INTEGRATED CLINICAL AND STATISTICAL REPORT

A Phase IIIb/IV, Multi-centre, Double-blind, Randomised, Placebo-controlled Parallel Group Study to Compare the Efficacy and Safety of Movicol® with Placebo in Patients with Constipation Associated with Irritable Bowel Syndrome (IBS)

PRODUCT NAME: MOVICOL®

INDICATION: Constipation associated with irritable bowel syndrome

STUDY PROTOCOL NUMBER: NRL920-01/2008 (IBSc)

EudraCT NUMBER: 2008-000550-12

PHASE: IIIb/IV

Date first patient entered: 05 Dec 2008
Date last patient completed: 30 Nov 2009

Principal Investigator: [redacted] K

Name of Sponsor signatory: [redacted]
Norgine Pharmaceuticals Ltd., Norgine House, Widewater Place, Moorhall Road, Harefield, Uxbridge, UK

Date of this report: FINAL – 10 June 2010
Date of any previous reports: Not applicable

This study was performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements, including the archiving of essential documents.

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2. SYNOPSIS

Name of Sponsor: Norgine Pharmaceuticals Ltd.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of finished product: Movicol®®	Volume:	
Name of active ingredient: Macrogol (PEG) 3350	Page:	

Title of study:	A Phase IIIb/IV, Multi-centre, Double-blind, Randomised, Placebo-controlled Parallel Group Study to Compare the Efficacy and Safety of Movicol® with Placebo in Patients with Constipation Associated with Irritable Bowel Syndrome (IBS)
Investigator:	[redacted] (Principal Investigator)
Study centres:	Multi-centre study conducted in 15 centres in 6 countries: the Czech Republic (3 centres), France (1 centre), Germany (2 centres), Italy (4 centres), Poland (4 centres), Sweden (1 centre)
Publication (reference):	None
Studied period (years):	Date of first enrolment: 05 Dec 2008 Date of last completed: 30 Nov 2009
Phase of development:	Phase IIIb/IV
Objectives:	
Primary:	To evaluate the efficacy of Movicol® versus placebo in the relief of constipation associated with irritable bowel syndrome (IBS-C).
Secondary:	To evaluate the effect of treatment on other symptoms of IBS-C, ie, pain, bloating, straining, and the feeling of incomplete evacuation; to evaluate the effect of treatment on patient's quality of life (QOL); to evaluate the use of any rescue medication; to evaluate the safety of Movicol® in the treatment of patients with constipation associated with IBS-C.
Methodology:	Randomised, double-blind, placebo-controlled multi-centre study in parallel groups. A run-in period of 14 ± 2 days (during which patients received no study medication, and prescription or over the counter (OTC) laxative medications and constipating medications were prohibited) was followed by a 28-day (± 2 days) randomised treatment period, and a follow-up telephone call at Day 56 (± 7 days).
Number of patients (planned and analysed):	planned: 210 screened: 219 drop-outs: 80 randomised: 139 withdrawn: 15 completed: 124 analysed (safety): 137 analysed (efficacy): 135
Diagnosis and main criteria for inclusion:	Patients with constipation associated with IBS were eligible for inclusion. The main inclusion criteria were males and females aged 18 to 80 years inclusive with a diagnosis of IBS-C (using Rome III criteria) for the last 3 months, with symptom onset at least 6 months prior to diagnosis. The Rome III criteria specify IBS as recurrent abdominal pain or discomfort for at least 3 days per month in the last 3 months associated with 2 or more of the following: improvement with defecation; onset associated with a change in the frequency of stool; onset associated with a change in form (appearance) of stool. Patients had to have no symptoms of IBS-diarrhoea or IBS-mixed in the last 3 months and less than 3 spontaneous bowel movements during the last 7 days of the run-in period.
Test products, dose and mode of administration, batch number:	Movicol® 13.8 g sachets administered orally (sachet contents dissolved in 125 mL water) Days 1 and 2: 2 sachets daily (1 in the morning, 1 in the evening) After Day 2: 1-3 sachets daily* (1-sachet dose: taken in the morning; 2-sachet dose: taken as 1 in the morning, 1 in the evening; 3-sachet dose taken as 1 in the morning and 2 in the evening) *Dose adjusted by patients according to stool consistency to achieve Bristol stool chart type 3-5 as follows: type 1-2, increase dose to 3 sachets daily; type 6-7 decrease dose to 1 sachet daily (if after 24 hours stools remain at type 6-7, discontinue medication for 24 hours, then resume at 1 sachet per day). Batch number: 74467

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Duration of treatment:	28 days (± 2 days)	
Reference therapy, dose and mode of administration, batch number:	Placebo matching the test product (Movicol®) administered orally, as described for test product (above). Batch numbers: 140508 and 150508	
Criteria for evaluation:		
	For the assessment of efficacy and safety, patients were issued patient diary cards at Visits 1 (Screening Visit), 2 (Randomisation Visit), and 3 (Day 14) to be completed daily, in the evening.	
Efficacy:	Primary: • The mean number of spontaneous bowel movements measured in the 7-day period prior to Visit 4 (Day 28). A spontaneous bowel movement was defined as a bowel movement that occurred without the use of rescue medication or as any bowel movement occurring ≥24 hours after the use of rescue medication. Secondary: • Responder analysis, with a full responder defined as a patient with >4 spontaneous bowel movements per week and a responder defined as a patient with 3 or 4 spontaneous bowel movements per week. • The mean number of spontaneous bowel movements measured in Weeks 1, 2, and 3 of treatment. • The severity of discomfort/pain measured in the 7-day period prior to Visit 4 (Day 28) and in Weeks 1, 2, and 3 of treatment. • The stool consistency measured in the 7-day period prior to Visit 4 (Day 28) and in Weeks 1, 2, and 3 of treatment. • The severity of bloating measured in the 7-day period prior to Visit 4 (Day 28) and in Weeks 1, 2, and 3 of treatment. • The severity of straining measured in the 7-day period prior to Visit 4 (Day 28) and in Weeks 1, 2, and 3 of treatment. • The frequency of feeling incomplete evacuation measured in the 7-day period prior to Visit 4 (Day 28) and in Weeks 1, 2, and 3 of treatment. • The use of any rescue medication. • The change in the QOL score measured from Visit 2 (Randomisation Visit) to Visit 4 (Day 28).	
Safety:	• The incidence of adverse events (AEs). • Changes in physical examination.	
Statistical methods:	Patient diary card parameters were summarised as the mean of the 7 days prior to Visit 4 (Day 28) and in Weeks 1, 2, and 3 of treatment. The summary parameters were described using appropriate descriptive statistics. The difference between treatment groups at Visit 4 (Day 28) for the efficacy parameters was analysed with an analysis of variance (ANOVA). Analyses of secondary efficacy variables were exploratory; no adjustment was required for multiple testing. Safety data were summarised using descriptive statistics.	
SUMMARY OF RESULTS		
EFFICACY RESULTS:	The treatment groups were comparable with regard to demographic and baseline characteristics. In the primary analysis of efficacy, Movicol® was statistically significantly superior to placebo; in the last week there were significantly more spontaneous bowel movements in the Movicol® group (4.55 versus 3.09), with an adjusted (least squares [LS]) mean difference of 1.73 (95% confidence interval [CI]: 1.34, 2.13; ANOVA p<0.0001). The mean number of spontaneous bowel movements per week was also higher for the Movicol® group than for the placebo group at each week of the	

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	trial. The effect of country was also significant in the primary analysis (ANOVA p<0.0001), however, consistent with the confirmatory analysis, the mean number of spontaneous bowel movements was higher in the Movicol® group than in the placebo group in all countries. All secondary analyses of efficacy were exploratory and the findings generally supported the primary analysis. The frequency of full responders in the last week of treatment was higher for the Movicol® group (31 patients, 51.7%) than the placebo group (12 patients, 18.8%), with the difference being statistically significant (32.9%, 95% CI: 17.1, 48.8, p<0.0001). The percentage of patients reporting less than 3 spontaneous bowel movements in the previous 7 days (ie, non-responders) was lower for patients treated with Movicol® (23.8% and 20.0% at Day 14 and Day 28, respectively) than for patients treated with placebo (52.2% and 37.5%, respectively). For 3 of the 4 weeks of the treatment period (weeks 2, 3 and 4), the use of rescue medication was less for patients on Movicol® than for placebo-treated patients, but the difference was not statistically significant (ANOVA p=0.3514 in the last week of treatment). The severity of straining at each bowel movement was less for patients treated with Movicol® than for patients on placebo and for the 7-day period prior to Visit 4 the difference between treatment groups was statistically significant (adjusted mean difference: -0.69; 95% CI: -0.87, -0.51, ANOVA p<0.0001). Also stool consistency score was slightly higher (indicating softer stools) for patients treated with Movicol® than for patients on placebo and for the 7-day period prior to Visit 4, the difference between treatment groups was statistically significant (adjusted mean difference: 1.25; 95% CI: 1.06, 1.44, ANOVA p<0.0001). There was no statistically significant difference between the 2 treatment groups with regard to severity of abdominal discomfort/pain, the percentage of bowel movements with a feeling of incomplete evacuation, or severity of bloating sensation during each week of the treatment period. There were no clinically meaningful differences between treatment groups with regard to changes in QOL scores (as measured using the SF-36) from Day 0 to Day 28.
SAFETY RESULTS:	In total, 38.8% of Movicol®-treated patients and 32.9% of placebo-treated patients experienced treatment-emergent AEs (TEAEs); 11 (16.4%) Movicol® patients and 6 (8.6%) placebo patients experienced drug-related TEAEs. Only headache (Movicol® 14.9%; placebo 11.4%) and abdominal pain (Movicol® 6.0%; placebo 0.0%) were reported by >5% of patients in either treatment group. Abdominal pain and diarrhoea were reported as the most common drug-related TEAEs by 4.5% of patients in the Movicol® group, and diarrhoea was reported as the most common drug-related TEAE by 4.3% of patients in the placebo group. Severe TEAEs were reported for 2 (3.0%) Movicol®-treated patients only, with TEAEs of abdominal distension, diarrhoea, back pain, headache, sciatica, and incontinence being reported. Two Movicol®-treated patients had TEAEs that were considered possibly drug-related and led to discontinuation from the study (abdominal rigidity, and flatulence with abdominal pain). No deaths or other serious TEAEs were reported. There were no clinically meaningful changes in physical examination findings.
CONCLUSION:	Movicol® was statistically significantly superior to placebo in relieving constipation associated with IBS over a 28-day treatment period. Movicol® was well tolerated in this patient population and no safety concerns were raised.
Date of the report:	10 June 2010