2. 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 (INN: Givinostat)	**Volume:**	
Name of active ingredients: dietyl-[6-(4-hydroxycarbamoyl-phenyl carbamoyloxymethyl) – naphtalen – 2 - ylmethyl] – ammonium; chloride; monohydrate	**Page:**	

Title of study: *A Phase IIA study of the histone-deacetylase inhibitor ITF2357 in patients with JAK-2 V617F positive chronic myeloproliferative diseases*

Investigators: Prof. PPD and Prof. Alessandro Rambaldi [(1)]; Prof. PPD [(2)]

Study Centres: [(1)] PPD Italy;

[(2)] PPD

Publication (reference):.

1) Rambaldi A. et al. A Phase 2A study of the Histone-Deacetylase Inhibitor ITF2357 in Patients with JAK2^{V617F} Positive Chronic Myeloproliferative Neoplasms, *ASH Annual Meeting Abstracts (Oral Session)*, November 2008, 112, 100 [20];
2) Rambaldi A. et al. A pilot study of the Histone-Deacetylase Inhibitor Givinostat in Patients with JAK2^{V617F} Positive Chronic Myeloproliferative Neoplasms, British Journal of Haematology (BJH), 2010, 368.

Studied period (weeks):

Date first subject entered (Signed Informed Consent Form Date): 11/12/2007
Date last subject completed: 30/12/2008

Phase of development: IIA

Objectives:

Primary Objective :

To evaluate efficacy and safety of ITF2357 in the treatment of patients with JAK2^{V617F} positive myeloproliferative diseases [Polycythemia Vera (PV), Essential Thrombocytosis (ET), Myelofibrosis (MF)]. Efficacy was evaluated by ad hoc haematological and clinical criteria for PV and ET, and by internationally established response criteria (EUMNET criteria) for MF. Safety was evaluated by number of subjects experiencing an Adverse Event (AE), type, frequency, severity, timing and relatedness of AEs, including changes in vital signs and clinical laboratory results.

Secondary Objective:

To evaluate the JAK2 mutated allele burden by quantitative Real-Time Polymerase Chain Reaction (qRT-PCR).

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Methodology: This is a non-randomized, open-label, pilot study testing ITF2357 in a population of patients with $JAK2^{V617F}$ positive myeloproliferative diseases. All recruited patients received an initial dose of 50 mg b.i.d. of ITF2357 that was subsequently escalated to 50 mg t.i.d. in case of lack of significant toxicity. Treatment lasted up to a maximum of 24 cumulative weeks of drug administration. The study was carried out in Italy. Enrolled patients were subjects of both genders, with an established diagnosis of PV/ET/MF according to the revised WHO criteria.		
Number of patients (planned/ analyzed): 27/29 (safety population)		

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Diagnosis:

Patients with $JAK2^{V617F}$ positive myeloproliferative diseases [Polycythemia Vera (PV), Essential Thrombocythosis (ET), Myelofibrosis (MF)].

Inclusion Criteria:

- Signed Informed Consent Form
- Male or female, age ≥ 18 years
- Confirmed diagnosis of PV/ET/MF according to the revised WHO criteria
- $JAK2^{V617F}$ positivity
- In need of cytoreductive therapy when hydroxyurea was not indicated (e.g. young patients) or when refractoriness to the drug was documented. Definition of refractoriness to hydroxyurea in ET was that issued by the Leukemianet European Collaboration; definition of refractoriness in PV and MF was: absence of major response after at least 3 months of treatment at the maximum tolerated dose.

Exclusion Criteria:

- Active bacterial or fungal infection requiring antimicrobial treatment on Day 1
- Patients of childbearing potential without a negative pregnancy test prior to initiation of the study drug
- Pregnancy or lactation
- A marked baseline prolongation of QT/QTc interval (e.g. repeated demonstration of a QTc interval > 450 ms, according to Bazett's correction formula – formula reported in appendix G of the protocol)
- The use of concomitant medications that prolong the QT/QTc interval (full list reported in appendix F of the protocol)
- Concomitant acute coronary syndromes; uncontrolled hypertension
- 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)
- Active EBV infection (i.e. positive serology IgM)
- Known HIV infection
- Active hepatitis B and/or C infection
- History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicated use of an investigational drug or that might affect interpretation of the results of the study or rendered the subject at high risk from treatment complications
- ECOG performance status 3 or greater
- Platelets count <100x109/l within 14 days before enrolment

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- Platelet count < 100 x 10^9/L, absolute neutrophil count < 1.2 x 10^9/L, percentage of blast cells in peripheral blood > 10% within 14 days before enrolment
- Serum creatinine > 2 x ULN, total serum bilirubin > 1.5 x ULN, serum AST/ALT > 3 x ULN
- Interferon-α and hydroxyurea within 14 days before enrolment
- Anagrelide within 7 days before enrolment
- Any other investigational drug within 28 days before enrolment

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

All recruited patients received an initial dose of 50 mg b.i.d. of ITF2357 that was subsequently escalated to 50 mg t.i.d in case of lack of significant toxicity.

ITF2357 (batch numbers: PPD and PPD) was supplied as 50 mg hard gelatine capsules for oral administration.

Duration of Treatment:

Treatment lasted up to a maximum of 24 cumulative weeks of drug administration.

Endpoints:

Efficacy:

Primary: number of Objective Responses (complete, major, moderate or minor responses) in terms of Best Overall Response.
Secondary: reduction of JAK2 mutated allele burden.

Safety: number of subjects experiencing an adverse event.

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Statistical Methods:

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

Efficacy data

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

Primary efficacy analysis

The main efficacy variable was the number of Objective Responses (complete, major, moderate or minor responses) in terms of Best Overall Response.

Secondary efficacy analysis

The $JAK2^{V617F}$ mutational status exam was described by visit in terms of percentage value. A complete patient data listing was also produced.

Safety data

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

Determination of sample size

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

A sample size of 27 patients was estimated using exact method (binomial) and assuming:

- π_0=0.05 as the largest value for the proportion of responders for which the treatment was considered ineffective.
- π_1=0.20 as the smallest value for the proportion of responders for which the treatment was considered effective.
- A probability of type 1 error equal to 0.05 (one-tail).
- A statistical power of 0.80.

The one-tailed statistical hypotheses were $\pi < 0.05$ (null hypothesis) versus $\pi \geq 0.20$ (alternative hypothesis), where π is the observed response probability.

- The following conclusion based on 27 patients could be made: if there are 3 or less responders, then there is less than desired activity
- if there are 4 or more responders, then there is some activity.

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Summary- conclusions:

Efficay results:

More than a half of patients had an Objective Response in both PP (61.54%) and ITT (58.62%) population. The Objective Response was achieved after on average 34.88 (±SD 4.39) days and 36.7 (±4.08) days of treatment in the PP and ITT population, respectively. As far as the analysis of Objective Response stratified by tumour characteristics is concerned, it was observed that all patients with Polycythemia Vera were responders in both populations. $JAK2^{V617F}$ mutational status decreased between screening and end of treatment in mean by 10% and by 9.2% in the PP and the ITT populations, respectively. The decrease of the $JAK2^{V617F}$ allele burden was particularly evident in PV patients (17,7% and 15.2% in the PP and the ITT populations, respectively).
With regard to the primary endpoint of the study, the number of Objective Response was >3 (cut-off defined in the sample size for 27 patients) then the primary endpoint was met and it can be concluded that the product showed a definite activity in the treatment of patients with $JAK2^{V617F}$ positive myeloproliferative diseases.
Moreover, at end of treatment 1 patient still showed complete response, 9 showed major response and 2 showed a moderate response.

Safety results:

In the present study, no further toxicity of ITF2357 surfaced beside what already known for the study drug. There were no deaths, and no SAE appeared as related to the study drug. The most frequent related adverse event was diarrhoea (18 patients). A moderate prolongation of QTc interval was reported in 5 patients. No serious adverse event related to the study drug was reported.

Conclusion:

ITF2357 induced an objective response in the majority of patients. The Objective Response was achieved after on average 34.12 (±SD 4.29) days and 35.42 (±4.02) days of treatment in the PP and ITT population. Interestingly, ITF2357 was surprisingly effective in inducing a clinical response in patients affected by Polycythemia Vera.

Even if the treatment period was short (24 weeks only) the test drug was proven to be able to reduce the $JAK2^{V617F}$ mutational status. This finding was particularly evident in the PV patient group. This seems to confirm that ITF2357 is particularly active in controlling this subtype of myeloproliferative disorders.

The safety profile emerged from the present clinical trial was good and in line with safety findings already documented in previous studies.

In conclusion, the test drug ITF2357 showed a positive risk:benefit ratio in the management of patients with $JAK2^{V617F}$ positive myeloproliferative diseases. The positive effect is evident in particular in patients with Polycythemia Vera.

Date of the report: final draft on 13.04.2010