1. SYNOPSIS

Name of Sponsor/Company: Italfarmaco S.p.A., Via dei Lavoratori, 54, 20092 Cinisello Balsamo (MI), Italy

Name of Active Ingredient: ITF2357 (INN Givinostat)

Name of Finished Product: Not applicable

Title of the study: Multicenter, randomized, double-blind, placebo-controlled study to evaluate the effect of ITF2357 on mucosal healing in patients with moderate-to-severe active Crohn's Disease

Investigators: 28 Principal Investigators (8 in The Netherlands, 9 in Belgium, 7 in Serbia, 3 in Israel and 1 in Italy) (see appendix 16.1.4)

Study centres: the study documentation was submitted to 36 centres, 28 of them were activated and 14 actively recruited patients (4 centres located in The Netherlands, 5 in Belgium, 3 in Serbia, 1 in Israel and 1 in Italy)

Publication (reference): None

Study period: First patient enrolled: 22/10/2007; Last patient completed: 11/03/2009 | **Phase of development:** II

Objectives: The primary objective of the study was to determine the ability of ITF2357, administered orally at the dose of 50 mg b.i.d. for 8 consecutive weeks, to induce complete healing of mucosal ulcerations of ileum and/or colon, assessed by endoscopy, in patients with endoscopic and clinical evidence of active moderate-to-severe Crohn's disease not controlled by conventional therapies.

The secondary objectives of the study were: to evaluate the effect of ITF2357 on endoscopic disease activity assessed using both the Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score of Crohn's Disease (SES-CD); to evaluate the effect of ITF2357 on clinical disease activity, assessed using the Crohn's Disease Activity Index (CDAI); to assess the safety and tolerability of ITF2357; to assess the pharmacokinetic profile of ITF2357.

Methodology:

The study was conducted according to a randomized, double-blind, placebo-controlled, parallel group design.

Eligible patients were randomly assigned to two parallel treatment groups (1:1 randomization ratio) receiving either ITF2357, as hard gelatine capsules for oral administration, or matching placebo capsules. Treatment was administered on an outpatient basis for 8 consecutive weeks, followed by a 4-week follow-up off treatment. During screening, in the 8-week treatment period and in the 4-week follow-up period, patients attended nine scheduled visits, with physical and laboratory assessments, in order to monitor disease evolution, and safety and tolerability of ITF2357.

Number of patients (total and in each arm):

	Randomised	ITT	PP	Safety	Completed
Total	51	51	33	51	33
ITF2357	25	25	17	25	18
Placebo	26	26	16	26	19

Diagnosis and main criteria for inclusion:

Age ≥ 18 years; diagnosis of CD, (re)-established by endoscopy and/or X-ray and/or surgery in the last 36 months; CD in active phase since at least 2 weeks before screening; CDAI between 220 and 450; CDEIS > 8; ulcerations greater than aphthous ulcers in at least 1 of the bowel segments from the ileum to the rectum; if any on-going treatment with corticosteroids (prednisone, prednisolone or budesonide), at a dose equivalent to or less than 30 mg/day prednisone, or 9 mg of budesonide, the use for at least one month and at a stable dose for at least two weeks before patient enrolment was required; if any on-going treatment with immunosuppressant (azathioprine, 6-mercaptopurine, methotrexate), the use for at least 3 months before patient enrolment was required; if any on-going treatment with 5-aminosalicilates, the use for at least 4 weeks before patient enrolment, at a dose ≥ 2 g, was required; females of childbearing potential with negative pregnancy tests; signed written informed consent to participate in this trial.

Test product, dose and mode of administration, batch no: ITF2357 50 mg capsules via oral route, one capsule in the morning and one in the evening. ITF2357 was provided in batch No. PPD (expiry PPD) and No. PPD (expiry PPD).

Duration of treatment: 8 weeks.

Reference therapy, dose and mode of administration, batch no: ITF2357 placebo capsules via oral route, one capsule in the morning and one in the evening. ITF2357 placebo was provided in batch No. PPD (expiry PPD, extended to PPD).

Criteria for evaluation:

Efficacy:

The primary efficacy variable in the study was the rate of complete mucosal healing at week 8. A complete healing was defined as absence of deep and superficial ulcerations.

The secondary efficacy variables were:

- Endoscopic remission rate. Endoscopic full remission was defined as a score ≤ 3 points in CDEIS at week 8; endoscopic remission was defined as a score ≤ 6 points in CDEIS at week 8;
- Endoscopic response rate. Endoscopic response was defined as a decrease by ≥ 4.5 points vs. baseline in CDEIS at week 8;
- Mean changes in CDEIS score at week 8 vs. baseline;
- Mean changes in SES-CD score at week 8 vs. baseline;
- Mean changes from baseline in the overall CDAI score;
- CDAI remission rate. Remission was defined as a CDAI score lower than 150 points;
- CDAI response rate. Response was defined as a decrease from baseline in CDAI score greater than 100 points;
- Mean changes from baseline in serum CRP.

Safety:

Safety variables were: haematology, blood chemistry and urine values; vital signs, ECG recording, physical examinations and adverse events (including premature study discontinuation due to toxicity).

Statistical methods:

The following populations were considered for analysis: intent-to-treat (ITT), defined as all randomized patients who received at least one dose of study medication (the ITT coincided with the safety population); per-protocol (PP), defined as all patients from the ITT population without major protocol deviations. Analyses of efficacy parameters were performed in the ITT population. Analyses of primary endpoint (complete healing), endoscopic full remission, endoscopic remission and endoscopic response were also repeated on the PP population. All safety analyses were performed in the safety population.

Two tables were presented for the primary endpoint (rate of patients achieving complete healing at week 8): a) A frequency analysis including the rate of responders in each treatment arm and the Wald statistics value compared with Exact superiority Z-score; b) A statement regarding the comparison between the two treatment arms, based on the use of the table "Discrete Continuation Region". A defaults summary statistics at each visit and their changes from baseline to each visit were presented for CDEIS score, SES-CD score, overall CDAI score, and serum CRP. Frequency tabulations (count and percentage) were presented for the following parameters: endoscopic full remission rate, endoscopic remission rate, endoscopic response rate, CDAI remission rate and CDAI response rate.

All adverse events recorded during the study were coded and assigned to a SOC and PT according to MedDRA Dictionary. Adverse events were reported on a per-patient basis. The relationship to the investigational drug administration was shown as related or unrelated using the following categories: "*definitely", "probably", "possibly", "unlikely" and "unknown".*

The measured laboratory values were classified as: 1) Normal; 2) Abnormal, not clinically relevant; 3) Abnormal due to Crohn's disease; 4) Abnormal, clinically relevant; 5) Classification not available. For each variable, where appropriate, the reported values and reference ranges were converted into SI units. For each variable the change from baseline to each post-baseline visit was calculated. The following tables were arranged: a) a default summary statistics for all variables at each scheduled visit and their changes from baseline; b) a shift-table of the changes from baseline to week 8 (end of treatment period) and follow-up in the laboratory values according to the classification reported above.

The results of blood pressure and heart rate were analysed in form of descriptive statistics. A default summary statistics for all variables at each visit and their changes from baseline to each visit were presented.

Possible responses of ECG results were "*Normal*" and "*Abnormal not clinically relevant*", "*Abnormal clinically relevant*". A default summary statistics for the QTc interval at each visit and their changes from baseline to each visit were presented. A shift-table of the changes in the overall assessment of the ECG tracing from baseline to week 8 and follow-up was arranged.

Study population:

A total number of 74 patients were screened for enrolment in this study and 51of them were randomised to the assigned treatment group: 25 (49.0% of total population) were randomised to receive ITF2357 and 26 (51.0%) were randomised to receive placebo. A total number of 37 patients, 18 in the ITF2357 group and 19 in the placebo group, completed the study, while 14 patients, 7 (28.0%) in the ITF2357 group and 7 (26.9%) in the placebo group, were withdrawn from the study after randomisation. No data were collected for screening failure patients.

Extent of exposure and compliance:

The mean cumulative dose of study drug (mg) was 4492 ± 1892 (range 500-6400) in the ITF2357 group and 4796 ± 1303 (range 1550-5900) in the placebo group. The mean compliance to study drug (%) was 80 ± 34 (range 9-114) in the ITF2357 group and 86 ± 23 (range 28-105) in the placebo group.

Efficacy results:

Primary efficacy variable: rate of patients achieving complete mucosal healing at week 8

In the ITT population, the number of patients achieving complete healing was 1 (4.0%) in the ITF2357 group and 0 (0.0)% in the placebo group. The delta rate between the ITF2357 group and the placebo group was 4.0% and the SE of the difference between rates was 0.039. The Z-score was equal to 1.030, thus showing that ITF2357 was not superior to placebo (Z-score limit for superiority was 2.808). The results in the PP population were similar to those observed in the ITT analysis.

Secondary efficacy variables:

Endoscopic remission:
In the ITT population, the full endoscopic remission (CDEIS score ≤ 3 points at week 8) was reached by 1 (4.0%) patient in the ITF2357 group and by 2 (7.7%) in the placebo group. The endoscopic remission (CDEIS score ≤ 6 points at week 8) was reached by 5 (20.0%) patients in the ITF2357 and by 3 (11.5%) in the placebo group. The results in the PP population were similar to those observed in the ITT analysis.

Endoscopic response:
In the ITT population, the endoscopic response (decrease of CDEIS score ≥ 4.5 points from baseline to week 8) was reached by 7 (28.0%) patients in the ITF2357 group and by 6 (23.1%) in the placebo group. The results in the PP population were similar to those observed in the ITT analysis.

CDEIS and SES-CD score:
The mean changes from baseline to week 8 of CDEIS score were -2.4 ± 4.2 in the ITF2357 group and -2.5 ± 5.6 in the placebo group. The mean changes from baseline to week 8 of SES-CD score were -2.0 ± 4.0 in the ITF2357 group and -2.6 ± 4.5 in the placebo group

CDAI score:
The mean decreases from baseline were -32.7 ± 84.5 in the ITF2357 group and -85.3 ± 95.9 in the placebo group at week 4; -54.7 ± 94.3 in the ITF2357 group and -119 ± 96.5 in the placebo group at week 8; and -83.8 ± 82.0 in the ITF2357 group and -106 ± 91.6 in the placebo group at follow-up.

Remission Rate:
The remission (CDAI < 150) was reached by 4 patients (16.0%) in the ITF2357 group and by 10 (38.5%) in the placebo group) at week 4; by 7 patients (28.0%) in the ITF2357 and by 14 (53.8%) in the placebo group at week 8; and by 9 patients (36.0%) in the ITF2357 group and by 11 (42.3%) in the placebo group at the follow-up after one month.

Responder Rate:
The number of responders (decrease of CDAI score > 100 points from baseline) was 6 (24.0%) in the ITF2357 group and 11 (42.3%) in the placebo group) at week 4, 8 (32.0%) in the ITF2357 group and 14 (53.8%) in the placebo group at

week 8, and 11 (44.0%) in the ITF2357 group and 14 (53.8%) in the placebo group at the follow-up after one month.

Safety results:

Adverse events:

Thirty-seven (37) patients in total, 20 (80% of patients in this group) in the ITF2357 group and 17 (65.4%) in the placebo group, reported at least one adverse event (AE). Five patients, 3 (12.0%) in the ITF2357 group and 2 (7.7%) in the placebo group, had at least one serious adverse event (SAE).

Twenty-five (25) patients in total, 12 (48.0%) in the ITF2357 group and 13 (50.0%) in the placebo group, had at least one AE related to the study treatment. Six (6) patients in total, 3 (12.0%) in the ITF2357 group and 3 (11.5%) in the placebo group, prematurely terminated the study treatment due to AE.

Gastrointestinal disorders and laboratory abnormalities (i.e. investigations) were the most common treatment-related adverse events, and were reported with similar rates in the two treatment groups. Vomiting (4 cases in the ITF2357 group) was the most common treatment-related adverse event.

Laboratory parameters:

The analysis of the haematology and blood chemistry parameters alterations (due or not due to Crohn's disease) showed that only few patients had abnormal values at baseline and/or at week 8 or at follow-up after one month, apart from some cases of abnormal ESR and/or CRP due to the Crohn's disease. There were only few cases of patients with abnormal clinically significant values at baseline, week 8 and/or follow-up, and all of them where due to Crohn's disease.

Treatment with ITF2357 was associated with a decrease from baseline to week 8 in WBCs and platelets count, compared to smaller decreases in the placebo group. ESR decreased from baseline to week 8 in the placebo group and remained unchanged in the ITF2357 group. The decrease from baseline to week 8 in mean CRP was more marked in the ITF2357 group than in the placebo group. An increase in mean values of alkaline phosphatase and creatinine was also observed from baseline to week 8 in the ITF2357 group. The mean value of alkaline phosphatase increased during the first 4 weeks of treatment with ITF2357 (peak at week 2, with an 8% increase vs. baseline) but subsequently decreased to a level comparable to baseline. Mean creatinine value showed a 9% increase versus baseline at week 8, then decreased to the baseline level after one month of follow up. In no cases out of range values were deemed as clinically significant by the investigators.

The analysis of liver function parameters did not show any evidence of detrimental effects following treatment with ITF2357.

Vital signs:

There were no substantial changes from baseline of heart rate and blood pressure.

ECG:

Abnormal clinically significant changes in ECG were observed in 2 patients in the ITF2357 group. One patient showed PPD possibly drug related after 2 weeks of treatment. The event recovered spontaneously after 2 weeks without any medical actions taken. Concomitantly, in the same patient a PPD was recorded but not reported by the investigator as AE because it was judged as a transient phenomenon not clinically significant. One further patient experienced a clinically significant PPD after 7 days of treatment. The patient discontinued treatment but after PPD of follow up PPD, which, in this specific case, is not in favour of a causative role of the experimental drug in triggering the event. Overall, the mean value of QTc interval increased from baseline to week 8 in a more marked extent in the ITF2357 group than in the placebo group.

Pharmacokinetic profile:

PK results are available in a separate report (TR2031/I)

Conclusions:

- The study was prematurely interrupted according to IDSMC (Indipendent Data and Safety Monitoring Committee) decision, based on the results of the interim analysis, which did not demonstrate any benefit of ITF2357 over placebo in the primary variable rate of patients achieving complete healing at week 8.
- There was also no evidence of benefits in patients treated with ITF2357 compared to placebo in the secondary efficacy endpoints (full remission rate, remission rate, CDEIS endoscopic response, changes from baseline of CDEIS score and SES-CD score, changes from baseline of CDAI score, CDAI remission rate, and CDAI response rate).
- The rate of patients reporting adverse events, treatment-related adverse events, serious adverse events and adverse

events leading to study discontinuation did not differ between the ITF2357 group and the placebo group.

- The results of haematology, blood chemistry and urinalysis parameters showed that ITF2357 exhibited an overall good safety profile, with no unexpected or new adverse effects.
- An increase in QTc interval at the end of treatment was observed in the ITF2357 group, compared to a smaller increase in the placebo group.