1. SYNOPSIS

Name of Sponsor: Italfarmaco S.p.A.	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of finished product: ITF2357	**Volume:**	
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Title of study: Phase II Trial of Histone-Deacetylase Inhibitor ITF2357 Followed by Mechlorethamine in Relapsed/Refractory Hodgkin's Lymphoma Patients		
Investigator: Prof. PPD		
Study centre: PPD (Italy)		
Publication (reference): None		
Studied period (weeks): 81 weeks (from the first drug administration date to the last visit date)		
Phase of development: II		
Objectives: Primary Objective To evaluate the anti-lymphoma efficacy of daily oral doses of ITF2357 followed by intravenous Mechlorethamine administered to patients with refractory/relapsed Hodgkin's lymphoma. Secondary Objective To evaluate the safety and tolerability of multiple courses of ITF2357 followed by Mechlorethamine in a population of chemotherapy pretreated patients.		
Methodology: Single-center, open label, non-randomized phase II study, testing the activity of multiple cycles of ITF2357 followed by Mechlorethamine in relapsed/refractory Hodgkin's lymphoma. Patients to be enrolled were 24 subjects of both genders, with histologically confirmed diagnosis of Hodgkin's lymphoma and refractory or relapsed.		
Number of patients (planned/ analyzed): 23 (planned) / 24 (safety population)		

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Diagnosis:

Histologically confirmed diagnosis of Hodgkin's lymphoma and refractory or relapsed

Main Criteria for Inclusion:

- Signed Informed Consent Form, age ≥18 years.
- Histologically confirmed diagnosis of Hodgkin's lymphoma, failed second-line or subsequent-line salvage chemotherapy regimens for whom no other treatment options of proven efficacy could be given.
- Adequate bone marrow, liver and renal function.
- At least one bi-dimensional lesion measurable by CT-scan or MRI.
- ECOG performance status of 0 or 1.
- Use of effective means of contraception for women of childbearing potential and men with partners of childbearing potential.
- Life expectancy >3 months.
- Subjects receiving intravenous Mechlorethamine (6 mg/m2) as single agent at least 4 weeks before study entry.
- Willingness and capability to comply with the requirements of the study.

Main Criteria for Exclusion:

- Active bacterial or mycotic infection requiring antimicrobial treatment.
- Pregnancy or lactation.
- Anticancer chemotherapy or radiotherapy during the study or within 4 weeks of study entry.
- A marked baseline prolongation of QT/QTc interval (e.g. repeated demonstration of a QTc interval >450 ms.
- Use of concomitant medications that prolong the QT/QTc interval.
- Clinically significant cardiovascular disease including:
  - Uncontrolled hypertension, myocardial infarction, unstable angina;
  - New York Heart Association (NYHA) Grade II or greater congestive heart failure;
  - History of any cardiac arrhythmia requiring medication (irrespective of its severity);
  - A history of additional risk factors for TdP (e.g. heart failure, hypokalemia, family history of Long QT Syndrome).
- Positive blood test for HIV, HBV and HCV.
- Identification of viral DNA by quantitative PCR for EBV and JC virus.
- History of other disease, metabolic dysfunctions, physical examination findings, or clinical laboratory findings giving reasonable suspicion of a disease or condition that contraindicated use of an investigational drug or that might have affected the interpretation of the study results or rendered the subject at high risk of treatment complications.

Dose and Mode of Administration, Batch Number of Test Agent:

All patients were given ITF2357 by oral route 50 mg every 6 hours, per os, days 1 – 3 (200 mg/day) followed by Mechlorethamine 6 mg/m2, intravenously, day 4.

ITF2357, batch number PPD , PPD and PPD were supplied as 50 mg hard gelatine capsules for oral administration.

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Duration of Treatment:

Study therapy was administered every 2/3 weeks as long as there was no evidence of progressive disease or unacceptable adverse events or patient's request to discontinue treatment, for a maximum of 12 cycles.

Evaluation Parameters:
Efficacy:

Primary: Objective Response (OR) rate, the proportion of responders (complete –CR– or partial –PR–) among patients treated.

Secondary: Progression-Free survival, Time To Response and Response Duration

Safety:

Adverse events
Physical examination
Vital signs
ECG evaluation and QT interval
ECOG
Laboratory test (Haematology, Biochemistry and Urinalysis)

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Statistical Methods:
A complete description of all collected data, including recorded and derived variables, was provided per visit on the patients valid for the safety. They were analysed by means of usual descriptive statistics: mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum values for continuous variables, and absolute and relative frequencies for categorical ones.

Efficacy data

The primary population was the ITT population. All efficacy analyses were also performed on the PP population. The results of efficacy on ITT and PP were evaluated for consistency.

Primary efficacy analysis

Description of results was done through the percentages of complete responses (CRs), partial responses (PRs), stable disease (SD) and progressive disease (PD) observed at each cycle. Best Overall tumor Response was defined for each patient.

The number of patients with objective response was calculated and presented in terms of absolute frequencies and proportions. For these proportions, confidence intervals at 95% were computed using exact binomial method.

Secondary efficacy analysis

Kaplan-Meier product-limit method was used to provide estimates, graphical representation of the curves for all named parameters.

Progression Free Survival, Time To Response and Duration of Response were also summarized by median and 95% confidence intervals, by mean and SE and by minimum, maximum, 25th and 75th percentile.

Safety data
Adverse events, laboratory parameters and vital signs were analysed by standard means.

Determination of sample size

Drug activity had to be evaluated on the basis of a one-stage Fleming study design for determination of response rates based on a single treatment group.

A sample size of 23 patients was estimated using exact method (binomial) and assuming:

1. π_0=0.05 as the largest value for the proportion of responders for whom the treatment was considered ineffective.
2. π_1=0.25 as the smallest value for the proportion of responders for whom the treatment was considered effective.
3. A probability of type 1 error = 0.05 (one-tail).
4. A power = 0.85.

The one-tailed statistical hypotheses were: $\pi < 0.05$ (null hypothesis) versus $\pi \geq 0.25$ (alternative hypothesis), where π is the observed response probability.

The following conclusions based on 23 patients could be possibly drawn:

- If there were 3 or less responders, there was less than desired activity;
- If there were 4 or more responders, there was some activity.

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Summary- conclusions:

EFFICACY RESULTS:

Primary parameter:

In the ITT population, one patient, subject PPD (4.17%), achieved a Complete Response (CR) during the study period, patient PP (4.17%) achieved a CR but it was not confirmed 4 weeks thereafter, thus the response was considered as PR in the analysis. PR was achieved by additional 4 patients (16.67%), 7 patients (29.17%) persisted in a state of stable disease and 9 (37.50%) experienced disease progression. Best overall response was not evaluable in 2 patients. The proportions were similar in PP population, with one patient reaching CR (6.25%), 5 (31.25%) achieving PR, 4 (25%) remained in SD and six (37.50%) progressed. In ITT the proportion of subjects achieving an objective response was 0.25 (95% CL 0.10-0.47). In PP population the proportion of subjects achieving an objective response was 0.38 (95% CL 0.15-0.65). The least number of responder stated by the statistical design of this study was 4 subjects, therefore on the basis of primary parameter, the study drug is endowed with a certain antitumor activity with a power of 0.85 in a sample of 23 patients with valid assessment of their relapsed/refractory Hodgkin's Lymphoma.

Secondary parameters:

Progression-free survival:

In ITT population, 78.26% of patients experienced disease progression or death during the study.. In PP set, 75% of subjects had disease progression or died. The median progression-free survival was 153 days in the ITT population and 159 days in the PP population.

Time to Response:

In ITT population, 25% reached an objective response during study period. In PP set, the percentage of responders was 37.50%. In ITT population, 25% of observed patients achieved a response after about 104 days from the start of the first cycle of treatment. In PP analysis the 25% of population responded after 57 days from the first day of ITF2357 administration and median time to response estimated was 151 days.

Response duration:

Among the 6 responders in both analysis sets, 3 (50.00%) experienced progression of disease or death. Response duration was 200 days in mean, 261 in median.

SAFETY RESULTS:

Haematologic toxicity was the most important matter of concern in this study. Nausea and vomiting was the second most frequent area of side effects of ITF2357. No patient died due to the study drug nor experienced other SAEs related to the study drug. Overall, 15 patients experienced a severe adverse event and 16 required a dose adjustment or temporary interruption. There was no evidence of general systemic toxicity reflected by changes in vital signs, hepatic or renal functions in the previous studies. Monitoring of QTc interval in all patients did not reveal a matter of concern for the product, within the limits of this study.

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CONCLUSION

The interest for the development of HDACIs in the management of Hodgkin's lymphoma is based on the observation that some histone deacetylases are highly expressed in classical Hodgkin's lymphoma [3] and preliminary studies indicate the study drug [9] and other HDACIs [2] to be effective in the treatment of this illness. It has been postulated that HDACIs might sensitize chemoresistant tumor cells to the cytotoxic activity of anticancer agents.

In this investigation, ITF2357 was administered to relapsed/refractory Hodgkin's lymphoma patients in combination to Mechlorethamine which is a potent anti-lymphoma agent. The data on efficacy indicated that this drug regimen was endowed with antitumor activity on HL, as out of the 24 patients enrolled in the study, 6 achieved a response (partial or complete), overcoming the threshold of 4 subjects stated by the statistical design as the minimum level of activity required.

Therefore, it could be concluded that the study met its primary objective.

The objective response was achieved in responder patients after 104 days from the study start, and lasted 200 days, confirming that the study met also its secondary objectives.

The product was not toxic at the investigated dosage regimen and no SAE was drug related.

In conclusion, the test drug ITF2357 may show a positive risk:benefit ratio in the management of relapsed/refractory Hodgkin's lymphoma patients in combination to Mechlorethamine at the investigated dosages and within the limits of this phase II trial.

Date of the report: May 31st 2011