Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Dulcolax®, Laxoberal®		**EudraCT No.:** 2007-002087-10	
Name of active ingredient: Sodium picosulfate (SPS)		**Page:** 1 of 9	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Report date: 06 JUL 2009	**Trial No. / U No.:** 1062.7 / U09-1609-01	**Date of trial:** 02 Nov 2007 - 07 Jan 2009	**Date of revision:** Not applicable

Title of trial:	A randomised, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of 4 weeks treatment with sodium picosulfate [Dulcolax®, Laxoberal®] drops 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 sodium picosulfate drops 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 sodium picosulfate 120 placebo (2:1 randomisation)
actual:	Enrolled: 468 treatment SPS: entered: 233, treated: 233, analysed (for primary endpoint): 229 (FAS) treatment placebo: entered: 134, treated: 134, analysed (for primary endpoint): 133 (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:	Sodium picosulfate [Laxoberal®]
dose:	10 mg (18 drops, reduction to 9 drops was allowed) once daily, in the evening
mode of admin.:	Oral
labelled batch no.:	PR07 / 20006
batch no.:	731706A (=B071002335)
Reference therapy:	Placebo
dose:	18 SPS-matching drops once daily, in the evening
mode of admin.:	Oral
labelled batch no.:	PR07 / 20006
batch no.:	B071002415
Rescue medication:	Bisacodyl suppositories [Dulcolax®]
dose:	10 mg
mode of admin.:	Rectal
labelled batch no.:	PR07 / 20006
batch no.:	731338A (=B071002333)
Duration of treatment:	4-week double-blind treatment phase (preceded by a 2-week baseline phase 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

- 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 still fulfilling Rome III diagnostic criteria for functional constipation
- 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, vital signs, laboratory values (serum chemistry and electrolytes), overall assessment of tolerability by patient and investigator

Statistical methods: Descriptive statistics; analysis of covariance for the mean number of 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 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 results:

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 SPS group from 0.9 (SE = 0.09) to 3.4 (SE = 0.20) and in the placebo group from 1.1 (SE = 0.12) to 1.7 (SE = 0.14) during this time interval. The adjusted (for centre effects and baseline) means after 4 weeks of treatment were 3.6 (SE = 0.25) in the SPS group and 1.8 (SE = 0.28) in the placebo group yielding a difference between both treatment groups of 1.8 (SE = 0.28), which was highly statistically significant ($p<0.0001$).

Secondary endpoints:

The number of CSBMs was analysed also 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 3.4 to 3.7 in the SPS group, whereas they ranged from 1.4 to 1.9 in the placebo group. The comparisons between the treatment groups for each week resulted in highly statistically significant differences in favour of SPS ($p<0.0001$).

The adjusted mean number (± SE) of SBMs / week over the 4 weeks treatment period was 7.2 (±0.31) in the SPS group and 4.0 (±0.34) in the placebo group.. The adjusted mean difference of 3.2 (±0.35) was statistically highly significant in favour of SPS ($p<0.0001$). The adjusted means for the weekly number of SBMs ranged from 6.7 to 7.7 in the SPS group compared to a range from 3.5 to 4.3 in the placebo group. The treatment comparisons for each week resulted in statistically highly significant differences in favour of SPS ($p<0.0001$).

Patients treated with SPS had their first SBM much earlier than those treated with placebo. The median time to the first SBM following the first dose of SM was 14 hours in the SPS group, whereas it was 24 hours in the placebo group.

The difference between the treatment groups was statistically significant ($p<0.0001$).

The percentage of patients with an increase of at least 1 CSBM per week over the 4 weeks treatment period compared with the last 7 days of the baseline period was 65.5% in the SPS group versus 32.3% in the placebo group. Taking into consideration the single weeks 1 to 4, the percentages ranged from 58.1% to 69.0% in the SPS group and from 36.1% to 42.1% in the placebo group. The differences were highly significant for each of the weeks and for the whole treatment period in favour of SPS ($p<=0.0008$).

The percentage of patients reaching a mean number of at least 1 CSBM a day over the 4 weeks treatment period was 9.6% in the SPS group, whereas no patient had at least 1 CSBM a day in the placebo group. The difference was highly significant ($p<0.0001$).
The percentage of patients reaching a mean number of at least 3 CSBMs per week over the 4 weeks treatment period was 51.1% in the SPS group versus 18.0% in the placebo group. The difference was again highly significant ($p<0.0001$).

There was no statistically significant difference ($p=0.6134$) in the number of premature withdrawals during the 4 weeks treatment period. In the group of patients treated with SPS, 5.2% of the patients discontinued the study prematurely, whereas the percentage in the placebo group was 3.8%.

The percentage of patients using RM at least once during the 4 weeks treatment period was 20.5% in the SPS group compared to 44.4% in the placebo group. When measured weekly, between 9.2% and 10.5% of the patients treated with SPS used RM, the percentages in the placebo group ranged between 22.6% and 27.8%. All differences between the treatment groups considering the total treatment period and the single weeks were significant (p-values ranged between <0.0001 and 0.0018).

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 highly significant comparing the SPS group versus the placebo group in favour of SPS ($p<0.0001$). The same applied for the symptoms ‘stool quality’ ($p<0.0001$) and ‘number of anorectal obstructions’ ($p<0.0001$) at each week. Also, the change in the ‘number of manual manoeuvres’ was statistically significant at each week

(p-values ranged between 0.0012 and 0.0165). For the constipation symptom 'number of incomplete evacuations', the difference was only significant at week 2 (p=0.0032) and week 3 (p=0.0309) but not at week 1 (p=0.0745) and at week 4 (p=0.0656). The results show that nearly all symptoms of constipation were significantly improved by SPS treatment at each week assessed.

The percentage of patients with an improved overall satisfaction with the bowel habits compared to baseline was ranging from 72.4% to 77.2% in the SPS group, whereas the corresponding percentage in the placebo group was ranging from 35.7% to 50.0% across the 4 weeks (p<0.0001). The percentage of patients with a reduced bothersomeness with their constipation compared to baseline was ranging from 66.7% to 75.3% in the SPS group, whereas the corresponding percentage in the placebo group was ranging from 33.3% to 50.5% across the 4 weeks. The treatment differences were highly statistically significant (p<0.0001). The percentage of patients with a reduced bothersomeness with abdominal bloating compared to baseline was ranging from 63.1% to 68.8% in the SPS group, whereas the corresponding percentage in the placebo group was ranging from 32.6% to 52.3% across the 4 weeks. The treatment differences were statistically significant in favour of SPS (p≤0.0014). The percentage of patients with a reduced bothersomeness with abdominal discomfort compared to baseline was ranging from 52.7% to 61.7% in the SPS group, whereas the corresponding percentage in the placebo group was ranging from 34.9% to 45.0% across the 4 weeks. The treatment differences were statistically significant in favour of SPS (p≤0.0081).

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' or 'satisfactory' in 86.9% of all patients treated with SPS and in only 48.2% of all patients allocated to placebo. The difference was highly significant (p<0.0001). The corresponding assessment by the patients was similar for both treatment groups, 89.5% in the SPS group and 87.2%in the placebo group (p=0.8801).

The patient friendly study course with the possibility to use rescue medication might be the cause for the good overall assessment by patients also in the placebo group. Rescue medication was more frequently taken in this patient group in comparison to SPS group.

The analysis of the QoL questionnaire SF-36™ only showed a significant

	improvement for the change from baseline in the SF-36™ dimensions 'General health' (p=0.0082) and 'Physical component summary' (p=0.0476). There were no significant improvements for the other dimensions (p ranged between 0.0547 and 0.9309). In the assessment of QoL by the constipation-related PAC−QoL© questionnaire, the overall score as well as the single scores 'Worries and concerns', 'Physical discomfort' and 'Satisfaction' were significantly improved in favour of SPS (p<0.0001, 'Psychosocial discomfort': p=0.0085) as measured as the change from baseline. The observed improvement in the PAC−QoL© score in SPS-treated patients compared to the patients of the placebo group shows that the treatment of constipation resulted in a subsequent increase in the patients' everyday functioning and well-being. In conclusion, the SPS treatment proved to be highly effective. Over the 4 weeks treatment period, the bowel function was significantly improved and the severity of symptoms in patients with functional constipation was reduced by SPS treatment compared to placebo. The vast majority of the analysed efficacy endpoints of this study showed a highly significant difference in favour of the SPS treatment: there was a significant increase in the number of CSBMs in the analysed time periods, and the time to the first SBM was significantly reduced compared to placebo. The number of patients using RM at least once was significantly reduced in the SPS group. In addition, the global assessment of efficacy by the investigator clearly supports these findings. Furthermore, the improvement of the constipation symptoms was significant for the whole treatment period as well as for the single weeks in favour of SPS. The number of patients who discontinued the study prematurely was low in both treatment groups without a significant difference.
Safety results:	No patient died during the course of the study. In the treated set (N = 367), 1 SAE (gastrointestinal disorders / constipation) occurred in 1 of 134 placebo-treated patients (0.7%) during the study. It was assessed as non-related to study medication. No SAE was reported in the group of patients treated with SPS. Other significant AEs according to ICH E3 occurred in 3 patients (2.2%) of the placebo group and in 71 patients (30.5%) of the SPS group. There was 1 patient (0.7%) in the placebo group and 8 patients (3.4%) in the SPS group with AEs leading to discontinuation of the study medication. In total, the number of patients in the placebo group (N = 134) affected by any

AEs was 25 (18.7%) and by severe AEs was 1 (0.7%). 102 patients (43.8%) suffered from AEs and 3 (1.3%) from severe AEs in the group of patients treated with SPS (N = 233). In the causality assessment to study medication, 8 patients (6.0%) in the placebo group and 86 (36.9%) patients had AEs in the SPS group which were defined as drug-related by the investigator. The higher number of SPS-treated patients, who suffered from AEs, may be due to an individually too high dosage of SPS (Laxoberal®, Dulcolax®) of 18 drops once daily at the beginning of the study. As a dose reduction (to 9 drops) was permitted, the number of AEs per week after the first week decreased until the end of the treatment.

The most frequent AE symptom by preferred term was diarrhoea, which occurred in 6 placebo-treated patients (4.5%) and in 74 SPS-treated patients (31.8%). Diarrhoea was assessed as ‘mild’ in 3 patients (2.2%), ‘moderate’ in 3 patients (2.2%) and ‘severe’ in no case in placebo-treated patients. The AE symptom diarrhoea in SPS-treated patients was assessed as ‘mild’ in 35 patients (15.0%), as ‘moderate’ in 37 patients (15.9%) and ‘severe’ in 2 patients (0.9%). Other adverse event symptoms occurred with a frequency ≤ 5% in all patients.

Expected adverse effects for SPS (Laxoberal®, Dulcolax®) drops, 7.5 mg / ml, are described in the current version of the SPC as episodes of abdominal discomfort, abdominal cramps and abdominal pain as well as diarrhoea. Isolated cases of allergic reactions, including skin reactions and angio-oedema, were listed in association with the administration of SPS. Expected adverse effects for bisacodyl (Dulcolax®) suppositories, 10 mg, are described in the current version of the SPC as abdominal discomfort (including cramps and abdominal pain) and diarrhoeas occurring occasionally. Also allergic reactions including isolated cases of angio-oedema and anaphylactoid reactions are listed as well as local irritation.

All reported AEs in the course of this study, beside diarrhoea, were observed with a similar frequency in both treatment groups. Due to the possibility to reduce the number of study medication drops per day to meet the patient’s individual needs, the number of patients with AEs decreased after week 1 to nearly the same low level as seen in patients with placebo treatment

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. During the course of the study, there

were only small changes in the assessed laboratory parameters without clinically significance.

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 22 cases (16.5%) by the investigator and in 64 cases (48.1%) by the patient. For the SPS group the tolerability was assessed as 'good' in 121 cases (52.8%) by the investigator and in 142 cases (62.0%) by the patient. Beside the higher frequency of diarrhoea in the first week of treatment, the tolerability was assessed significantly better in the SPS-treated patients than in the placebo group by the investigator ($p<0.0001$) as well as by the patient ($p=0.0007$).

Conclusions:

In conclusion, during the treatment period of 4 weeks the SPS 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 SPS proved to be generally well tolerated and safe. 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.