This Summary of Clinical Study Report is provided for patients and healthcare professionals to demonstrate the transparency efforts of the Menarini Group. This document is not intended to replace the advice of a healthcare professional and can't be considered as a recommendation. Patients must always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document can not be considered as prescribing advice.

The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

2. SYNOPSIS

Title Of Study: Otilonium Bromide in Irritable Bowel Syndrome – (OBIS) Double blind, randomized, parallel group, placebo-controlled study to evaluate the effect of otilonium bromide on abdominal pain and quality of life in patients with irritable bowel syndrome Protocol number: MeFi/04/OBR-IBS/001. EudraCT number 2005-001655-38	
Investigator(s): [redacted] List of Investigators: see Appendix 16.1.4	
Study Center(s): 34 centres in 8 countries: Spain (7 centres), Romania (8 centres), Greece (3 centres), Portugal (2 centres), Turkey (2 centres), Belgium (3 centres), Russia (6 centres) and Germany (3 centres). List of sites see Appendix 16.1.3	
Publication(s): Abstract accepted to Gastro 2009 UEGW/WCOG - London 21-25 Nov 09	
Studied Period: First patient enrolled: 16.01.2006 Last patient completed: 21.11.2008	**Clinical Phase:** IV/ III for Germany
Objective(s): **Primary:** • To confirm the efficacy of otilonium bromide (OB) in terms of symptom control (frequency of abdominal pain) in patients with irritable bowel syndrome (IBS) in a superiority trial versus placebo. **Secondary:** • Definition of the pattern of pharmacological effects of otilonium bromide on the other IBS symptoms • Assessment of the impact of treatment with otilonium bromide on the patients' quality of life • To evaluate whether long term treatment with otilonium bromide can have long term effects on IBS symptoms, thereby delaying symptom relapse following treatment discontinuation • To evaluate the economic impact of therapy • To evaluate the safety of treatment	
Methodology: superiority trial with a randomized, double-blind, parallel group, placebo-controlled design. Following a run-in period of 2 weeks of single-blind placebo treatment, patients were randomized to receive in double-blind conditions either otilonium bromide or placebo for 15 weeks. Thereafter "treatment success" patients entered a 10-week post-treatment follow-up period without any additional treatment.	
Number of Subjects: Planned: 336 randomised patients Screened: 413 patients Randomized: 356 patients (179 to otilonium bromide OB and 177 to placebo). Completed treatment phase: 295 patients (OB 146 and placebo 149) Analyzed - Safety: 355 patients - Efficacy (FAS): 339 patients (OB 169 and placebo 170)	
Diagnosis and Criteria for Inclusion: Patients meeting the following criteria were included: – Mentally competent, able to give written informed consent prior to study entry and available for all the visits scheduled in the study – Male or female patients aged over 18 years – Positive diagnosis for IBS according to the following symptom-based criteria (Rome II): – 12 weeks or more, which did not have to be consecutive, over the last 12 months of abdominal pain/discomfort that had two of the following three features: (a) Relieved by defecation (b) Associated with a change in frequency of stools (c) Associated with a change in consistency of stools – At least 2 episodes of abdominal pain for each week during the two weeks of run-in (at visit 2).	

Test Product, Dose, Mode of Administration, Batch No(s):
Otilonium bromide, 40 mg tablets three times daily before meals, i.e. 120 mg daily, by oral route
Batch N: 73015

Duration of Treatment:
For the individual patient:
Run-in: 2 weeks Treatment: 15 weeks Post-treatment follow-up: 10 weeks (Total: 27 weeks)
Global study duration:
Total recruitment period (first patient in to last patient in): 122 weeks
Study conduct (last patient in to last patient completed): 27 weeks
Total study duration: 149 weeks

Reference Therapy, Dose, Mode of Administration, Batch No(s):
Otilonium bromide placebo tablets by oral route, 1 tablet before each meal (t.i.d.)
Batch N: TFE0516

Criteria for Evaluation:
Main efficacy criteria

Primary efficacy variable:
• ***Frequency of abdominal pain (primary study endpoint)*** assessed on a 4-point score scale at the end of the 15-week treatment period based on the number of pain episodes during week:
0 = 0 episode during the week;
1 = 1 to 3 episodes during the week,
2 = 4 to 7 episodes during the week,
3 = 8 or more episodes during the week.

Secondary variables:
• Patient assessment of global treatment efficacy on IBS symptoms using a 4 point scale (from 0=no efficacy to 3=excellent efficacy)
• Physician assessment of global treatment efficacy on IBS symptoms using a 4 point scale (from 0=no efficacy to 3=excellent efficacy)
• Patient assessment of treatment efficacy on individual IBS symptoms (pain intensity, bloating-meteorism, stool consistency, mucus and frequency)
• Quality of life (QoL) using an IBS-QoL questionnaire (Patrick 1998)
• Weekly, monthly and treatment response rates
• Rates of symptom relapse and time to symptom relapse during the post-treatment 10 week follow-up period
• Pharmacoeconomics (Work Productivity and Activity Impairment Questionnaire (WPAI) and four questions)

Safety criteria
• Adverse events
• Laboratory safety assessments
• Vital signs and ECG

Statistical Methods:
The primary endpoint was the change from baseline to the end of the treatment period in the frequency of abdominal pain expressed on a 4-point scale. Primary efficacy end-point data and quality of life data were analysed using an analysis of covariance model; baseline value was included as covariate, and treatment and centre as factors. In case of early discontinuation or missing data, the last value available after randomisation was considered (Last Observation Carried Forward (LOCF) method).
Secondary efficacy endpoints were analysed using a logistic regression for proportional odds, including the treatment and centres effects. Responder data were analysed using a binary logistic regression model including factors for treatment, centres and any relevant covariates. Relapse rates during follow-up were calculated on the subpopulation of "successfully treated patients" and were analysed using a Cox proportional Hazard model, Kaplan-Meier curves were provided.
Additional variables, such as severity of pain, and safety data, were analysed descriptively.
The Intent-to-treat population (or full analysis set - FAS) was defined for the main analysis. The level of significance was established at 0.05 (two-sided).

SUMMARY – CONCLUSIONS

RESULTS:

Baseline characteristics

There were no relevant differences between the treatment groups in demographics and baseline characteristics.
The patient population recruited in this study consisted of patients of both sexes, with a high prevalence of women (252 out of 355; 71.0%) and the median age was 46.2 years.
The most common type of IBS was mixed (43.4 % in the total population), but also the other types were fairly well represented: the diarrhoea-predominant type was reported by 25.6% of patients and the constipation-predominant type by 31.0%.
About one fourth of the patients had a history of at least one previous disease other than IBS (24% in the total population, 23% in the OB group and 25% in the placebo group) and 15% of at least one previous treatment (17.0% in the OB group and 12.0% in the placebo group). The most common diseases were infections (6%), depression (4%) and miscellaneous gastrointestinal disorders (4%). The previous treatments consisted mainly in a variety of preparations related to the alimentary tract (10%).
About half of the patients had at least one concomitant disease and were taking concomitant treatment.

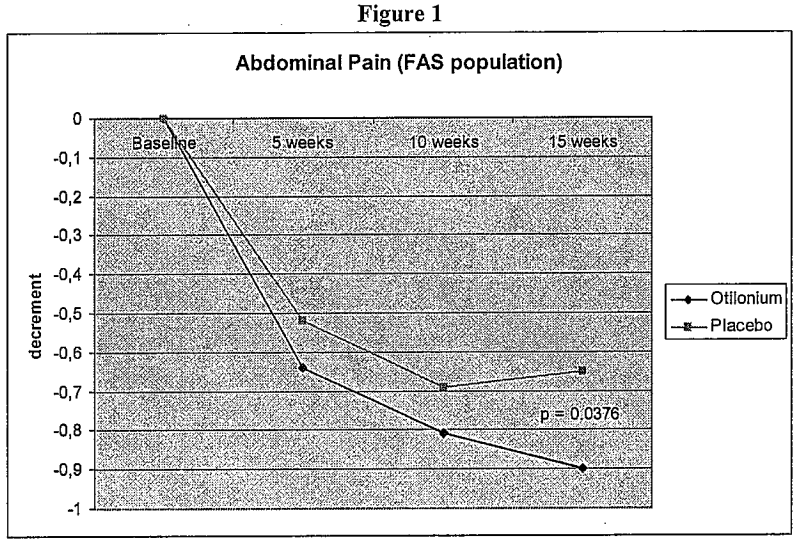
Efficacy
Primary endpoint

FAS population
At the end of the treatment the frequency of abdominal pain diminished significantly both in the OB group and the placebo group. The comparison between groups showed a favourable trend in the OB group in comparison to placebo at all visits with statistical significant differences for the primary endpoint (p=0.038).
Table 1 and Figure 1 show the comparison of treatment groups with respect to change from baseline at each visit.

Table 1 - Mean reduction (±SD) of frequency of abdominal pain episodes during the treatment period

	Baseline	Week 5	Week 10	Main variable Week 15
OB	1.86 ± 0.64	-0.64 ± 0.76	-0.81 ± 0.81	-0.90 ± 0.88*
Placebo	1.71 ± 0.67	-0.52 ± 0.85	-0.69 ± 0.84	-0.65 ± 0.91
*p<0.038 vs placebo				

Figure 1



PPS population
The results were similar in the PP population. The frequency of abdominal pain decreased significantly in both groups with a favourable trend in the OB group at each visit which reached statistical significance at the end of the treatment period (p=0.039).

Secondary endpoints:

Symptom severity
All symptoms were significantly ameliorated by treatment in both treatment groups starting from week 5 (all p<0.0001) and the improvement persisted until the end of treatment. The average number of stools improved significantly vs baseline only in the OB group at the end of treatment (p=0.004).
Among the symptoms assessed, abdominal bloating/meteorism was significantly improved with OB from week 10 (OB -1.1 ± 1.1 vs placebo -0.9 ± 1.1 p=0.03) and week 15 (OB -1.2 ± 1.2 vs placebo -0.9 ± 1.1 p=0.02) versus placebo. No significant differences

were observed in pain intensity, mucus and consistency of stools.

Global efficacy according to the patient
The global efficacy of treatment according to patients' judgment significantly improved in both treatment groups from week 5 (OB+0.8±0.9 , placebo +0.7±1.0; both p<0.0001 vs baseline) to the end of the treatment period (OB+1.3±1.1 placebo 1.0±1.1 p<0.0001 vs baseline). The comparison between groups became significant at the end of the treatment period in favour of the OB group (p=0.04).

Global efficacy according to the investigator
Also according to the investigator, the global efficacy of treatment improved significantly in both treatment groups starting at 5 weeks (OB +0.9±0.9 placebo +0.8±1.0 both p<0.0001 vs baseline) and persisted until the end of the treatment period (OB+1.3±1.1 placebo 1.1±1.1 p<0.0001 vs baseline). Although statistical differences between the treatment groups were not reached, the comparison between groups showed a favourable trend in the OB group in comparison to placebo at all visits.

Response rates
The weekly response rates were similar in the two treatment groups throughout the study. At the end of treatment the weekly response rate was 76.1% in the OB group and 73.1% in the placebo group (p=0.60).
The same was true for the monthly response rates, which were almost identical in the two treatment groups at the end of treatment (OB 82.6% placebo 82.5%).
The treatment response rate at the end of treatment (OB 61.5% vs placebo 57.8% p=0.55) and the treatment success rate (OB 59.9% placebo 55.3% p=0.48) were similar in the two treatment groups.

Quality of life
IBS quality of life raw scores were transformed to a 0-100 scale. The quality of life improvement was similar in the two treatment groups throughout the study. At the end of treatment the mean change was -15.14 ± 18.4 in the OB group and -15.77 ± 19.05 in the placebo group (p=0.95).

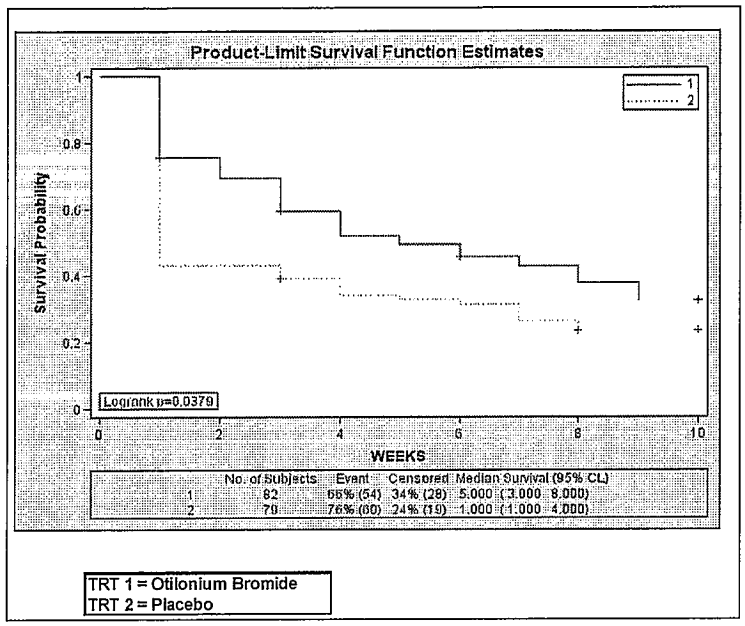
Pharmacoeconomic questions
Very few patients reported that they had consulted their general practitioner during the treatment period (7.7% in the OB group and 5.9% in the placebo group) or during follow-up period (1.2% in the OB group and 1.3% in the placebo group); the same was true for specialist consultations (treatment period: OB 4.7% placebo 5.3%; follow-up period: OB 1.2% placebo 0.0%).
Very few patients had had any laboratory tests or procedures done at any visit during treatment period (4.7% in the OB group and 1.2% in the placebo group) or during follow-up period (1.2% in the OB group and 0.0% in the placebo group) and few took any other medication for IBS (treatment period: OB 18.3% placebo 20.0%; follow-up period: OB 9.8% placebo 11.3%).

WPAI questionnaire
Slightly more than half the patients reported that they were employed during treatment period (OB 57.7% placebo 59.8%) and during the follow-up period (OB 63.4% placebo 55.7%).
During treatment period the mean number of hours missed from work per week due to problems related to IBS was 1.43 ± 3.89 in the otilonium bromide group and 0.61 ± 1.87 in the placebo group. During follow-up period this number decreased to 0.49 ± 2.41 in the OB group and to 0.57 ± 2.09 in the placebo group.
The VAS score related to the interference of IBS with productivity was similar in the two groups during treatment period (OB group: 2.19; placebo group: 1.92), but a major decrease was observed in the OB group during the follow-up period (OB group: from 2.19 to 0.52 – mean reduction-1.67; placebo group: from 1.92 to 1.24 – mean reduction -0.68).
Also the VAS score related to the interference of IBS with regular daily activities was similar in both groups during treatment period: it was 2.38 in the OB group and 2.41 in the placebo group. The decrease during follow-up period was slightly higher in the OB group (from 2.38 to 0.78: mean reduction -1.60) respect the placebo group (from 2.41 to 1.09: mean reduction 1.32).

Follow-up of successfully treated patients
At the end of double-blind period, 86 patients (59%) in OB group and 81 patients (54%) in placebo group, were treatment success and were eligible for entering the follow-up period. Four patients (3 patients in OB group and 1 patient in placebo group) refused to continue the study, while another patient in OB group started the follow-up period, but was lost before visit 6. A total of 162 patients (82 in OB group and 80 in placebo group) were considered for the follow-up analysis. During the follow-up period the withdrawal rate due to symptom relapse was significantly higher in the placebo group compared to OB group (27.2% vs 10.4% p=0.0089) indicating the sudden loss of the placebo effect.
According to the patients, the global efficacy of OB was significantly better than placebo at week 18 (p=0.0001) and 21 (p=0.009), and tended to be better than placebo at week 25 (p=0.06).
According to the investigators, the global efficacy of OB was significantly better than that of placebo throughout the whole follow-up period (week 18 p=0.0004, week 21 p<0.0001) and week 25 (p=0.0009).

Considering the overall follow-up period, the probability of being relapse-free was significantly higher in the OB group (p=0.038). Figure 2 shows the Kaplan-Meyer curves by treatment group during the follow-up period.

Figure 2



Safety:
Three hundreds and fifty-five patients were included in the Safety Population: 178 and 177 of which received OB and placebo, respectively.
No serious adverse events were reported during the whole study period.
A total of 43 patients (24%) in the OB group and of 30 patients (17%) in the placebo group reported at least one adverse event. Most of the patients reported adverse events during the treatment period: 36 patients (20%) in the OB group and 28 (16%) in the placebo group.
During treatment period only 3 events in the OB group (2 cases of dry mouth and 1 case of nausea) and none in the placebo group were judged related to the treatment by the Investigator.
Only 1 patient in each group was withdrawn because of safety reasons:

- Placebo - patient 008 site 50 was withdrawn during treatment period due to pregnancy
- Otilonium bromide – patient 004 site 82 was withdrawn during follow-up period for a food poisoning judged not related to the treatment by the Investigator.

Another patient (patient 015 site 55) randomized to otilonium bromide withdrew at visit 3 for an adverse event (abdominal pain) started during the placebo run-in phase of the study, but judged probably related to the treatment by the Investigator.

The most common treatment-emergent adverse events were gastrointestinal events (abdominal pain, flatulence, worsening IBS) and infections.
Nearly all the adverse events were mild to moderate (98.6% in the OB group and 98% in the placebo group) and were not related to study treatment (91.7% in the OB group and 94.2%).
Two pregnancies were reported during the study: one in the placebo group resulted in the birth of a healthy male baby, the other in the otilonium bromide group was terminated at week 9 when the mother decided to have an abortion.

CONCLUSIONS:

This study shows that Otilonium Bromide is safe, well tolerated and superior to placebo in reducing the frequency of abdominal pain, severity of abdominal bloating and protecting from symptom relapse in patients with Irritable Bowel Syndrome. Moreover, patients and investigators' assessments of global efficacy are also significantly superior in patients treated with OB. These results further confirm that patients with Irritable Bowel Syndrome can improve during and following treatment with Otilonium Bromide.