0.05)	0.5 (0.04)
Adjusted* mean (SE)	0.7 (0.05)	0.5 (0.04)
Change from baseline		

* Adjusted for centre effects and baseline value

Table 15.2.2.13: 2 Adjusted mean (SE) and ANCOVA results for the change from baseline in the mean score/week for constipation symptoms at each week - FAS

	Placebo	BIS
Mean (SE)	-0.1 (0.04)	-0.2 (0.04)
Adjusted* mean (SE)	-0.1 (0.05)	-0.2 (0.04)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.1 (0.06)
95% Confidence interval		(-0.2 , -0.0)
p-value		0.0127
Week 4		
Number of patients	104	188
Mean (SE)	0.6 (0.05)	0.5 (0.04)
Adjusted* mean (SE)	0.7 (0.06)	0.5 (0.05)
Change from baseline		
Mean (SE)	-0.1 (0.04)	-0.3 (0.04)
Adjusted* mean (SE)	-0.1 (0.06)	-0.2 (0.05)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.2 (0.06)
95% Confidence interval		(-0.3 , -0.0)
p-value		0.0064
Number of anorectal obstructions		
Baseline		
Mean (SE)	1.2 (0.10)	1.3 (0.06)
Week 1		
Number of patients	105	222
Mean (SE)	1.1 (0.10)	0.4 (0.04)
Adjusted* mean (SE)	1.2 (0.07)	0.4 (0.06)
Change from baseline		

* Adjusted for centre effects and baseline value

Table 15.2.2.13: 2 Adjusted mean (SE) and ANCOVA results for the change from baseline in the mean score/week for constipation symptoms at each week - FAS

	Placebo	BIS
Mean (SE)	-0.1 (0.07)	-0.9 (0.06)
Adjusted* mean (SE)	-0.1 (0.08)	-0.9 (0.06)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.7 (0.08)
95% Confidence interval		(-0.9 , -0.6)
p-value		<.0001
Week 2		
Number of patients	105	204
Mean (SE)	1.2 (0.10)	0.4 (0.05)
Adjusted* mean (SE)	1.2 (0.09)	0.4 (0.07)
Change from baseline		
Mean (SE)	-0.1 (0.09)	-0.9 (0.06)
Adjusted* mean (SE)	-0.1 (0.09)	-0.9 (0.07)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.8 (0.09)
95% Confidence interval		(-1.0 , -0.6)
p-value		<.0001
Week 3		
Number of patients	100	190
Mean (SE)	1.1 (0.10)	0.4 (0.05)
Adjusted* mean (SE)	1.1 (0.08)	0.4 (0.07)
Change from baseline		
Mean (SE)	-0.2 (0.08)	-0.9 (0.07)
Adjusted* mean (SE)	-0.1 (0.08)	-0.9 (0.07)

* Adjusted for centre effects and baseline value

Table 15.2.2.13: 2 Adjusted mean (SE) and ANCOVA results for the change from baseline in the mean score/week for constipation symptoms at each week - FAS

	Placebo	BIS
Comparison vs Placebo		
Adjusted* mean (SE)		-0.7 (0.09)
95% Confidence interval		(-0.9 , -0.5)
p-value		<.0001
Week 4		
Number of patients	96	178
Mean (SE)	1.1 (0.10)	0.5 (0.05)
Adjusted* mean (SE)	1.1 (0.09)	0.5 (0.07)
Change from baseline		
Mean (SE)	-0.2 (0.08)	-0.8 (0.07)
Adjusted* mean (SE)	-0.1 (0.09)	-0.8 (0.07)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.6 (0.09)
95% Confidence interval		(-0.8 , -0.5)
p-value		<.0001
Number of manual manoeuvres		
Baseline		
Mean (SE)	0.2 (0.04)	0.2 (0.02)
Week 1		
Number of patients	105	222
Mean (SE)	0.2 (0.04)	0.0 (0.01)
Adjusted* mean (SE)	0.2 (0.03)	0.0 (0.02)
Change from baseline		
Mean (SE)	-0.0 (0.04)	-0.2 (0.03)
Adjusted* mean (SE)	-0.0 (0.03)	-0.2 (0.03)

* Adjusted for centre effects and baseline value

Table 15.2.2.13: 2 Adjusted mean (SE) and ANCOVA results for the change from baseline in the mean score/week for constipation symptoms at each week - FAS

	Placebo	BIS
Comparison vs Placebo		
Adjusted* mean (SE)		-0.2 (0.03)
95% Confidence interval		(-0.2 , -0.1)
p-value		<.0001
Week 2		
Number of patients	105	204
Mean (SE)	0.2 (0.04)	0.0 (0.01)
Adjusted* mean (SE)	0.3 (0.03)	0.0 (0.03)
Change from baseline		
Mean (SE)	-0.0 (0.04)	-0.2 (0.03)
Adjusted* mean (SE)	0.0 (0.04)	-0.2 (0.03)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.2 (0.04)
95% Confidence interval		(-0.3 , -0.1)
p-value		<.0001
Week 3		
Number of patients	100	190
Mean (SE)	0.2 (0.04)	0.0 (0.01)
Adjusted* mean (SE)	0.2 (0.03)	0.0 (0.03)
Change from baseline		
Mean (SE)	-0.1 (0.04)	-0.2 (0.03)
Adjusted* mean (SE)	-0.0 (0.03)	-0.2 (0.03)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.2 (0.04)
95% Confidence interval		(-0.2 , -0.1)
p-value		<.0001

* Adjusted for centre effects and baseline value

Table 15.2.2.13: 2 Adjusted mean (SE) and ANCOVA results for the change from baseline in the mean score/week for constipation symptoms at each week - FAS

	Placebo	BIS
Week 4		
Number of patients	96	178
Mean (SE)	0.2 (0.04)	0.0 (0.02)
Adjusted* mean (SE)	0.2 (0.03)	0.0 (0.03)
Change from baseline		
Mean (SE)	-0.1 (0.04)	-0.2 (0.03)
Adjusted* mean (SE)	-0.1 (0.04)	-0.2 (0.03)
Comparison vs Placebo		
Adjusted* mean (SE)		-0.1 (0.04)
95% Confidence interval		(-0.2 , -0.0)
p-value		0.0018

* Adjusted for centre effects and baseline value

Table 15.2.2.14: 2 Frequency distribution and treatment comparison for the change from baseline (decreased, unchanged, increased score) in the weekly assessments of efficacy - FAS

	Placebo	BIS
Overall satisfaction with bowel habits		
Week 1		
Number of patients	112	224
Change in Score [N (%)]		
Score decreased	44 (39.3)	153 (68.3)
Score unchanged	46 (41.1)	45 (20.1)
Score increased	22 (19.6)	26 (11.6)
Comparison vs Placebo		
p-value*		<.0001
Week 2		
Number of patients	111	212
Change in Score [N (%)]		
Score decreased	41 (36.9)	163 (76.9)
Score unchanged	48 (43.2)	37 (17.5)
Score increased	22 (19.8)	12 (5.7)
Comparison vs Placebo		
p-value*		<.0001
Week 3		
Number of patients	104	195
Change in Score [N (%)]		
Score decreased	44 (42.3)	153 (78.5)
Score unchanged	43 (41.3)	31 (15.9)
Score increased	17 (16.3)	11 (5.6)
Comparison vs Placebo		
p-value*		<.0001
Week 4		
Number of patients	98	175
Change in Score [N (%)]		
Score decreased	37 (37.8)	135 (77.1)
Score unchanged	47 (48.0)	32 (18.3)
Score increased	14 (14.3)	8 (4.6)
Comparison vs Placebo		
p-value*		<.0001

Table 15.2.2.14: 2 Frequency distribution and treatment comparison for the change from baseline (decreased, unchanged, increased score) in the weekly assessments of efficacy - FAS

	Placebo	BIS
Bothersomeness of constipation		
Week 1		
Number of patients	112	224
Change in Score [N (%)]		
Score decreased	36 (32.1)	168 (75.0)
Score unchanged	51 (45.5)	46 (20.5)
Score increased	25 (22.3)	10 (4.5)
Comparison vs Placebo		
p-value*		<.0001
Week 2		
Number of patients	111	212
Change in Score [N (%)]		
Score decreased	35 (31.5)	160 (75.5)
Score unchanged	45 (40.5)	36 (17.0)
Score increased	31 (27.9)	16 (7.5)
Comparison vs Placebo		
p-value*		<.0001
Week 3		
Number of patients	104	195
Change in Score [N (%)]		
Score decreased	39 (37.5)	147 (75.4)
Score unchanged	41 (39.4)	30 (15.4)
Score increased	24 (23.1)	18 (9.2)
Comparison vs Placebo		
p-value*		<.0001
Week 4		
Number of patients	98	175
Change in Score [N (%)]		
Score decreased	30 (30.6)	125 (71.4)
Score unchanged	47 (48.0)	35 (20.0)
Score increased	21 (21.4)	15 (8.6)
Comparison vs Placebo		
p-value*		<.0001

Table 15.2.2.14: 2 Frequency distribution and treatment comparison for the change from baseline (decreased, unchanged, increased score) in the weekly assessments of efficacy - FAS

	Placebo	BIS
Bothersomeness of abdominal bloating		
Week 1		
Number of patients	112	224
Change in Score [N (%)]		
Score decreased	33 (29.5)	136 (60.7)
Score unchanged	47 (42.0)	59 (26.3)
Score increased	32 (28.6)	29 (12.9)
Comparison vs Placebo		
p-value*		<.0001
Week 2		
Number of patients	111	212
Change in Score [N (%)]		
Score decreased	31 (27.9)	142 (67.0)
Score unchanged	46 (41.4)	43 (20.3)
Score increased	34 (30.6)	27 (12.7)
Comparison vs Placebo		
p-value*		<.0001
Week 3		
Number of patients	104	195
Change in Score [N (%)]		
Score decreased	27 (26.0)	129 (66.2)
Score unchanged	45 (43.3)	49 (25.1)
Score increased	32 (30.8)	17 (8.7)
Comparison vs Placebo		
p-value*		<.0001
Week 4		
Number of patients	98	175
Change in Score [N (%)]		
Score decreased	25 (25.5)	107 (61.1)
Score unchanged	46 (46.9)	49 (28.0)
Score increased	27 (27.6)	19 (10.9)
Comparison vs Placebo		
p-value*		<.0001

Table 15.2.2.14: 2 Frequency distribution and treatment comparison for the change from baseline (decreased, unchanged, increased score) in the weekly assessments of efficacy - FAS

	Placebo	BIS
Bothersomeness of abdominal discomfort		
Week 1		
Number of patients	112	224
Change in Score [N (%)]		
Score decreased	37 (33.0)	93 (41.5)
Score unchanged	46 (41.1)	62 (27.7)
Score increased	29 (25.9)	69 (30.8)
Comparison vs Placebo		
p-value*		0.6773
Week 2		
Number of patients	111	212
Change in Score [N (%)]		
Score decreased	29 (26.1)	104 (49.1)
Score unchanged	49 (44.1)	67 (31.6)
Score increased	33 (29.7)	41 (19.3)
Comparison vs Placebo		
p-value*		0.0002
Week 3		
Number of patients	104	195
Change in Score [N (%)]		
Score decreased	34 (32.7)	101 (51.8)
Score unchanged	33 (31.7)	63 (32.3)
Score increased	37 (35.6)	31 (15.9)
Comparison vs Placebo		
p-value*		0.0001
Week 4		
Number of patients	98	175
Change in Score [N (%)]		
Score decreased	31 (31.6)	97 (55.4)
Score unchanged	36 (36.7)	46 (26.3)
Score increased	31 (31.6)	32 (18.3)
Comparison vs Placebo		
p-value*		0.0005

Table 15.2.2.15: 1 Frequency distribution and treatment comparison for the final global clinical assessment of efficacy by the investigator - FAS

	Placebo		BIS		Total	
	N	(%)	N	(%)	N	(%)
Number of patients [N]	117		239		356	
Number of patients with non-missing data	117	(100.0)	239	(100.0)	356	(100.0)
Global assesment						
Good	26	(22.2)	156	(65.3)	182	(51.1)
Satisfactory	37	(31.6)	59	(24.7)	96	(27.0)
Not satisfactory	30	(25.6)	18	(7.5)	48	(13.5)
Bad	24	(20.5)	6	(2.5)	30	(8.4)
Comparison vs. Placebo						
Wilcoxon rank sum test			28178.5			
Exact p-value (two-sided)			< 0.0001			

Table 15.2.2.15: 2 Frequency distribution and treatment comparison for the final global clinical assessment of efficacy by the patient - FAS

	Placebo		BIS		Total	
	N	(%)	N	(%)	N	(%)
Number of patients [N]	117		239		356	
Number of patients with non-missing data	117	(100.0)	239	(100.0)	356	(100.0)
Global assesment						
Good	23	(19.7)	132	(55.2)	155	(43.5)
Satisfactory	35	(29.9)	58	(24.3)	93	(26.1)
Not satisfactory	40	(34.2)	27	(11.3)	67	(18.8)
Bad	19	(16.2)	22	(9.2)	41	(11.5)
Comparison vs. Placebo						
Wilcoxon rank sum test			26528.0			
Exact p-value (two-sided)			< 0.0001			

Table 15.2.2.16: 2 Adjusted mean (SE) and ANCOVA results for the change from baseline in the SF-36 dimensions - FAS

	Change from baseline in mean score/week Adjusted* mean (SE)		Comparison vs Placebo		
	Placebo (N=117)	BIS (N=239)	Adjusted* mean (SE)	95% confidence interval	p-value
Physical functioning					
End of treatment phase	-0.6 (1.92)	-0.0 (1.55)	0.5 (2.01)	(-3.4 , 4.5)	0.7980
Role limitations physical problems					
End of treatment phase	-0.2 (1.96)	0.9 (1.58)	1.0 (2.05)	(-3.0 , 5.1)	0.6129
Bodily pain					
End of treatment phase	-2.3 (2.21)	-0.2 (1.78)	2.1 (2.31)	(-2.4 , 6.7)	0.3567
General health					
End of treatment phase	-1.3 (1.28)	0.7 (1.03)	2.0 (1.34)	(-0.7 , 4.6)	0.1407
Vitality					
End of treatment phase	-1.6 (1.66)	2.7 (1.34)	4.3 (1.74)	(0.9 , 7.7)	0.0130
Social functioning					
End of treatment phase	-2.6 (2.04)	-1.5 (1.64)	1.2 (2.14)	(-3.0 , 5.3)	0.5849
Role limitations emotional problem					
End of treatment phase	-0.5 (1.85)	0.1 (1.49)	0.6 (1.94)	(-3.2 , 4.4)	0.7543
Mental health					
End of treatment phase	-2.9 (1.52)	0.6 (1.22)	3.5 (1.58)	(0.4 , 6.6)	0.0273
Mental component summary					
End of treatment phase	-1.0 (0.82)	0.3 (0.66)	1.3 (0.87)	(-0.4 , 3.0)	0.1290
Physical component summary					
End of treatment phase	-0.4 (0.66)	0.3 (0.53)	0.6 (0.70)	(-0.8 , 2.0)	0.3780

* Adjusted for centre effects and baseline value
Note: A higher score for SF-36 dimensions indicates better health

Table 15.2.2.17: 2 Adjusted mean (SE) and ANCOVA results for the change from baseline in the PAC-QoL scale scores - FAS

	Change from baseline in mean score/week Adjusted* mean (SE)		Comparison vs Placebo		
	Placebo (N=117)	BIS (N=239)	Adjusted* mean (SE)	95% confidence interval	p-value
QOL Worries and concerns					
End of treatment phase	-0.1 (0.07)	-0.6 (0.06)	-0.5 (0.08)	(-0.6 , -0.3)	<.0001
QOL Physical discomfort					
End of treatment phase	-0.2 (0.09)	-1.0 (0.07)	-0.8 (0.09)	(-1.0 , -0.7)	<.0001
QOL Psychosocial discomfort					
End of treatment phase	-0.1 (0.07)	-0.3 (0.06)	-0.2 (0.07)	(-0.3 , -0.1)	0.0070
QOL Satisfaction					
End of treatment phase	-0.2 (0.12)	-1.4 (0.10)	-1.2 (0.13)	(-1.5 , -1.0)	<.0001
QOL Overall score					
End of treatment phase	-0.1 (0.08)	-0.8 (0.06)	-0.7 (0.08)	(-0.8 , -0.5)	<.0001

* Adjusted for centre effects and baseline value
Lower PAC-QOL scores indicates better QoL