SURPASS-ET Trial: A Phase 3, Open-label, Multicenter, Randomized, Active-controlled Study to Assess Pharmacokinetics and Compare the Efficacy, Safety, and Tolerability of P1101 vs Anagrelide as Second-Line Therapy for Essential Thrombocythemia

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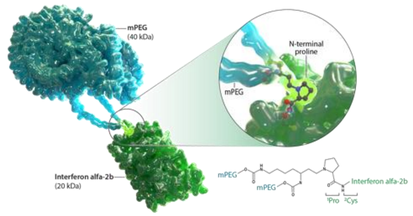
BACKGROUND

- 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]
- Ideal therapeutic approaches should achieve adequate control of platelets and WBC, reduce the risk of thrombo-hemorrhagic complications, and prevent progression to post-ET myelofibrosis or secondary AML.[2]
- Low-dose aspirin with HU is typically given as first-line therapy in high-risk patients.[2] However, 20% of ET patients become HU-intolerant or -resistant and their disease is inadequately controlled.[3] In ET, HU-resistance may preface complications, transformation, or death.[3]
- 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 next generation monopegylated interferon (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 P1101 for PV[4-6]
  - The MTD, safety, efficacy, and PK of P1101 were assessed in a phase 1 study in healthy males (A09-102-P1101)
  - P1101 was well-tolerated by all subjects, and there were no serious adverse reactions reported
  - Clinical experience with P1101 in PV shows that the compound, with proper dose modifications, may be effective in controlling disease in a significant proportion of subjects with ET

HU, hydroxyurea; ET, essential thrombocytopenia; MPN, myeloproliferative neoplasm; MTD, maximum tolerated dose; PK, pharmacokinetics; PV, polycythemia vera; SC, subcutaneous.

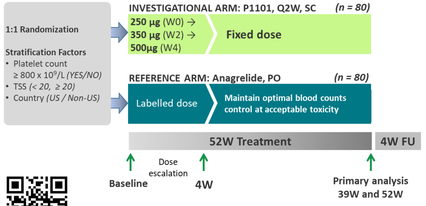
P1101

- P1101 is a monopegylated interferon alfa-2b[6]
- It is a PEG recombinant manufactured analogue of native IFN-α, with improved PK properties due to proprietary, innovative PEGylation technology[6]
- Specifically engineered as only 1 single isoform, it is anticipated a reduced dosing frequency will be possible[6]



STUDY DESIGN

Phase 3, open-label, multicenter, randomized, active-controlled study to assess the efficacy, safety, tolerability, and pharmacokinetics of P1101 after 12 months of treatment compared with anagrelide as second-line therapy for subjects 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.[6,7]



ClinicalTrials.gov Identifier NCT04285086

ET, essential thrombocytopenia; FU, follow-up; HU, hydroxyurea; PO, oral; Q2W, every 2 weeks; SC, subcutaneous; TSS, total symptom score; W, week. WHO, World Health Organization.

SURPASS ET ESSENTIAL THROMBOCYTHEMIA

MAJOR INCLUSION CRITERIA

- Subjects diagnosed with high-risk ET (> 60 years and JAK2V617F-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 14 days
- IFN naïve or anti-P1101 binding antibody negative with an interferon 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
- Clinically significant medical conditions

DATA ANALYSIS

EFFICACY & SAFETY

- Cochran-Mantel-Haenszel test will be used for comparing the primary endpoint in the two 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
- Total of 130 randomized subjects is planned to detect a difference of 40% (P1101) versus 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 subjects will be randomized in this study to get 130 completed patients

STUDY STATUS

ENROLLMENT UPDATE

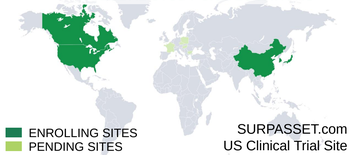
- 123 patients randomized (117 Asian, 6 Caucasian)
- Mean age 58.6 (SD: 13.9)
- Median age 62 (range 21-80)
- 58 men (47.2%), 65 women (52.8%)
- 98 (76.7%) had a TSS < 20

SD, standard deviation; TSS, total symptom score.

60 SITES ENROLLING

8 COUNTRIES

GLOBAL STUDY SITE LOCATIONS



SURPASSET.com
US Clinical Trial Site

STUDY ENDPOINTS

PRIMARY EFFICACY ENDPONTS

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 the 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 JAK-2 allelic burden over time
- Improvement or non-progression of spleen size assessment

EXPLORATORY ENDPONTS:

- 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 events, hemorrhagic, TEs, and psychiatric events)

PPK AND E-R ANALYSES 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 subjects who are ADA positive and negative
- Neutralizing antibody in P1101 arm

ADA, antidrug antibody; AE, adverse event; CALR, calreticulin; ELN, European Leukemia Network; CTCAE, Common Terminology Criteria for Adverse Events; 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; TE, thrombotic events; 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 trial is a multinational phase 3, open-label, multicenter, randomized, active-controlled study to assess PK and to compare the efficacy, safety, and tolerability of P1101 to anagrelide as a second-line therapy in subjects with ET resistant or intolerant to HU
- P1101 would represent a landmark addition to the therapeutic options for patients with ET

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