1. SYNOPSIS

<table>
<tr><td>Name of Sponsor:
Italfarmaco S.p.A</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:

Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of finished product:
GIVINOSTAT (ITF2357)</td></tr>
<tr><td>Name of active ingredients:</td></tr>
<tr><td colspan="3">Title of study: Open label, uncontrolled, pilot, phase II study of histone-deacetylase inhibitor ITF2357 administered orally to subjects with CLL refractory/relapsed after conventional chemotherapy or relapsed after autologous bone marrow transplantation</td></tr>
<tr><td colspan="3">Investigators: 6 Principal Investigators (1 in Italy and 5 in Serbia)</td></tr>
<tr><td colspan="3">Study centres: 6 Centers, 1 located in Italy and 5 in Serbia</td></tr>
<tr><td colspan="3">Publication (reference): None to date.</td></tr>
<tr><td colspan="3">Studied period (weeks): First patient enrolled 27/02/2008, last patient completed 12/08/2008</td></tr>
<tr><td colspan="3">Phase of development: Phase II</td></tr>
<tr><td colspan="3">Objectives:
The primary objective of the study was to determine overall response-rate, complete response (CR) or partial response (PR) to ITF2357 (Givinostat) given at 100 mg x 2/die for up to three months.
The secondary objectives of the study were to assess the safety and tolerability of ITF2357, to assess the rate of total responders (complete + partial responders), to determine the 6 month progression free survival and to determine the effects of the drug on haematological parameters.</td></tr>
<tr><td colspan="3">Methodology: The study was a pilot trial conducted according to an open label, uncontrolled design.
Eligible patients received ITF2357 orally at the dose of 100 mg x 2/die for three months with subsequent dose modifications if requested by the patient’s conditions.
Treatment was administered on an outpatient basis and patients were followed regularly with physical and laboratory tests, as specified in the protocol, in order to monitor disease evolution, and safety and tolerability of ITF2357.</td></tr>
<tr><td colspan="3">Number of patients (planned/ analyzed): 23/3</td></tr>
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Diagnosis:

Established diagnosis of CLL according to the National Cancer Institute (NCI) criteria and refractory or relapsed within one month after conventional chemotherapy or relapsed within 3 months after autologus bone marrow transplantation

Main Criteria for Inclusion:

Male and female patients of age ≥18 and ≤75 years with confirmed diagnosis of CLL according to the NCI Working Group criteria; relapsed/refractory within 1 month after conventional chemotherapy (≥1 polychemotherapy regimen) or relapsed within 3 months after autologous bone marrow transplantation; ECOG performance score of ≤2; Limphocytes ≥10.0x109/l and platelets >75.0x109/l after recovery from a previous therapy; percentage of CD19+/CD5+ leukemic cells >50%; adequate cardiac, pulmonary and renal function; serum bilirubine <1.5xULN; AST and ALT <2.5xULN; serum potassium, phosphorus, total calcium, magnesium >LLN; normal values for FT4 and TSH (patients may be on thyroid hormone replacement); negative test for beta-HCG for women in fertile age; documentation of written informed consent to participate in the trial; willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

Main Criteria for Exclusion:

Patients with Autoimmune haemolytic anaemia, Autoimmune Thrombocytopenic Purpura and Fischer Evans Syndrome; other autoimmune diseases; marked baseline prolongation of QTc interval (e.g. repeated demonstration of a QTc interval >450 ms), with history of additional risk factors for torsade de pointes (e.g. hearth failure, family history of Long QT Syndrome); use of concomitant medications with potential risk of torsade de pointes and/or that can prolong QTc interval; prior treatment with an HDAC inhibitor; treatment with Rituximab or Alemtuzumab within 90 days prior to study therapy; patients HIV positive, with active EBV, HBV, HCV infection or liver cirrhosis; active uncontrolled viral or bacterial or mycotic infection; major surgeries within 4 weeks from study start or not fully recovered from any previous surgical procedure; presence of any medical or psychiatric condition which may limit full compliance with the study or increase the risk associated with study participation or study drug administration; treatment with corticosteroids within 1 month before study start; significant cardiovascular disease (i.e., uncontrolled arrhythmias, unstable angina), or a major thromboembolic event (myocardial infarction, stroke, transient ischemic attack, pulmonary embolism, or non-catheter-related deep-vein thrombosis) in the last 6 months; uncontrolled hypertension; malabsorption syndromes; breast feeding women.

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

ITF2357 was supplied as hard gelatine capsules for oral administration at the strength of 100 or 50 mg. Patients had to receive ITF2357 100 mg x 2/die at 12-hour intervals, in fed conditions, for three consecutive months.

Dosage reduction (from 100 mg b.i.d. to 50 mg b.i.d.) was envisaged in case of toxicity

The batches number of ITF2357 used in this study were:

Batch number	Expiry date*	Country
PPD	PPD	Serbia
PPD	PPD	Italy

* Expiry date extended to PPD

Duration of Treatment:

3 months

Evaluation Parameters:

Efficacy: Rate of complete or partial response in all patients; total rate of responders (complete + partial responders); 6 month progression free survival.

Safety: number of subjects experiencing an AE, type, frequency, severity, timing and relatedness of AEs, physical examination, changes in laboratory results

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Statistical Methods:

A positive response was defined to be a patient experiencing a complete or partial remission

Drug activity was evaluated based upon a one-stage Fleming study design for determination of response rates based on a single treatment group [40].

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

1. $\pi_0 = 0.05$ as the largest value for the proportion of responders for which the treatment was to be considered ineffective.
2. $\pi_1 = 0.25$ as the smallest value for the proportion of responders for which the treatment was to be considered effective.
3. A probability of type 1 error equal to 0.05 (one-tail).
4. A power equal to 0.85.

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

The following conclusions based on 23 patients could be made:

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

Based on the estimation of the response rate, a decision of whether there was adequate drug activity for initiating Phase IIb testing was to be reached.

Descriptive statistics consisting in Mean, SD, Median and Range were employed for continuous variables, whilst absolute and relative (percentage) frequencies were employed to summarize categorical variables. As for “time to event” variables, Kaplan-Meier together with associated 95% CL was computed.

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Summary- conclusions:

EFFICACY RESULTS: only 3 patients were enrolled; one patient remained on study for PPD, whilst the other two patients dropped out within the first month due to thrombocytopenia. Two patients showed a stable disease and one a progression of disease as best response.

SAFETY RESULTS: Two patients were prematurely withdrawn from the study due to an AE (thrombocytopenia). Most relevant observed adverse events were thrombocytopenia grade 2, cutaneous infection grade 2, nephrolithiasis grade 2, parotitis grade 2 and cutaneous rash grade 1. No SAEs were observed. The dose was reduced from 100 mg bid to 50 mg bid in two patients due to thrombocytopenia.

CONCLUSION: The study was prematurely discontinued for the following reasons:

- Since February 2008, date of first patient enrolment, through April 2009, date of early discontinuation, only 3 patients were enrolled: one in Site P – Prof. PPD – and two in Site P – Prof. PPD.
- Only one patient remained on study for 9 weeks, whilst the other two patients dropped out within the first month due to thrombocytopenia.
- Centres consistently highlighted significant issues in recruiting patients fulfilling all the inclusion criteria, to the point that new recruitments appeared highly unlikely and the target accrual of 23 patients within an acceptable period of time seemed almost impossible.
- The combination of profound difficulties in recruiting more patients and the appearance of repeated episodes of thrombocytopenia in the very few patients recruited convinced the sponsor and the participating centres to prematurely discontinue the study, whose feasibility had become rather questionable

Date of the report: 04/09/2009