Randomized, open-label, multicenter phase 3 study to assess the efficacy and safety of GIVinostat versus hydroxyurea IN JAK2V617F-positive high-risk Polycythemia Vera patients: the GIV-IN PV TRIAL (DSC/08/2357/32)

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Sindromi MIELOPROLIFERATIVE CRONICHE target: POLICITEMIA VERA

Inclusion Criteria
To be eligible for inclusion in this study, patients must meet all the following inclusion criteria:

- Patients (or their legally authorized representative) must be able to provide informed consent and willing to sign an ICF.
- Patients must be 18 years of age or older.
- Patients must have been diagnosed with PV according to the 2016 WHO criteria within 3 years before randomization.
- Patients must have JAK2V617F-positive disease.
- Patients with PV must meet the definition of HR for thrombosis (i.e., HR) at screening as follows:
  – Age > 60 years, and/or
  – Prior thrombosis.
- Patients must be in need of treatment at screening, defined by the presence of at least one of the following:
  – HCT ≥ 45% or HCT < 45% with at least 1 phlebotomy performed in the 3 months before screening, or
  – WBC count > 10 × 109/L, or
  – PLT count > 400 × 109/L.
  In addition, patients pre-treated with HU must not have a documented history of resistance or intolerance to HU (see exclusion criterion 1).
- Patients must have normalized HCT (i.e., HCT < 45%) at randomization
- Patients must have an ECOG performance status ≤ 2 at screening.
- Patients must have a peripheral blood blast count of 0% at screening.
- Female patients must be either postmenopausal, sterilized or, if of childbearing potential and sexually active, effectively practicing a highly effective method of contraception (either oral, parenteral, intravaginal, transdermal, injectable or implantable hormonal contraceptives; intrauterine device; intrauterine hormone-releasing system, bilateral tubal occlusion; vasectomized/sterilized partner; or sexual abstinence).
- Female patients of childbearing potential must agree to use highly effective contraception during the study and for at least 6 months after the last dose of study treatment if the patient received hydroxyurea.
- Male patients must use condoms and ensure that they or their female partner(s) use a highly effective method of contraception as described in inclusion criterion 10 during the study and for at least 1 year after the last dose of study treatment if the patient received hydroxyurea.
- Male patients must not donate sperm during the study and for at least 1 year following the last study drug administration if the patient received hydroxyurea.
- Patients must be willing and capable to comply with the requirements of the study.

Exclusion criteria

To be eligible for this study, patients must not meet any of the following criteria:

- Patients pre-treated with HU with a documented history of resistance or intolerance to HU defined by the original ELN criteria as:
  - Need for phlebotomy to keep HCT < 45% after 3 months of at least 2 g/day of HU OR
  – Uncontrolled myeloproliferation, defined as PLT count > 400 × 109/L and WBC count > 10 × 109/L after 3 months of at least 2 g/day of HU OR
  – Failure to reduce massive splenomegaly (defined as organ extending by >10 cm from the costal margin) by more than 50% as measured by palpation after 3 months of at least 2 g/day of HU OR
  – ANC < 1 × 109/L or Hb level < 100 g/L or PLT count < 100 × 109/L at the lowest dose of HU required to achieve a CR or PR, as assessed by ELN response criteria
  OR
  – Presence of leg ulcers or other unacceptable HU-related non-hematologic toxicities e.g., muco-cutaneous manifestations, GI symptoms, pneumonitis or fever at any HU dose.
- Patients with clinically significant bacterial, fungal, parasitic or viral infection that requires treatment.
- Patients with a positive test for hepatitis B virus surface antigen, hepatitis C virus antibodies (anti-HCV) or human immunodeficiency virus (HIV) antibodies at screening.
- Patients diagnosed with primary immunodeficiency syndromes, e.g., X-linked agammaglobulinemia and common variable immune deficiency.
- Patients with a QTcF value of > 450 msec for males and > 460 msec for females at the Screening visit (as the mean of 3 consecutive readings 5 minutes apart in the event a first ECG demonstrates a prolonged QTcF interval); congenital or acquired history of QTc prolongation or ventricular arrhythmias, at the Screening visit.
- Patients with clinically significant cardiovascular disease, including uncontrolled hypertension, New York Heart Association Grade III or greater congestive heart failure, torsades de pointes (TdP) and hypokalemia at screening.
- Patients with myocardial infarction, stroke or unstable angina within the 6 months prior to screening.
- Splanchnic thrombosis and/or thrombosis of the cerebral venous sinuses and/or splenectomy in the medical history.
- Patients with inadequate liver or renal function at screening, as demonstrated by any of the following:

  – Encephalopathy grade 2 or higher as per the Child-Pugh System
  – Known hepatocellular disease, including active hepatitis B virus or HCV infection,cirrhosis or other hepatocellular disease
  – Total serum bilirubin > 1.5 × ULN, except in case of documented Gilbert’s disease or pattern consistent with Gilbert’s disease (test may be repeated once)
  – Serum aspartate aminotransferase/alanine aminotransferase (AST/ALT) levels> 3 × ULN (test may be repeated once)
  – Serum creatinine levels > 2 × ULN (test may be repeated once)
  – Serum cystatin C levels > 2 × ULN for 2 subsequent evaluations (i.e., if the value of serum

cystatin C is > 2 × ULN, the test will be repeated once, and if the value is again > 2 × ULN, this becomes an exclusion criterion).
1PLT count ≤ 150 × 109/L at screening (test may be repeated once).

- ANC < 1.2 × 109/L at screening (test may be repeated once).
- Uncontrolled hypertriglyceridemia at screening, i.e., triglycerides > 1.5 × ULN (test may be repeated once).
- Presence of other clinically significant disease that, in the Investigator's opinion, could adversely affect the safety of the patient, making it unlikely that the course of treatment or FU is completed, or could impair the assessment of study results.
- History of major organ transplantation.
- Patients with documented GI disease that may significantly alter the absorption of oral drugs.
- Patients with an active malignancy over the 5 years prior to screening, except intraepithelial neoplasia, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma in situ of the cervix or early-stage prostate cancer, treated and considered cured.
- Previous treatment with a JAK2 or HDAC inhibitor or 32-phosphorus (radioactive isotope) therapy.
- Patients receiving treatment with interferon or pipobroman within the 5 weeks prior to screening.
- Patients receiving anagrelide within the 7 days prior to screening.
- Patients receiving busulfan or chlorambucil within the 2 weeks prior to screening.
- Patients being treated concurrently with any investigational agent or prior participation in an interventional clinical study within the 30 days prior to screening or within 5 half-lives of the investigational product, whichever is longer.
- Patients with known hypersensitivity to the components of the study drugs.
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception, confirmed by a positive serum human chorionic gonadotropin (hCG) laboratory test (i.e., > 5 mIU/mL) and until the termination of gestation.