A Phase 1/2, Open-label, Dose-escalation, Safety, Pharmacokinetic, and Pharmacodynamic Study of Oral TP-3654 in Patients with Intermediate or High-risk Primary or Secondary Myelofibrosis (BBI-TP-3654-102).

Contatti: Giulia Benevolo gbenevolo@cittadellasalute.to.it

AOU Città della Salute e della Scienza di Torino, SC Ematologia Universitaria - P.O. Molinette

Sindromi MIELOPROLIFERATIVE CRONICHE target: MIELOFIBROSI

Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible:

1. Adult (age defined by local/country law or regulation)
2. Confirmed pathological diagnosis of primary myelofibrosis (PMF) or post-PV- MF/post-ET- MF as per WHO diagnostic criteria (Section 10.2.4), and intermediate or high-risk primary or secondary MF based on the Dynamic International Prognostic Scoring System (DIPSS)65; (Section 10.2.2)
3. Previously treated with a JAK inhibitor and are intolerant, resistant, refractory or lost response to the JAK inhibitor, or are ineligible to be treated with ruxolitinib or fedratinib as determined by the Investigator in accordance with the local product labels
4. Grade ≥ 2 bone marrow fibrosis, as confirmed by bone marrow biopsy within 12 weeks prior to Screening; (Section 10.2.3)
5. Fulfill the following clinical laboratory parameters:
a. Platelet count ≥ 25 × 109/L (without the assistance of growth factors or platelet transfusions)
b. Absolute Neutrophil Count (ANC) ≥ 1 × 109/L without the assistance of granulocyte growth factors
6. Peripheral blood blast count < 10%
7. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (see Section 10.11)
8. Life expectancy ≥ 3 months
9. Adequate renal function, as determined by clinical laboratory tests (serum creatinine ≤ 1.5 x upper limit of normal (ULN), and calculated creatinine clearance ≥ 30 mL/min) (using Cockcroft-Gault formula)
10. Adequate hepatic function (ALT/AST ≤ 3 × ULN, total bilirubin ≤ 1.5 × ULN; or ALT/AST ≤ 5 × ULN, direct bilirubin ≤ 2 × ULN if due to myelofibrosis); and coagulation ([PT and PTT] ≤ 1.5 × ULN)
11. Agree to provide bone marrow biopsies during the study: at baseline or within 12 weeks prior to enrollment, and every 6 months during treatment.
12. Capable of providing signed informed consent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol
13. Non-fertile or agree to use an adequate method of contraception as described in Section 10.4 while on study and for 6 months following the study, and have a negative pregnancy test (if female of childbearing potential [Section 8.1.7]) and not currently nursing; males agree to use an adequate method of contraception as described in Section 10.4 while on study and for 3 months following the study
14. Splenomegaly during the screening period as demonstrated by splenic length ≥ 5 cm below the costal margin by palpation or spleen volume of ≥ 450 cm3 by magnetic resonance Imaging (MRI) or computerized tomography (CT) scan

15. Show at least 2 symptoms measurable (score ≥ 1) using the Myelofibrosis Symptom Assessment Form (MFSAF), v4.0.
16. Able to take orally administered medication

Exclusion Criteria

Patients meeting any one of these exclusion criteria will be prohibited from participating in this study:

1. Received previous systemic antineoplastic therapy (including unconjugated therapeutic antibodies, toxin immunoconjugates, ESA, and alpha-interferon) or any experimental therapy within 14 days or 5 half-lives, whichever is longer, before the first dose of study treatment
2. Major surgical procedure for any cause within 4 weeks before the first dose of study drug and/or the patient has not recovered adequately from complications of the surgical intervention prior to the first dose of study drug
3. Splenic irradiation within 6 months prior to Screening or prior splenectomy
4. AML, MDS, or peripheral blasts ≥ 10%.
5. Prior autologous or allogeneic stem cell transplant at any time.
6. Eligible for and willing to undergo allogeneic bone marrow or stem cell transplantation. Patients who are not a candidate, who are unwilling to undergo transplantation, or for whom a suitable donor is not available are considered transplant ineligible.
7. Currently receiving treatment with a prohibited medication that cannot be discontinued at least one week prior to the start of treatment (Section 6.6).
8. Experiencing electrolyte abnormalities of NCI CTCAE21 Grade ≥ 2 (eg, serum potassium, magnesium and calcium) unless they can be corrected during screening and are deemed not clinically significant by the Investigator.
9. History of congestive heart failure, myocardial infarction within the past 6 months prior to Cycle 1/Day 1; left ventricular ejection fraction < 45% by echocardiogram, unstable arrhythmia, or evidence of ischemia on electrocardiogram (ECG) within 28 days prior to Cycle 1/Day 1.
10. Corrected QT interval (using Fridericia's correction formula) of > 450 msec in men and > 470 msec in women.
11. Central nervous system (CNS) cancer or metastases, meningeal carcinomatosis, malignant seizures, or a disease that either causes or threatens neurologic compromise (eg, unstable vertebral metastases).
12. Other invasive malignancies within the last 3 years, except non-melanoma skin cancer, and localized cured prostate and cervical cancer
13. Experienced portal hypertension or any of its complications.
14. Active, uncontrolled bacterial, viral, or fungal infections, requiring systemic antimicrobial within 14 days.
15. Known bleeding diathesis or signs of uncontrolled active bleeding (hematuria, GI bleeding) other than self-limited causes of benign etiology that have been adequately investigated at the discretion of the Investigator.
16. Requiring anticoagulation with aspirin >100 mg daily, unfractionated heparin, low molecular weight heparin (LMWH), direct anti-thrombin inhibitors, or vitamin K antagonists (eg, warfarin).
17. Severe chronic obstructive pulmonary disease with hypoxemia (defined as resting O2 saturation of < 90% breathing room air).

18. Unwilling or unable to comply with procedures required in this protocol
19. Known infection with human immunodeficiency virus, hepatitis B, or hepatitis C. Patients with history of chronic hepatitis that is currently not active are eligible.
20. Serious nonmalignant disease (eg, hydronephrosis, liver failure, or other conditions) that could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor.
21. Currently receiving any other investigational agent.
22. Exhibited allergic reactions to a similar structural compound, biological agent, or formulation.
23. Medical condition or have undergone significant surgery to the gastrointestinal tract that could impair absorption or that could result in short bowel syndrome with diarrhea due to malabsorption.
24. Used hydroxyurea or anagrelide within 24 hours prior to the first dose
25. Systemic steroid therapy (>10 mg daily prednisone or equivalent) within 7 days prior to the first dose of study treatment (note: topical, inhaled, nasal, and ophthalmic steroids are not prohibited).
26. Unresolved >Grade 1 non-hematological toxicity related to prior treatment (however, stable Grade 2 exceptions may be permitted if discussed in advance with the Sponsor).