MPN-628

SURPASS-ET Trial: A Phase 3, Open-label, Multicenter, Randomized, Active-Controlled Study to Assess Pharmacokinetics and Compare the Efficacy, Safety, and Tolerability of Ropeginterferon alfa-2b-njft vs Anagrelide as Second-Line Therapy for Essential Thrombocythemia

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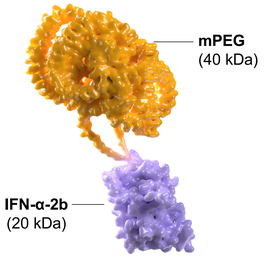
Background

- ET is a subtype of chronic MPN characterized by thrombocytosis and associated with a higher risk of thrombosis and hemorrhage, as well as transformations[1,2]
- Therapeutic approaches to ET include achieving adequate control of platelets and WBCs, reducing the risk of thrombo-hemorrhagic complications, and preventing progression to post-ET myelofibrosis or secondary AML[3]
- Low-dose aspirin with HU is typically given as first-line therapy in high-risk patients.[3] However, 20% of ET patients become HU-intolerant or -resistant and their disease is inadequately controlled. In ET, HU-resistance may preface complications, transformation, or death[4]
- There is a paucity of prospective clinical trial data to guide the management of ET patients who are HU-resistant or -intolerant. Ropeginterferon alfa-2b-njft (P1101) is a monopegylated IFN-alfa-2b, developed specifically to treat MPNs, including ET
- The approach for SURPASS-ET is based on phase 1/2 and phase 3 clinical studies that demonstrated the safety and efficacy of ropeginterferon alfa-2b-njft for PV[5-7]
  - The safety and PK of ropeginterferon alfa-2b-njft were assessed in a phase 1 study in healthy males (A09-102-P1101); ropeginterferon alfa-2b-njft was well tolerated by all patients, with no serious adverse reactions reported
  - Clinical experience with ropeginterferon alfa-2b-njft in PV shows that the compound, with proper dose modifications, may be effective in controlling disease in a significant proportion of patients with ET

AML, acute myeloid leukemia; HU, hydroxyurea; ET, essential thrombocythemia; IFN, interferon; MPN, myeloproliferative neoplasm; PK, pharmacokinetics; PV, polycythemia vera; WBC, white blood cell.

Ropeginterferon alfa-2b-njft

- Ropeginterferon alfa-2b-njft is a monopegylated IFN-alfa-2b
- It is a PEG-recombinant manufactured analogue of native IFN-α, with improved PK properties due to proprietary, innovative pegylation technology
- Specifically engineered as only 1 single isoform, it is anticipated a reduced dosing frequency will be possible

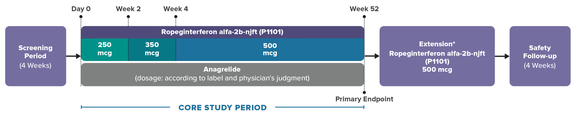


IFN-α, interferon-α, kDa, kilodalton; mPEG, monopegylated; PEG, pegylated, PK, pharmacokinetics.

Study Design

Phase 3, open-label, multicenter, randomized, active-controlled study to assess the efficacy, safety, tolerability, and PK of ropeginterferon alfa-2b-njft after 12 months of treatment compared with anagrelide as second-line therapy for patients with ET who have shown resistance or intolerance to HU. Total duration is approximately 14 months, with a screening period of 28 days, a treatment period of 12 months, and a follow-up period of 28 days.[7,8]

STUDY DESIGN



STUDY VISITS

Study participants are required to attend study visits every other week during the core study period; visits on Weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, and 50 are performed via telephone. Study visits occur every 2, 3, or 4 weeks during the Extension period and all can be a telephone visit, except for once every three months.

FOR A LIST OF PARTICIPATING SITES PLEASE SEE CLINICALTRIALS.GOV

ClinicalTrials.gov Identifier: **NCT04285086**
Study Start Date: **August 25, 2020**

Major Inclusion Criteria

- Patients diagnosed with high-risk ET (>60 years and *JAK2* V617F-positive at screening or having disease-related thrombosis or hemorrhage in the past), diagnosed according to WHO 2016 criteria
- Documented resistance/intolerance to HU; washout between the last dose of HU and randomization no shorter than 7 days
- IFN-naïve or anti-P1101-antibody–negative with an IFN washout of 14 days

Key Exclusion Criteria

- Pregnant or lactating females
- Significant cardiovascular disease
- Documented autoimmune disease
- History or presence of clinically significant depression or neurological disease
- Other clinically significant medical conditions, such as pulmonary hypertension, infection, and retinopathy

ET, essential thrombocythemia; HU, hydroxyurea; IFN, interferon; WHO, World Health Organization.

Data Analysis

Efficacy and Safety

- Cochran-Mantel-Haenszel test will be used for comparing the primary endpoint in the 2 treatment arms
- The PK parameters will be derived using PPK analysis, and the relationship between exposure and efficacy and safety endpoints will be examined using E-R analysis
- A total of 130 randomized patients is planned to detect a difference of 40% (ropeginterferon alfa-2b-njft) vs 15% (anagrelide) in durable ELN response rate with 90% power at alpha level = 0.05 using the chi-square test
- To account for possible non-evaluability (eg, no follow-up data), approximately 160 patients will be randomized in this study to have 130 completed patients

ELN, European Leukemia Network; E-R, exposure-response; PK, pharmacokinetic; PPK, population pharmacokinetics.

Study Status

Enrollment Update

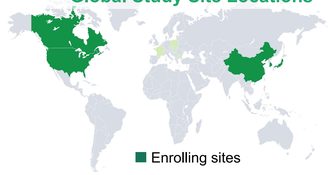
- 161 patients randomized (154 Asian, 7 Caucasian)
- Mean age 58.3 (SD: 14.3)
- Median age 62 (range 20-83)
- 75 men (46.6%), 86 women (53.4%)
- 130 (80.8%) had a TSS < 20

SD, standard deviation; TSS, total symptom score.

61 Sites Enrolling[8]

8 Countries

Global Study Site Locations



SURPASSET.com
US Clinical Trial Site

Study Endpoints

Primary Efficacy Endpoint

The primary endpoint is durable modified ELN composite response at 9 and 12 months

- Peripheral blood count remission (platelets ≤ 400 x 10^9/L *AND* WBC < 9.5 x 10^9/L), *AND*
- Improvement or non-progression in disease-related signs (splenomegaly), *AND*
- Large symptoms improvement or maintain non-progression based on the MPN-SAF TSS, *AND*
- Absence of hemorrhagic or thrombotic events

Secondary Efficacy Endpoints

- Durable response at months 3 and 6
- Longitudinal rate of change in the ELN response rates over 12 months
- Response rates based on peripheral blood count remission, no signs of progressive disease, and absence of any hemorrhagic or thrombotic events
- Occurrence of thromboembolic events
- Time to first peripheral blood count remission response
- Duration of peripheral blood count remission response
- Symptomatic improvement assessed by the EQ-5D-3L questionnaire and the 10-item MPN-SAF TSS
- Change of *CALR*, *MPL*, and *JAK2* allele burden over time
- Improvement or non-progression of spleen size

Exploratory Endpoints

- Bone marrow (optional) histological remission, defined as the disappearance of megakaryocyte hyperplasia and absence of >grade 1 reticulin fibrosis

Safety Endpoints

- AEs according to CTCAE v5.0 and AEs of special interest (eg, cardiovascular, hemorrhagic, thrombotic, and psychiatric events)

PPK and E-R Endpoints

- PK parameters will be derived using PPK analysis, and the relationship between exposure and efficacy and safety endpoints will be examined using E-R analysis

Immunogenicity Endpoints

- Proportion of patients who are ADA-positive and -negative
- Neutralizing antibody in ropeginterferon alfa-2b-njft arm

ClinicalTrials.gov
Identifier NCT04285086

ADA, antidrug antibody; AE, adverse event; CALR, calreticulin; CTCAE, Common Terminology Criteria for Adverse Events; ELN, European Leukemia Network; EQ-5D-3L, EuroQOL 5 dimensions 3-level–version questionnaire; E-R, exposure-response; JAK-2, Janus kinase-2; MPL, myeloproliferative leukemia; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; PK, pharmacokinetic; PPK, population pharmacokinetics; WBC, white blood cell.

Summary

- Ropeginterferon alfa-2b-njft (P1101) is currently being investigated in patients with ET
- No prospective clinical trial data exist to guide management of ET patients who are HU-resistant or -intolerant; treatment options are limited; and, several second-line treatment options are associated with increased risk of disease transformation
- The SURPASS-ET study is a multinational, phase 3, open-label, multicenter, randomized, active-controlled trial to assess PK and compare the efficacy, safety, and tolerability of ropeginterferon alfa-2b-njft with anagrelide as a second-line therapy in patients with ET resistant or intolerant to HU
- Ropeginterferon alfa-2b-njft would represent a significant addition to the therapeutic options for patients with ET

ET, essential thrombocythemia; HU, hydroxurea; PK, pharmacokinetic

References

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