A Two-part Study to Assess the Safety and Preliminary Efficacy of Givinostat in Patients With Polycythemia Vera

Purpose

This is a two-part, multicenter, open label, non-randomized, phase Ib/II study to assess the safety and tolerability, Maximum Tolerated Dose and preliminary efficacy of Givinostat in patients with JAK2V617F positive Polycythemia Vera. Part A is the dose finding part while Part B is assessing the preliminary efficacy. Patients will be enrolled either in Part A or Part B and transition from one part to the other is not allowed.

Eligible patients for this study will have a confirmed diagnosis of Polycythemia Vera according to the revised World Health Organization criteria. Only if the enrolment in Part A is slow (i.e. < 5 patients enrolled in 3 months), eligibility for this part of the study may be expanded to all patients with chronic myeloproliferative neoplasms.

Study therapy will be administered in 28 day cycles (4 weeks of treatment). Disease response will be evaluated according to the European LeukemiaNet criteria after 3 and 6 cycles (i.e. at weeks 12 and 24, respectively) of treatment with Givinostat for both parts of the study. All phlebotomies performed in the first 3 weeks of treatment will not be counted to assess the clinico-haematological response.

The study will last up to a maximum of 24 weeks of treatment. However, after completion of the trial, all patients achieving clinical benefit will be allowed to continue treatment with Givinostat (at the same dose and schedule) in a long-term study.

Safety will be monitored at each visit throughout the entire duration of the study. Treatment will be administered on an outpatient basis and patients will be followed regularly with physical and laboratory tests, as specified in the protocol; in case of hospitalization, the treatment will be continued or interrupted according to the Investigators' decision.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
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<tbody>
<tr>
<td>Polycythemia Vera</td>
<td>Drug: Givinostat</td>
<td>Phase 1 Phase 2</td>
</tr>
</tbody>
</table>

Resource links provided by NLM:

Genetics Home Reference related topics: essential thrombocytethmia, polycythemia vera, primary myelofibrosis

MedlinePlus related topics: Cancer

Genetic and Rare Diseases Information Center resources: Chronic Myeloproliferative Disorders, Myelofibrosis, Essential Thrombocytopenia

U.S. FDA Resources

Further study details as provided by Italfarmaco:

Primary Outcome Measures:

- Part A: Maximum Tolerated Dose [ Time Frame: 168 days (i.e. 6 cycles) ] [ Designated as safety issue: No ]
  Determination of the Maximum Tolerated Dose of Givinostat based on cycle 1 Dose Limiting Toxicity's.

- Part B: Preliminary efficacy after 3 cycles of treatment [ Time Frame: 84 days (i.e. 3 cycles) ] [ Designated as safety issue: No ]
  Overall response rate - i.e. Complete Response and Partial Response - of Givinostat at the Maximum Tolerated Dose after 3 cycles; the
response will be evaluated according to the clinico-haematological European LeukemiaNet response criteria.

- **Part A: Safety and tolerability** [Time Frame: 168 days (i.e. 6 cycles)] [Designated as safety issue: No]
  
  Safety and tolerability evaluated as following:
  - Number of patients experiencing adverse events;
  - Type, incidence, and severity of treatment-related adverse events.

- **Part B: Safety and tolerability after 3 cycles of treatment** [Time Frame: 84 days (i.e. 3 cycles)] [Designated as safety issue: No]
  
  Safety and tolerability of Givinostat at the Maximum Tolerated Dose after 3 cycles evaluated as following:
  - Number of patients experiencing adverse events;
  - Type, incidence, and severity of treatment-related adverse events.

**Secondary Outcome Measures:**

- **Part A: characterization of pharmacokinetic** [Time Frame: 84 and 168 days (i.e. cycles 3 and 6)] [Designated as safety issue: No]
  
  Individual Givinostat concentrations tabulated by dose cohort along with descriptive statistics.

- **Part B: characterization of pharmacokinetic** [Time Frame: 168 days (i.e. 6 cycles)] [Designated as safety issue: No]
  
  Individual Givinostat concentrations tabulated with descriptive statistics.

- **Part A: preliminary efficacy after 3 and 6 cycles of treatment** [Time Frame: 84 and 168 days (i.e. cycles 3 and 6)] [Designated as safety issue: No]
  
  Overall response rate - i.e. Complete Response and Partial Response - of Givinostat at the Maximum Tolerated Dose after 3 and 6 cycles; the response will be evaluated according to the clinico-haematological European LeukemiaNet response criteria.

- **Part B: preliminary efficacy of Givinostat at the Maximum Tolerated Dose after 6 cycles** [Time Frame: 168 days (i.e. 6 cycles)] [Designated as safety issue: No]
  
  Overall response rate - i.e. Complete Response and Partial Response - of Givinostat at the Maximum Tolerated Dose after 6 cycles; the response will be evaluated according to the clinico-haematological European LeukemiaNet response criteria.

- **Part B: safety and tolerability after 6 cycles** [Time Frame: 168 days (i.e. 6 cycles)] [Designated as safety issue: No]
  
  Safety and tolerability of Givinostat at the Maximum Tolerated Dose after 6 cycles evaluated as following:
  - Number of patients experiencing adverse events;
  - Type, incidence, and severity of treatment-related adverse events.

**Other Outcome Measures:**

- **Exploratory endpoints of Parts A and B** [Time Frame: 84 and 168 days (i.e. 3 and 6 cycles)] [Designated as safety issue: No]
  
  - To evaluate the effect of Givinostat on each single response parameter according to the European LeukemiaNet response criteria.
  - To evaluate the effects of Givinostat on pharmacodynamic markers by messenger ribonucleic acid (mRNA) analysis.
  - To evaluate the effects of Givinostat on spleen size in patients with confirmed splenomegaly at baseline.
  - Improvement of constitutional symptoms.
  - Reduction of the allele burden of the mutated Janus Kinase 2 (JAK2V617F).
  - Reduction of the symptomatic treatment of pruritus in term of dosage and/or days of treatment.

## Arms

<table>
<thead>
<tr>
<th>Experimental: Givinostat</th>
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<tr>
<td>In Part A patients will treated in dose levels at the following daily doses of Givinostat:</td>
</tr>
<tr>
<td>- 50 mg b.i.d.,</td>
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<tr>
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<tr>
<td>- 150 mg b.i.d.,</td>
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## Assigned Interventions

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</table>

**Estimated Enrollment:** 52

**Study Start Date:** October 2013

**Estimated Study Completion Date:** September 2016

**Estimated Primary Completion Date:** September 2015 (Final data collection date for primary outcome measure)
- 200 mg b.i.d.;
- 150 mg t.i.d.;
- 200 mg t.i.d. Intermediate dose levels and, consequently, additionally dose levels may be used to establish the Maximum Tolerated Dose.

In Part B patients will be treated at the Maximum Tolerated Dose established in Part A.
The product will be supplied as hard gelatine capsules for oral administration at the strength of 50 and/or 100 mg each.

### Eligibility

**Ages Eligible for Study:** 18 Years and older

**Genders Eligible for Study:** Both

**Accepts Healthy Volunteers:** No

#### Criteria

**Inclusion Criteria:**

1. Patients must be able to provide informed consent and be willing to sign an informed consent form;
2. Patients must have an age ≥ 18 years;
3. Patients must have a confirmed diagnosis of Polycythemia Vera according to the revised World Health Organization criteria;
4. Patients must have mutated Janus Kinase 2 (mutation V617F) positive disease;
5. Patients must have an active/not controlled disease defined as:
   a. hematocrit ≥ 45% or hematocrit < 45% in need of phlebotomy, and
   b. platelet count > 400 x 10⁹/L, and
   c. white blood cell count > 10 x 10⁹/L;
6. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 in Part A, ECOG performance status ≤ 2 in Part B within 7 days of initiating study drug;
7. Female patient of childbearing potential has a negative serum or urine pregnancy test within 72 hours of the first dose of study therapy;
8. Use of an effective means of contraception for women of childbearing potential and men with partners of childbearing potential;
9. Adequate and acceptable organ function within 7 days of initiating study drug;
10. Willingness and capability to comply with the requirements of the study.

**Exclusion Criteria:**

1. Active bacterial or mycotic infection requiring antimicrobial treatment;
2. Pregnancy or nursing;
3. A clinically significant corrected QT interval prolongation at baseline;
4. Use of concomitant medications known to prolong the corrected QT interval;
5. Clinically significant cardiovascular disease including:
   a. Uncontrolled hypertension despite medical treatment, myocardial infarction, unstable angina within 6 months from study start;
   b. New York Heart Association Grade II or greater congestive heart failure;
   c. History of any cardiac arrhythmia requiring medication (irrespective of its severity);
   d. A history of additional risk factors for torsade de pointes;
6. Known positivity for human immunodeficiency;
7. Known active hepatitis B virus and/or hepatitis C virus infection;
8. Platelet count < 100 x 10⁹/L within 14 days before enrolment;
9. Absolute neutrophil count < 1.2 x 10⁹/L within 14 days before enrolment;
10. Serum creatinine > 2 times the upper limit of normal;
11. Total serum bilirubin > 1.5 times the upper limit of normal except in case of Gilbert's disease;
12. Serum aspartate aminotransferase/alanine aminotransferase (AST/ALT) > 3 times the upper limit of normal;
13. History of other diseases (including active tumours), metabolic dysfunctions, physical examination findings, or clinical laboratory findings giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or render the subject at high risk from treatment complications;
14. Prior treatment with a Janus Kinase 2 or Histone Deacetylase inhibitor or participation in an interventional clinical trial for chronic myeloproliferative neoplasms;

15. Systemic treatment for chronic myeloproliferative neoplasms other than aspirin/cardio aspirin;

16. Hydroxyurea within 28 days before enrolment;

17. Interferon alpha within 14 days before enrolment;

18. Anagrelide within 7 days before enrolment;

19. Any other investigational drug or device within 28 days before enrolment;

20. Patient with known hypersensitivity to the components of study therapy.

Contact and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT01901432

Contacts

Contact: Paolo Bettica, MD, PhD  +390264432584  p.bettica@italfarmaco.com
Contact: Silvia Di Tollo, PhD  +390264432523  s.ditollo@italfarmaco.com

Locations

France

CHU Amiens - Hôpital Sud  Not yet recruiting
Amiens Cedex 1, France, 80054
Contact: Jean-Pierre Marolleau, MD, PhD  marolleau.jean-pierre@chu-amiens.fr
Principal Investigator: Jean-Pierre Marolleau, MD, PhD

Hôpital Morvan - CHRU de Brest  Not yet recruiting
Brest Cedex, France, 29609
Contact: Jean-Christoph Iannotto, MD  jean-christophe.ianotto@chu-brest.fr
Principal Investigator: Jean-Christoph Iannotto, MD

Hôpital Saint Vincent de Paul - GHICL Lille  Not yet recruiting
Lille Cedex, France, 59020
Contact: Nathalie Cambier, MD  cambier.nathalie@ghicl.net
Principal Investigator: Nathalie Cambier, MD

Hôpital Saint-Louis (AP-HP), Centre Investigations Cliniques  Not yet recruiting
Paris Cedex 10, France, 75475
Contact: Jean-Jacques Kiladjian, MD  jean-jacques.kiladjian@sls.aphp.fr
Principal Investigator: Jean-Jacques Kiladjian, MD, PhD

Groupe Hospitalier Sud - Hôpital Haut-Lévêque  Not yet recruiting
Pessac, France, 33604
Contact: Axelle Lascaux, MD  axelle.lascaux@chu-bordeaux.fr
Principal Investigator: Axelle Lascaux, MD

Germany

Charite Research Organisation GmbH  Not yet recruiting
Berlin, Germany, 10117
Contact: Antonio Pezzuto, MD  antonio.pezzuto@charite.de
Principal Investigator: Antonio Pezzuto, MD

Klinikum Darmstadt GmbH  Not yet recruiting
Darmstadt, Germany, 64283
Contact: Helga Bernhard, MD  med5@klinikum-darmstadt.de
Principal Investigator: Helga Bernhard, MD

Universitaetsklinikum Carl Gustav Carus TU Dresden  Not yet recruiting
Dresden, Germany, 01307
Contact: Uwe Platebecker, MD  Uwe.Platebecker@uniklinikum-dresden.de
Principal Investigator: Uwe Platebecker, MD

Universitaetsklinikum Freiburg  Not yet recruiting
Freiburg, Germany, 79108
Contact: von Bubnoff Nikolaus, MD  nikolas.bubnoff@uniklinik-freiburg.de
Principal Investigator: Nikolaus von Bubnoff, MD

Universitaetsklinikum Koeln  Not yet recruiting
Koeln, Germany, 50937
Contact: Christof Scheid, MD  christoph.scheid@uk-koeln.de
Principal Investigator: Christof Scheid, MD

Italy

Azienda Ospedaliera Papa Giovanni XXIII  Not yet recruiting
A Two-part Study to Assess the Safety and Preliminary Efficacy of Givi...
Health Authority: Italy: The Italian Medicines Agency
Italy: Ethics Committee
France: Agence Nationale de Sécurité du Médicament et des produits de santé
France: Committee for the Protection of Personnes
Germany: Federal Institute for Drugs and Medical Devices
Germany: Ethics Commission
United Kingdom: Medicines and Healthcare Products Regulatory Agency
United Kingdom: Research Ethics Committee
Poland: Ethics Committee
Poland: Ministry of Health

Keywords provided by Italfarmaco:
chronic myeloproliferative neoplasms
Polycythemia Vera
Essential Thrombocytemia
Primary Myelofibrosis

Additional relevant MeSH terms:
Polycythemia
Polycythemia Vera
Hematologic Diseases
Myeloproliferative Disorders
Bone Marrow Diseases

ClinicalTrials.gov processed this record on February 25, 2014