EXCEED-ET: A Single-Arm Multicenter Study to Assess the Efficacy, Safety, and Tolerability of Ropeginterferon alfa-2b-njft in North American Adults With Essential Thrombocythemia

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MPN-633

Context

- ET is a chronic MPN subtype caused by specific driver mutations with subsequent clonal expansion of neoplastic HSCs. It leads to thrombocytosis (and, in certain cases, leukocytosis) and is associated with a higher risk of thrombosis and hemorrhage as well as transformation to MF and/or AML.[1-4]
- An analysis of SEER data collected from 2002 to 2016 showed that the incidence rates for ET among US adults ranged from 1.55-2.50 per 100,000 person-years,[3,5] with a five-year mortality rate of 19.2%.[5]
- Therapeutic approaches to ET include achieving adequate control of platelets and WBC, reducing the risk of thrombo-hemorrhagic complications, and preventing progression to MF or secondary AML.[2]
- No new treatments have been approved for ET in over a decade. Current agents do not typically produce desired durable responses in *JAK2* V617F AB or otherwise mitigate the course of the disease.[6]
- Low-dose aspirin with HU is typically given as first-line therapy in high-risk patients.[2] However, HU can be poorly tolerated and at least 20% of ET patients become HU-intolerant or -resistant.[7] In addition, HU has not been shown to consistently produce long-term control of AB[5] and may favor the expansion of mutated HSCs instead of the non-mutated or normal HSCs.[8]
- A paucity of clinical trial data, as well as an unmet medical need exist for the management of patients with ET who are cytoreduction-naïve or are HU-resistant/intolerant.
- Ropeginterferon alfa-2b-njft (formerly P1101) is a next-generation monopegylated IFN alfa-2b, developed specifically to treat MPNs, such as ET.
- The objective of the EXCEED-ET (NCT05482971) Study is to assess the efficacy, safety, and tolerability of ropeginterferon alfa-2b-njft in adults with ET who live in the United States or Canada.

AB, allele burden; AML, acute myeloid leukemia; ET, essential thrombocythemia; HSC, hematopoietic stem cell; HU, hydroxyurea; IFN, interferon; MF, myelofibrosis; MPN, myeloproliferative neoplasm; SEER, Surveillance, Epidemiology, and End Results; V617F JAK2, V617F mutation Janus associated kinase 2; WBC, white blood cell.

EXCEED-ET Study Status

Enrollment Update

- Estimated enrollment is 64 patients
- Approximately 35-40 clinical sites

Study Site Locations



64 Patients

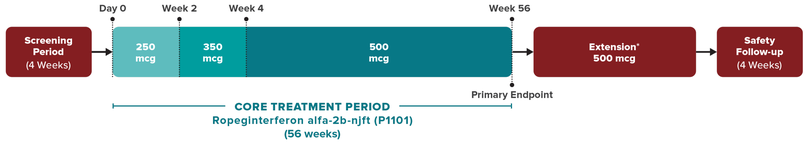
40 Clinical Sites

ClinicalTrials.gov

Design

- EXCEED-ET is a Phase 2b, single-arm, multicenter trial that will evaluate the efficacy, safety, and tolerability of ropeginterferon alfa-2b-njft for the treatment of adult patients with ET.
- Ropeginterferon alfa-2b-njft will be administered SC Q2W at a starting dose of 250 mcg (Week 0), then 350 mcg at Week 2, and a target dose of 500 mcg (Week 4).
  - Dose adjustment allowed for safety or tolerability concerns.
- Patient visits will be scheduled every 14 days (±3 days) during the core 56-week study period.
  - Telephone visits plus assessment of local laboratory results will be permitted once a patient reaches the core treatment phase, if the patient has confirmed the ability to self-administer the treatment and has shown stable blood counts with no clinically meaningful toxicity or ET-related event in the acute phase.
- The total duration of the study is approximately 15 months including a 4-week screening period, a 4-week titration period, a 56-week core treatment phase, and a 4-week follow-up phase (**Figure 1**).
  - For patients who derive a benefit from therapy, a subsequent extension phase will allow them a continual supply of ropeginterferon alfa-2b-njft until an alternative source is available.

Figure 1. Study Design



Note: Patients entering the study receiving HU or ANA must discontinue HU or ANA prior to initiating the first dose of ropeginterferon alfa-2b-njft on Day 0.
*Extension part of the study will end with the availability of ropeginterferon alfa-2b-njft via routine prescription or with alternative sources becoming available to patients with ET.
ANA, anagrelide; ET, essential thrombocythemia; HU, hydroxyurea; Q2W, every 2 weeks; SC, subcutaneous; WHO, World Health Organization.

Key Inclusion Criteria

- Diagnosed with ET according to WHO 2016 criteria
- Cytoreductive treatment-naïve, or pre-exposed to HU and/or ANA
- Platelet count >450 × 10^9/L at screening

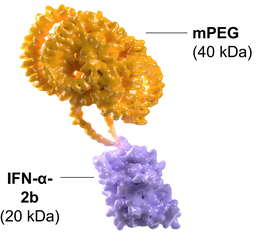
Key Exclusion Criteria

- Stopping prior interferon alfa therapy due to low efficacy or poor tolerability
- Pregnant or lactating females
- Documented autoimmune disease
- History or presence of clinically relevant depression or clinically significant neurological disease
- Clinically relevant comorbidities that may impair protocol compliance

Ropeginterferon alfa-2b-njft

- Ropeginterferon alfa-2b-njft is a monopegylated, long-acting interferon alfa-2b, engineered as a single isoform (**Figure 2**).[9]
- It is thought that ropeginterferon alfa-2b-njft impacts the source of ET in the bone marrow.[5]

Figure 2. Ropeginterferon alfa-2b-njft Structure (symbolic)



ET, essential thrombocythemia; IFN-α, interferon-α; kDa, kilodalton; mPEG, monopegylated.

Main Outcome Measures

Primary Efficacy Endpoints

The endpoint is a durable response rate

- Peripheral blood count remission (platelets ≤400 x 10^9/L and WBC <10 x 10^9/L) for at least 80% of the bi-weekly measurements for a consecutive 32 weeks during the core treatment period between Week 4 and Week 56

Secondary Efficacy Endpoints

- Clinical response as defined by the Modified ELN Criteria
- Hematological response, defined as peripheral blood count remission (platelets ≤400 x 10^9/L and WBC <10 x 10^9/L)
- Durable response at quarterly intervals both during the 13-month active treatment study period and the extension phase
- Response rates based separately on the individual components of the ELN clinical response definition
- 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
- Disease progression to post-ET MF and secondary AML
- Change of *CALR*, *MPL*, and *JAK2* allele burden over time

Exploratory Endpoints

- Symptomatic improvement assessed by the 10-item MPN-SAF TSS and quality of life by EQ-5D-3L
- 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/or psychiatric events)
- Other safety data, including ECOG performance status, vital signs, ECGs, echos, clinical laboratory tests, physical examinations, chest X-rays, and ocular examinations will be summarized

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 or ADA-negative
- Presence of neutralizing antibodies to ropeginterferon alfa-2b-njft

ADA, antidrug antibody; AE, adverse event; AML, acute myeloid leukemia; CALR, calreticulin gene; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; ECG, electrocardiogram; ECHO, echocardiogram; ELN, European Leukemia Network; EQ-5D-3L, EuroQOL 5 dimensions 3 level version questionnaire; E-R, exposure-response; ET, essential thrombocythemia; JAK-2, Janus kinase-2; MF, myelofibrosis; 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 is currently being investigated in patients with ET.
- No pivotal prospective clinical trial data exist to guide management of ET patients who are HU-resistant or -intolerant. Treatment options are limited; several second-line treatment options are associated with increased risk of disease transformation.
- The EXCEED-ET Study is a Phase 2b, single arm, multicenter trial that will evaluate the efficacy, safety, and tolerability of ropeginterferon alfa-2b-njft for the treatment of adult patients with ET in Canada and the US.
- Ropeginterferon alfa-2b-njft could represent an important addition to the therapeutic landscape for ET.

ET, essential thrombocythemia; HU, hydroxyurea.

References

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