~~2.~~ CLINICAL STUDY SYNOPSIS

Name of Company: **Alfa Wassermann S.p.A.**	**Volume:** (For national authority use only)
Name of Finished Product: Rifaximin-EIR (Extended Intestinal Release) Tablet	**Page:**
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Title of Study:	A Phase II, multicentre, double-blind, randomised, dose range finding placebo controlled study of Rifaximin- EIR tablet: clinical effectiveness and tolerability in the treatment of moderate, active Crohn's disease
Protocol Number:	RETIC/03/06
EudraCT Number:	2007-001014-17
Study Period:	**Phase of Development:** II
Date of first enrolment:	27 September 2007
Date of last completed:	23 September 2009
Study Coordinating Investigator:	[redacted]
German Coordinating Investigator:	[redacted]
Study Centres:	The study was conducted in 55 centres in France, Germany, Hungary, Israel, Italy, Poland, and Russia.
Publications:	Not applicable.
Objectives:	To assess the efficacy and safety of 3 doses of Rifaximin-Extended Intestinal Release (EIR) tablets (800 mg, 1,600 mg, and 2,400 mg, per day) compared to Placebo in the treatment of moderate, active Crohn's disease.
Study Design:	Multicentre, randomised, double-blind, placebo-controlled study. Patients were randomised to one of the following treatment groups: • Rifaximin-EIR tablet 1 x 400 mg (400 mg) + 2 Placebo tablets / twice daily (bid) (Rifaximin-EIR 400 mg bid group) • Rifaximin-EIR tablets 2 x 400 mg (800 mg) + 1 Placebo tablet / bid (Rifaximin-EIR 800 mg bid group) • Rifaximin-EIR tablets 3 x 400 mg (1,200 mg) / bid (Rifaximin-EIR 1,200 mg bid group) • Placebo tablets 3 x 400 mg (1,200 mg) / bid (Placebo group). For each patient, the study lasted up to 27 weeks (up to 2 weeks screening period, 12 weeks treatment period, and up to 13 weeks follow-up period).

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Number of Patients (planned and analyzed):

Planned: 424 patients were planned to be randomised.

Analysed: 410 patients were randomised (106 Rifaximin-EIR 400 mg bid group, 99 Rifaximin-EIR 800 mg bid group, 103 Rifaximin-EIR 1,200 mg bid group, and 102 Placebo group).

Diagnosis and Main Criteria for Inclusion:

Diagnosis: Patients with moderate, active Crohn's disease as defined by a CDAI score of ≥ 220 and ≤ 400.

Main criteria for inclusion:

- Patients of either sex,
- Patients aged between 18 and 75 years old, inclusively,
- Diagnosis of Crohn's disease localised in the ileum and/or colon, documented either radiologically or endoscopically at least 3 months previously,
- Patients with a CDAI of ≥ 220 to ≤ 400,
- Patients capable of and willing to conform to the study protocol,
- Patients who have provided signed and dated written informed consent.

Test Product, Dose and Mode of Administration, and Lot Numbers:

Rifaximin-EIR tablet, 400 mg, oral

Kit No.	Batch No.	Expiry Date
10001 - 11440	0890/2006	October 2008
	0891/2006	
	0892/2006	
	0893/2006	
11441 - 12344	1073/2007	November 2009
	1074/2007	

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Reference Therapy, Dose and Mode of Administration, and Lot Numbers:

Placebo tablet, 400 mg, oral

Kit No.	Batch No.	Expiry Date
10001 - 11440	0507/2006	October 2008
	0553/2006	
	0554/2006	
	0555/2006	
	0556/2006	
11441 - 12344	0114/2008	November 2009
	0115/2008	
	0116/2008	
	0117/2008	

Duration of Treatment: 12 weeks (84 ± 4 days)

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint:

- Clinical remission (defined as CDAI score < 150 points) after 12 weeks of treatment (Visit 6), irrespective of a reduction of 70 or 100 points of the CDAI score.

Secondary Efficacy Endpoints:

- Clinical remission (CDAI < 150) after 2, 4 and 8 weeks of treatment (at Visits 3, 4, and 5),
- Clinical response defined as a reduction in CDAI of ≥ 100 points from baseline value after 12 weeks of treatment (Visit 6),
- Clinical response defined as a reduction in CDAI of ≥ 70 points from baseline value after 12 weeks of treatment (Visit 6),
- Time to obtain clinical remission,
- Mean changes of CDAI absolute value at each visit,
- Clinical remission (CDAI < 150) at second week after stopping therapy, i.e., remission at Visit 7,
- Maintenance of clinical remission (CDAI < 150) at second week after stopping therapy, i.e., remission at Visit 6, which is maintained at Visit 7,
- Clinical remission (CDAI < 150) at the end of follow-up, i.e., remission at Visit 8,
- Maintenance of clinical remission (CDAI < 150) at the end of follow-up (12 weeks after stopping therapy), i.e., remission at Visit 6, which is maintained at Visit 7 and Visit 8,
- Treatment failure (increase of CDAI of > 100 points from baseline at any

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	time during treatment, or absence of a decrease of ≥ 70 points of CDAI from baseline at the last visit in the treatment period, or administration of rescue medication and/or a surgical procedure during the treatment period).
Safety:	<u>Safety Endpoints:</u> • Adverse events (AEs), • Withdrawals due to AEs, • Vital signs, • Safety laboratory parameters, • Physical examination.

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Statistical Methods:

Efficacy analyses were done both for the full analysis (FA) set (randomised patients receiving at least one dose of study drug), the modified full analysis (mFA) set (patients in FA set with at least one non-missing post-baseline CDAI score without prior use of rescue medication) and the per protocol (PP) set (patients of the FA set without major protocol violations). All analyses were of an exploratory nature.

Primary efficacy analysis:

The percentages of patients with clinical remission after 12 weeks of treatment was compared between the 3 Rifaximin-EIR doses and Placebo using a hierarchical testing strategy, starting with the highest dose group versus Placebo, based on the χ^2 test at the 2-sided 5% level. 95% confidence intervals for each pair-wise difference between remission rates were also computed.

To assess the effect of potentially confounding variables (age, sex, disease duration, country, smoking habits, baseline CRP, localisation of disease, previous surgery for Crohn's disease), clinical remission at Visit 6 was modelled by a logistic regression.

Secondary efficacy endpoints:

Clinical remission dates at each visit, clinical response, maintenance of clinical remission 2 weeks after stopping therapy and at the end of the follow-up and number of treatment failures were analysed in the same way as for the primary endpoint, including descriptive summaries of response rates within subgroups, except for logistic regression analysis.

Time to remission was analysed via Kaplan-Meier estimates per treatment group (including graphical displays) and by log-rank tests (overall and for pair-wise comparisons versus Placebo).

Score values and changes from baseline were summarised per visit (Visits 2 to 6) and treatment group by descriptive statistics.

Safety analysis:

The incidence of treatment emergent adverse events (TEAEs) was presented by treatment group (and overall), body system and preferred term. The frequency of TEAEs by intensity, causality to study drug and outcome were presented in tables. Serious adverse events (SAEs) and TEAEs leading to permanent discontinuation were included in a listing and summarized by treatment group and overall. The percentages of patients affected were compared between the four treatment groups by means of the exact version of the 2-sided Cochram-Armitage trend test, using the planned doses (Placebo, 400 mg, 800 mg, 1,200 mg bid) as scores.

Haematology, blood chemistry, and urinalysis evaluations were presented in tables, and a summary of shifts from baseline to End of Study was provided for each parameter.

Vital sign measurements, physical examination and concomitant medications were summarized.

Efficacy Results:

A total of 402 patients (98.0% of randomised patients) received at least one dose of study drug: 101 (99.0%) patients in the Placebo group, 104 (98.1%) patients in the Rifaximin-EIR 400 mg bid group, 98 (99.0%) patients in the Rifaximin-EIR 800 mg bid group and 99 (96.1%) patients in the Rifaximin-EIR 1,200 mg bid group.

Both the safety and the FA set consisted of 402 (98.0%) patients each, the mFA set consisted of 389 (94.9%) patients, the PP set consisted of 366 (89.3%) patients.

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In the FA set using the last value carried forward, the remission rates were highest in the Rifaximin-EIR 800 mg group (61 [62.2%] patients) and the Rifaximin-EIR 400 mg group (56 [53.8%] patients), compared with the Rifaximin-EIR 1,200 mg group (47 [47.5%] patients) and the Placebo group (43 [42.6%] patients). For the Rifaximin-EIR pooled treatment, the remission rate was 54.5% (164 patients).

In the confirmatory analysis, the difference in remission rate between Rifaximin-EIR 800 mg bid and Placebo was statistically significant (χ^2 test: $p = 0.005$), showing a superior treatment effect of Rifaximin-EIR 800 mg bid over Placebo. The difference in remission rate between Rifaximin-EIR pooled treatment and Placebo was statistically significant (χ^2 test: $p = 0.038$), showing a superior treatment effect of Rifaximin-EIR over Placebo. The difference in remission rate between Rifaximin-EIR 1,200 mg bid and Rifaximin-EIR 800 mg bid was statistically significant (χ^2 test: $p = 0.037$), showing a superior treatment effect of Rifaximin-EIR 800 mg bid over Rifaximin-EIR 1,200 mg bid.

Results were similar in the FA set using the complete cases (including treatment failures), and in the mFA set and PP set with the only exception of the pooled Rifaximin-EIR doses which was not statistically superior to Placebo (χ^2 test: $p = 0.057$) in the mFA set.

The results for the clinical remission rates in Rifaximin-EIR 800 mg bid treatment group were confirmed by a logistic regression analysis (last value carried forward) to assess the effect of potentially confounding factors.

Data for the secondary endpoint, clinical remission defined as CDAI score < 150 points after 2, 4 and 8 weeks of treatment (at Visits 3, 4, 5), at the second week after stopping treatment (Visit 7) and at the end of follow-up (Visit 8) showed for the FA set (complete cases, including treatment failures) that the remission rates increased from Visit 3 to Visit 5 and remained stable or slightly decreased to Visit 8 in all treatment groups. At Visits 3, 4, 5, 7 and 8, the remission rates were highest in the Rifaximin-EIR 800 mg bid group (22.8%, 50.0%, 59.6%, 57.5% and 59.0%, respectively) and lowest in the Placebo group (14.6%, 36.2%, 47.9%, 44.9% and 41.4%, respectively). The confirmatory analysis showed a statistically significant difference in remission rate between Rifaximin-EIR 800 mg bid and Placebo (χ^2 test: $p = 0.021$). Results were similar in the mFA set and PP set

Data for the secondary endpoint, clinical response defined as a reduction in CDAI of $\geq$ 100 points from baseline value after 12 weeks of treatment (i.e., at Visit 6) showed for the FA set (complete cases, including treatment failures) that the response rates at Visit 6 were highest in the Rifaximin-EIR 800 mg bid group (67 out of 93 patients [72.0%]) and the Rifaximin-EIR 400 mg bid group (59 out of 94 patients [62.8%]), compared with the Rifaximin-EIR 1,200 mg bid group (50 out of 87 patients [57.5%]) and the Placebo group (52 out of 93 patients [55.9%]). For the Rifaximin-EIR pooled treatment, the response rate was 64.2% (176 out of 274 patients). In the confirmatory analysis, the difference in response rate between Rifaximin-EIR 800 mg bid and Placebo was statistically significant (χ^2 test: $p = 0.022$), showing a superior treatment effect of Rifaximin-EIR 800 mg bid over Placebo. The difference in response rate between Rifaximin-EIR 1,200 mg bid and Rifaximin-EIR 800 mg bid was statistically significant (χ^2 test: $p = 0.041$), showing a superior treatment effect of Rifaximin-EIR 800 mg bid over Rifaximin-EIR 1,200 mg bid. Results were similar in the mFA set and PP set.

Data for the secondary endpoint, clinical response defined as a reduction in CDAI of $\geq$ 70 points from baseline value after 12 weeks of treatment (i.e., at Visit 6) showed for the FA set (complete cases, including treatment failures) that the response rates at Visit 6 were highest in the Rifaximin-EIR 800 mg bid group (72 out of 93 patients [77.4%]) and the Rifaximin-EIR 400 mg bid group (64 out of 94 patients [68.1%]), compared with the Rifaximin-EIR 1,200 mg bid group (58 out of 87 patients [66.7%]) and the Placebo group (57 out of 93 patients [61.3%]). For the Rifaximin-EIR pooled treatment, the response rate was

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70.8% (194 out of 274 patients). In the confirmatory analysis, the difference in response rate between Rifaximin-EIR 800 mg bid and Placebo was statistically significant (χ^2 test: p = 0.017), showing a superior treatment effect of Rifaximin-EIR 800 mg bid over Placebo. Results were similar in the mFA set and PP set. The pooled Rifaximin-EIR doses were statistically superior to Placebo (χ^2 test p = 0.045) in the PP set.

Data for the secondary endpoint, time to remission (CDAI < 150) showed for the FA set that the number of patients with an event increased during treatment in all treatment groups. At Week 26, the number of patients with event was the highest in the Rifaximin-EIR 800 mg bid group (71 patients), compared to the Rifaximin-EIR 400 mg bid group (66 patients), the Placebo group (61 patients) and the Rifaximin-EIR 1,200 mg bid group (60 patients). The median of time to remission (CDAI < 150) for the Placebo group was 47 days, for the Rifaximin-EIR 400 mg bid group was 35 days, for the Rifaximin-EIR 800 mg bid group was 27 days and for the Rifaximin-EIR 1,200 mg bid group was 38 days. The 2-sided log rank test for overall (any difference), for the difference between Rifaximin-EIR 400 mg bid and Placebo, the difference between Rifaximin-EIR 800 mg bid and Placebo and the difference between Rifaximin-EIR 1,200 mg bid and Placebo showed no statistical significance (p = 0.271, 0.368, 0.113 and 0.921, respectively). Results were similar in the mFA set and PP set.

Data for the secondary endpoint, maintenance of clinical remission (CDAI < 150 at Visits 6 and 7) showed for the FA set (unclear cases excluded) that the rates for maintenance of remission at Visits 6 and 7 were highest in the Rifaximin-EIR 800 mg bid group (47 out of 92 patients [51.1%]) and the Rifaximin-EIR 400 mg bid group (45 out of 101 patients [44.6%]), compared with the Rifaximin-EIR 1,200 mg bid group (37 out of 95 patients [38.9%]) and the Placebo group (35 out of 99 patients [34.4%]). For the Rifaximin-EIR pooled treatment, the rate for maintenance of remission was 44.8% (129 out of 288 patients). In the confirmatory analysis, the difference in the rate for maintenance of remission between Rifaximin-EIR 800 mg bid and Placebo was statistically significant (χ^2 test: p = 0.028), showing a superior treatment effect of Rifaximin-EIR 800 mg bid over Placebo. Results were similar in the mFA set and PP set. The pooled Rifaximin-EIR doses was statistically superior to Placebo (χ^2 test p = 0.045) in the PP set.

Data for the secondary endpoint, maintenance of clinical remission (CDAI < 150 at Visits 6, 7 and 8) showed for the FA set (unclear cases excluded) that the rates for maintenance of remission at Visits 6, 7, and 8 were highest in the Rifaximin-EIR 800 mg bid group (40 out of 89 patients [44.9%]) and the Rifaximin-EIR 400 mg bid group (39 out of 102 patients [38.2%]), compared with the Rifaximin-EIR 1,200 mg bid group (30 out of 94 patients [31.9%]) and the Placebo group (28 out of 98 patients [28.6%]). For the Rifaximin-EIR pooled treatment, the rate for maintenance of remission was 38.2% (109 out of 285 patients). In the confirmatory analysis, the difference in the rate for maintenance of remission between Rifaximin-EIR 800 mg bid and Placebo was statistically significant (χ^2 test: p = 0.020), showing a superior treatment effect of Rifaximin-EIR 800 mg bid over Placebo. Results were similar in the mFA set and PP set.

Data for the secondary endpoint, summary of CDAI score values (baseline value imputed only for treatment failures) showed for the FA set that the mean of observed values for the CDAI score decreased from Visit 2 (enrolment) to Visit 5 in all treatment groups and remained similar or slightly increased at Visit 6 (end of treatment). From Visit 6 to Visit 8 (final visit), the mean of observed values for the CDAI score increased slightly for the Placebo, the Rifaximin-EIR 400 mg bid and the Rifaximin-EIR 800 mg bid groups, while the mean of observed values for the CDAI score remained similar to the value at Visit 6 for the Rifaximin-EIR 1,200 mg bid group. The mean change from baseline to Visit 6 (end of treatment) for the CDAI score for the Placebo, Rifaximin-EIR 400 mg bid, Rifaximin-EIR 800 mg bid and Rifaximin-EIR 1,200 mg bid treatment group was -107.1, -121.5, -144.6 and -115.9, respectively. At Visit 8 (final visit), the mean change for the Placebo, Rifaximin-EIR 400 mg bid, Rifaximin-EIR 800 mg bid and

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Rifaximin-EIR 1,200 mg bid treatment group was -95.4, -110.4, -133.1 and -113.6, respectively. Results were similar in the mFA set and PP set.

Data for the secondary endpoint, treatment failures, showed for the FA set that the treatment failure rates were highest in the Placebo group (45 out of 101 patients [44.6%]), compared with the Rifaximin-EIR 400 mg bid group (40 out of 104 patients [38.5%]), the Rifaximin-EIR 800 mg bid group (25 out of 98 patients [25.5%]) and the Rifaximin-EIR 1,200 mg bid group (38 out of 99 patients [38.4%]). For the Rifaximin-EIR pooled treatment, the treatment failure rate was 34.2% (103 out of 301 patients). In the confirmatory analysis, the difference in treatment failure rates between Rifaximin-EIR 800 mg bid and Placebo was statistically significant (χ^2 test: $p = 0.005$), showing a superior treatment effect of Rifaximin-EIR 800 mg bid over Placebo. The difference in the treatment failure rate between Rifaximin-EIR 800 mg bid and Rifaximin-EIR 400 mg bid was also statistically significant (χ^2 test: $p = 0.049$). Results were similar in the mFA set and PP set.

Safety Results:

For the 301 patients who received active study drug, a mean (± SD) duration of exposure to Rifaximin-EIR of 70.1 ± 25.7 days (range: 2 to 119 days) was reported. The mean (± SD) dose of study drug was 55.36 ± 20.259, 116.11 ± 36.33 and 157.31 ± 68.10 g for Rifaximin-EIR 400 mg bid, 800 mg bid and 1,200 mg bid treatment group, respectively.

During the treatment period, 163 (40.5%) patients experienced at least one treatment emergent adverse event (TEAE) (in total 315 TEAEs); 45 (44.1%) patients in the Placebo group (85 TEAEs), 35 (33.7%) patients in the Rifaximin-EIR 400 mg bid group (73 TEAEs), 38 (38.4%) patients in the Rifaximin-EIR 800 mg bid group (76 TEAEs), and 45 (45.5%) patients in the Rifaximin-EIR 1,200 mg bid group (81 TEAEs).

A total of 48 (11.9%) patients experienced at least one drug-related TEAE (in total 77 TEAEs); 13 (12.7%) patients in the Placebo group (21 TEAEs), 9 (8.7%) patients in the Rifaximin-EIR 400 mg bid group (16 TEAEs), 8 (8.1%) patients in the Rifaximin-EIR 800 mg bid group (16 TEAEs) and 18 (18.2%) patients in the Rifaximin-EIR 1,200 mg bid group (24 TEAEs).

A total of 13 (3.2%) patients experienced at least one severe TEAE (in total 15 TEAEs); 4 (3.9%) patients in the Placebo group (5 TEAEs), 1 (1.0%) patient in the Rifaximin-EIR 400 mg bid group (one TEAE), 3 (3.0%) patients in the Rifaximin-EIR 800 mg bid group (3 TEAEs), and 5 (5.1%) patients in the Rifaximin-EIR 1,200 mg bid group (6 TEAEs). Of these severe TEAEs, the TEAE was related to study drug in 5 (1.2%) patients; one (1.0%) patient in the Placebo group, one (1.0%) patient in the Rifaximin-EIR 800 mg group and 3 (3.0%) patients in the Rifaximin-EIR 1,200 mg group.

A total of 6 (1.5%) patients experienced at least one serious TEAE (in total 6 TEAEs); 1 (1.0%) patient in the Placebo group (one TEAE), 2 (1.9%) patients in the Rifaximin-EIR 400 mg bid group (2 TEAEs), 1 (1.0%) patient in the Rifaximin-EIR 800 mg bid group (one TEAE), and 2 (2.0%) patients in the Rifaximin-EIR 1,200 mg bid group (2 TEAEs). Of these serious TEAEs, the TEAE was related to study drug in one (1.0%) patient in the Rifaximin-EIR 1,200 mg group. No patients died during the treatment period.

Study drug was stopped due to a TEAE in 32 (8.0%) patients; 6 (5.9%) patients in the Placebo group, 5 (4.8%) patients in the Rifaximin-EIR 400 mg bid group, 5 (5.1%) patients in the Rifaximin-EIR 800 mg bid group, and 16 (16.2%) patients in the Rifaximin-EIR 1,200 mg bid group.

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During the follow-up period, 53 (19.1%) patients experienced at least one TEAE (in total 66 TEAEs); 11 (17.7%) patients in the Placebo group (13 TEAEs), 14 (18.7%) patients in the Rifaximin-EIR 400 mg bid group (20 TEAEs), 16 (21.6%) patients in the Rifaximin-EIR 800 mg bid group (18 TEAEs), and 12 (17.9%) patients in the Rifaximin-EIR 1,200 mg bid group (15 TEAEs). Two (0.7%) patients experienced at least one drug-related TEAE (in total 2 TEAEs); 1 (1.6%) patient in the Placebo group (one TEAE), and 1 (1.5%) patient in the Rifaximin-EIR 1,200 mg bid group (one TEAE). A total of 4 (1.4%) patients experienced at least one severe TEAE (in total 5 TEAEs); 2 (2.7%) patients in the Rifaximin-EIR 400 mg bid group (3 TEAEs), and 2 (2.7%) patients in the Rifaximin-EIR 800 mg bid group (2 TEAEs). A total of 6 (2.2%) patients experienced at least one serious TEAE (in total 6 TEAEs); 1 (1.3%) patient in the Rifaximin-EIR 400 mg bid group (one TEAE), 3 (4.1%) patients in the Rifaximin-EIR 800 mg bid group (3 TEAEs), and 2 (3.0%) patients in the Rifaximin-EIR 1,200 mg bid group (2 TEAEs). One patient (0.2%) (Rifaximin-EIR 800 mg bid group) died due to a TEAE (sudden death, considered unrelated to study drug).

There were no significant differences between the treatment groups regarding the overall AE profile, apart from a significantly higher proportion of patients in the Rifaximin-EIR 1,200 mg bid group, who discontinued the study drug due to a TEAE (Exact Cochran-Armitage trend test showed differences between treatment groups for 'drug stopped due to TEAE' and 'drug stopped due to drug-related TEAE' with $p = 0.010$ and 0.006, respectively). Most of the events which led to treatment discontinuation, regardless of the drug relation, reflect the underlying disease.

The most common TEAEs during the treatment period were headache (overall 26 [6.5%] patients), Crohn's disease (25 [6.2%] patients), and nausea (15 [3.7%] patients). The most common possibly related TEAEs were headache and nausea (9 [2.2%] patients, each), flatulence (7 [1.7%] patients), and abdominal pain upper and Crohn's disease (4 [1.0%] patients, each). The most common probably related TEAEs were diarrhoea and pruritus (2 [0.5%] patients, each). One certainly related TEAE (vomiting) was reported. The most common severe TEAE was headache (2 [0.5%] patients).

The most common SAEs by SOC were gastrointestinal disorders (3 [1.5%] patients in the treatment period and 2 [0.7%] patients in the follow-up period). One patient, who experienced an SAE during the follow-up period, died. The event (sudden death) was assessed as unlikely related to the study drug.

In general, there were no clinically relevant abnormalities or changes of laboratory parameters, vital signs, and physical examination findings during the study.

Conclusions:

- Rifaximin-EIR 800 mg bid is superior to Placebo in the induction of clinical remission and clinical response, defined as a decrease of CDAI $\geq$ 100 or 70 points from baseline. The clinical remission was significantly maintained during the 12 week follow-up period.
- Rifaximin-EIR 800 mg bid is superior to Rifaximin-EIR 1,200 mg bid in the induction of clinical remission and clinical response (CDAI reduction $\geq$100). Superiority is not statistically significant for other endpoints.
- Rifaximin-EIR is safe and well tolerated at all dose regimens tested. A significantly higher proportion of patients in the Rifaximin-EIR 1,200 mg group discontinued the study drug due to a TEAE.

Date of Report: 09 Jun 2010