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: GIVINOSTAT (ITF2357)	**Volume:**	
Name of active ingredients:	**Page:**	
Title of study: Phase IIa High Pulse Dose Clinical Trial of Orally Administered ITF 2357 In Patients with Relapsed/Refractory Multiple Myeloma		
Investigators: 2 Principal Investigators (1 in Italy and 1 in Serbia)		
Study centres: 4 Centers, 2 located in Italy and 2 in Serbia		
Publication (reference): None to date.		
Studied period (weeks): First patient enrolled 06/10/2009, last patient completed 02/01/2010		
Phase of development: Phase II		

Objectives:

Primary:

To assess the safety of ITF 2357 administered once weekly at high pulse dose in patients with relapsing/refractory multiple myeloma.

Secondary:

1. To evaluate the anti-tumour activity of ITF 2357 administered once weekly at high pulse dose in patients with advanced multiple myeloma, measured as decrease of M protein.
2. To assess the therapeutic response to ITF3257 according to EBMT criteria.
3. To determine pharmacokinetic profile of ITF 2357 administered following high pulse dose schedule.

Methodology: the study was a multicenter, phase IIa, Open label, non randomized, uncontrolled study

Eligible patients had to be treated with weekly single doses of ITF2357 according to the following treatment plan:

Weeks 1-6

Patient PP had to be administered ITF 2357 at 400 mg in one single dose on day 1, 8, 15, 22, 29 and 36. Safety assessments had to be performed twice a week. If no issue (grade >3 neutropenia or any other grade ≥3 toxicity) had emerged at day 15 two further patients (PP and PP) would have had to be enrolled and receive the same dose. If patientsPPD andPPD had showed a favourable safety profile at day 15, and in the meantime no safety concerns had arisen from patient PP , the further patients would have had to be enrolled and treated according to the below reported scheme:

- 8 more patients (PPD) would have had to receive 400 mg once weekly; safety assessments had to be performed weekly.
- 1 patient (PP) would have had to receive PPD once weekly; safety assessments had to be performed twice a week.

If no safety concern had emerged from patient PP at day 15, two further patients (PP and PP) would have had had to be enrolled and treated with 600 mg once weekly. If patients PP and PP had not showed relevant safety concerns (grade >3 neutropenia or any other grade ≥3 toxicity) at day 15, and in the meanwhile patient PP had maintained a favourable safety profile, eight further patients (PPD) would have had to be recruited and to receive the same treatment regimen.
If grade >3 neutropenia or any other grade ≥3 toxicity had appeared at any time during week 1-6, the treatment would have had to be permanently discontinued.
In this phase treatment had to be administered on an inpatient basis.

Weeks 7-12
For patients still on therapy at day 43 visit, M protein had to be quantified and the treatment continued or possibly modified as follows on the basis of this parameter:

M protein at day 43	**400 mg/week group**	**600 mg/week group**
Decrease ≥25%	continue 400 mg for 6 further weeks	continue 600 mg for 6 further weeks
Stable (±25%)	increase to 600 mg and continue for 6 further weeks	add dexamethasone 40 mg for 4 days/wk (day 1-4) and continue 600 mg for 6 further weeks
Increase >25%	add dexamethasone 40 mg for 4 days/wk (day 1-4) and continue 400 mg for 6 further weeks	failure: out of study

Safety assessments had to be performed at weekly intervals. In case of grade >3 neutropenia or any other grade ≥3 toxicity the treatment had to be permanently discontinued.
In this phase treatment had to be administered on an inpatient basis.

Weeks 13-18
For patients still on therapy at day 85 (week 13, day 1), the response rate had to be quantified according to EBMT criteria. In case of response (complete, partial or minimal) or stable disease (no change) the treatment had to be prolonged until week 18, whereas in case of disease progression the patient had to leave the study. A new complete efficacy evaluation had to be performed at day 127 (end of treatment).
During this phase safety had to be assessed at weekly intervals and in case of grade >3 neutropenia or any other grade ≥3 toxicity the treatment had to be permanently discontinued.
This phase of the study had to be conducted on an outpatient basis.

No dosage modification or temporary discontinuation was admitted.

Number of patients (planned/ analyzed): 1/22

Main inclusion criteria

Established diagnosis of multiple myeloma according to International Myeloma Working Group diagnostic criteria; Age ≥ 18 years; Patient relapsed after at least 2 lines of conventional chemotherapy or high dose therapy with autologous or allogeneic stem cell support, and/or for whom no alternative treatments are available/suitable; Increasing trend of monoclonal immunoglobulin or Bence-Jones proteinuria through the last 4 consecutive pre-screening measurements, already available in the patient history; No chemotherapy or other investigational anticancer therapy for at least 3 weeks before the start of the study; Full recovery from previous toxicities; ECOG performance status 0-2; Adequate bone marrow reserve: absolute neutrophil count ≥ 1000/ml; platelet count ≥ 90000/ml; Adequate liver function: total bilirubin within normal institutional limits (PI center); AST(SGOT)/ALT(SGPT) ≤ 2.5 x institutional upper limit of normal (PI center); Adequate renal function: Creatinine ≤ 2.5 mg/dl or creatinine clearance ≥ 50 ml/min; Either men or women, accepting to practice effective contraception during the entire study period unless documentation of infertility exists; Able to understand and willing to sign the informed consent form.

Main exclusion criteria

Planned autologous or allogeneic bone marrow transplantation within 4 weeks of the initiation of ITF 2357 administration; Concurrent use of medicines that would confound the interpretation of toxicities and anti-tumour activity of ITF 2357 (i.e. quinolons, macrolides, 5-HT3 antagonists except for palonosetron,); Clinically significant illness including, but not limited to, the following: active infection, uncontrolled hypertension, symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within the past 6 months, cardiac arrhythmia (present or documented in the past, of any kind), any other condition (including laboratory abnormalities) that in the opinion of the Investigator places the patient to unacceptable risk for adverse outcome if he/she were to participate in the study; Psychiatric illness/social situations that would limit compliance with study medication and protocol requirements; Pregnant or lactating women; Positive blood tests for HIV, HBV, HCV, active EBV and CMV; Diseases related to active viral infections; Patients with a marked baseline prolongation of QTc interval (e.g. repeated demonstration of a QTc interval >440 ms for men and >450 ms for women); Patients with history of additional risk factors for Torsade de Pointes (e.g. heart failure, family history of Long QT Syndrome). The use of concomitant medications with potential risk of Torsade de Pointes and/or that can prolong QTc interval

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

ITF2357 was supplied as hard gelatine capsules for oral administration at the strength of 200 mg.

Patients had to receive ITF2357 for 18 consecutive weeks.

The batch number of ITF2357 used in this study was:

Batch number	Expiry date*	Country
PPD	PPD	Serbia, Italy

Duration of Treatment:

18 weeks

Evaluation Parameters:

Efficacy: Rate of complete, partial or minor response according to the EBMT criteria for Multiple Myeloma.

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

Statistical Methods:

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

A sample size of 22 patients was estimated using exact method (binomial) and assuming:

1. $\pi_0 = 0.15$ as the largest value for the proportion of responders for which the treatment would have been be considered ineffective.
2. $\pi_1 = 0.40$ as the smallest value for the proportion of responders for which the treatment would have been considered effective.
3. A probability of type 1 error equal to 0.05 (one-tail)
4. A power equal to 0.80.

The one-tailed statistical hypotheses are: $\pi < 0.15$ (null hypothesis) versus $\pi \geq 0.40$ (alternative hypothesis), where π is the observed response probability.

The following conclusions based on 22 patients could be made:

- If there are 6 or less responders, then there is less than desired activity.
- If there are 7 or more responders, then there is some activity.

Summary- conclusions:

EFFICACY RESULTS: Only one patient has been enrolled. The drug was ineffective in determining an improvement of the patient's disease status according to the EBMT response criteria.

SAFETY RESULTS: the most frequently reported AEs were haematological in nature. In particular, the patient experienced PPD , PPD , PPD and PPD). Other AEs reported by the patients were PPD .

Two SAEs were reported (PPD – unlikely related to ITF2357, and PPD – probably related to ITF2357)

CONCLUSION: The study was prematurely discontinued for lack of recruitement. No firm conclusion on the safety and efficacy of ITF2357 administered at high (400 or 600 mg) single weekly doses can be drawn from the data collected from the only one patient recruited.

Date of the report: 30/07/2010