The Telomerase Inhibitor Imetelstat in Patients With Intermediate-2- or High-Risk Myelofibrosis Previously Treated With Janus Kinase Inhibitors: A Phase 2, Randomized Study

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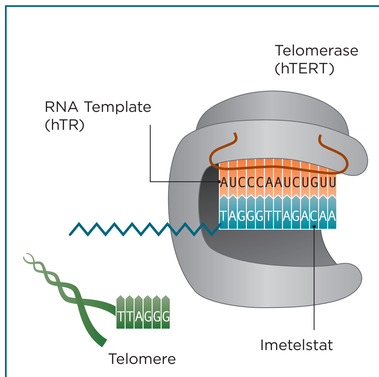
BACKGROUND

- Myelofibrosis (MF) is a Philadelphia chromosome–negative myeloproliferative neoplasm that arises from malignant progenitor cell clones with shorter telomeres, and is associated with a poor prognosis.[1-4]
- The Janus kinase (JAK) 1/2 inhibitor ruxolitinib is currently the only approved therapy for MF,[5] and there are no approved treatment options for patients for whom ruxolitinib fails.
  - As such, there is a significant unmet medical need for effective treatments in this patient population.
- Imetelstat sodium (hereafter imetelstat) is a 13-mer oligonucleotide that specifically targets the RNA template of human telomerase and is a potent first-in-class competitive inhibitor of telomerase enzymatic activity[6,7] (**Figure 1**).



- **Proprietary:** a 13-mer N3'-P5' thio-phosphoramidate oligonucleotide complementary to the RNA template region (hTR) of the telomerase enzyme, which has a covalently bound 5' lipophilic (palmitoyl) group to increase cell permeability and tissue distribution
- **Long half-life:** long tissue residence time in bone marrow, spleen, and liver (0.19-0.51 µM observed in human bone marrow at 41-45 hours post 7.5 mg/kg dose)
- **Potent competitive inhibitor of telomerase:** IC_{50} = 0.5-10 nM (cell-free assay)
- **Does not elicit its effect through an antisense inhibition of protein translation**
- **Target:** malignant progenitor cell proliferation

Figure 1. Imetelstat: a telomerase inhibitor that binds to the RNA template preventing maintenance of telomeres

- Previously published data on short telomeres and upregulated telomerase activity in myeloproliferative neoplasms, such as MF,[4,8] have suggested that the mechanism of action for imetelstat may provide clinical benefits in patients with MF.
- In a pilot study of 33 patients with intermediate-2-risk or high-risk MF, 48% of whom were previously treated with JAK inhibitors, imetelstat was found to be active.[9]
  - 7 patients (21%) achieved a complete or partial remission, bone marrow fibrosis was reversed in all 4 patients who had a complete remission, and a molecular response also occurred in 3 of the 4 patients.
  - The most clinically significant side effect of imetelstat was myelosuppression, which was the primary reason for the protocol-mandated dose reduction that occurred in 22 patients (67%).
- Herein, we describe an ongoing phase 2 clinical trial of imetelstat in patients with intermediate-2- or high-risk MF who are relapsed after or refractory to JAK inhibitor treatment.

METHODS

- This is a randomized (1:1), single-blind, multicenter, phase 2 study of 2 dosing regimens of imetelstat (9.4 mg/kg and 4.7 mg/kg, intravenously, every 3 weeks) (NCT02426086) in adult patients with Dynamic International Prognostic Scoring System (DIPSS) intermediate-2- or high-risk MF whose disease progressed during or after JAK inhibitor therapy (**Figure 2**).

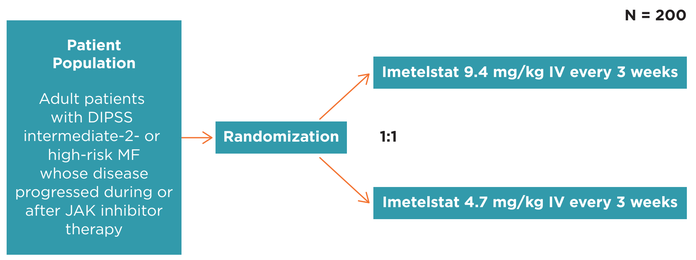


Figure 2. MYF2001 study design
Patients will receive imetelstat until disease progression, unacceptable toxicity, or study end.

- Eligible patients will be stratified based on spleen size ≥ 15 cm below the left costal margin by palpation (yes vs no) and platelet count at study entry (platelets ≥ 75 × 10^9/L and < 150 × 10^9/L vs ≥ 150 × 10^9/L).
- Study treatment will be administered on a 21-day cycle.
- The end of study is defined as 18 months after the last patient is enrolled or when the sponsor terminates the study, whichever comes first.
- Approximately 200 patients will be enrolled across North America, Europe, and Asia (**Figure 3**) according to key inclusion and exclusion criteria (**Table 1**).

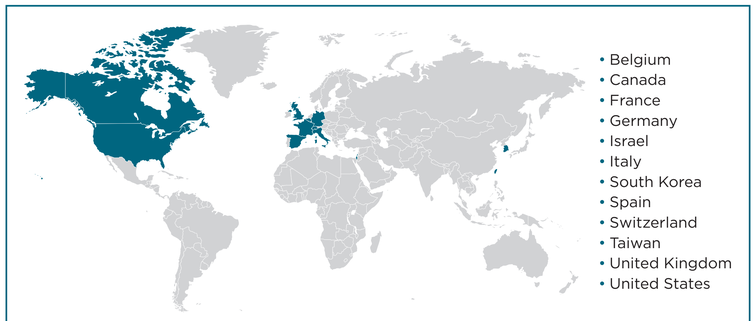


Figure 3. Worldwide study site distribution

Table 1. Key study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Diagnosis of primary MF according to the revised World Health Organization criteria or post-essential thrombocythemia MF or post-polycythemia vera MF according to the IWG-MRT criteria • DIPSS intermediate-2- or high-risk MF • Measurable splenomegaly prior to study entry as demonstrated by palpable spleen measuring ≥ 5 cm below the left costal margin or spleen volume of ≥ 450 cm^3 measured by magnetic resonance imaging • Active symptoms of MF as demonstrated by a symptom score of at least 5 points (on a 0-10 scale) on at least 1 of the symptoms or a score of ≥ 3 on at least 2 of the symptoms • Documented progressive disease during or after JAK inhibitor therapy • Hematology laboratory test values within the following limits within 21 days prior to randomization: – Absolute neutrophil count ≥ 1500/mm^3 independent of growth factor support – Platelets 75,000/mm^3 independent of platelet transfusion support • Eastern Cooperative Oncology Group performance status ≤ 2	• Peripheral blood blast count of ≥ 10% or bone marrow blast count of ≥ 10% • Prior treatment with imetelstat • Major surgery within 4 weeks prior to randomization • Any chemotherapy, investigational drug regardless of class or mechanism of action or hydroxyurea within 14 days prior to randomization; immunomodulatory or immunosuppressive therapy, corticosteroids > 30 mg/d prednisone or equivalent, growth factor treatment or JAK inhibitor therapy ≤ 14 days prior to randomization • Active systemic hepatitis infection requiring treatment (carriers of hepatitis virus are permitted to enter the study), of any type or known acute or chronic liver disease including cirrhosis • Prior history of hematopoietic stem cell transplant

IWG-MRT, International Working Group-Myeloproliferative Neoplasms Research and Treatment.

STUDY END POINTS

- The co-primary end points of this study (both at Week 24) are:
  - The proportion of patients achieving ≥ 35% reduction in spleen volume (spleen response rate);
  - The proportion of patients achieving ≥ 50% reduction in total symptom score (symptom response rate).
- Secondary end points include safety, treatment response per modified IWG-MRT criteria for MF, duration of response, overall survival, and pharmacokinetic and pharmacodynamic relationships.
- Exploratory end points include baseline levels and change from baseline levels of telomerase activity, telomere length, and human telomerase reverse transcriptase; cytogenetic and molecular responses; and leukemia-free survival.

STATUS

- Approximately 97 sites are planned in 12 countries (**Figure 3**).
- Enrollment began in June 2015 and is ongoing.
- As of May 25, 2016, there are 77 active sites.

REGISTRATION

- This study is registered at ClinicalTrials.gov (NCT02426086).

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