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Poster 1808.2

POIESIS: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Global, Phase 3 Study of Navtemadlin as Add-On Therapy to Ruxolitinib in JAK Inhibitor-Naïve Patients With Myelofibrosis Who Have a Suboptimal Response to Ruxolitinib Treatment

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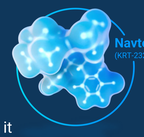
Introduction

An Unmet Need in Myelofibrosis – Ruxolitinib Suboptimal Responder

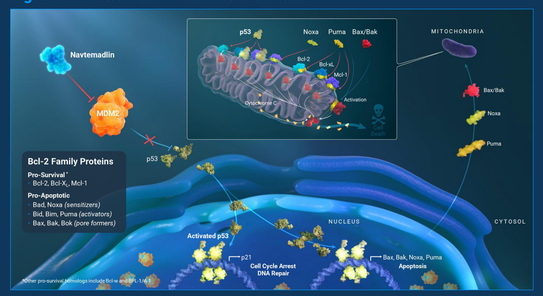
- Myelofibrosis (MF) is a clonal myeloproliferative neoplasm characterized by progressive bone marrow fibrosis, splenomegaly, constitutional symptoms, and increased risk of leukemic transformation[1]
- Ruxolitinib, a Janus kinase inhibitor (JAKi), can improve MF-related splenomegaly and symptoms, however many treated patients fail to achieve an optimal response: spleen volume reduction ≥ 35% (SVR35) and total symptom score reduction ≥ 50% (TSS50)[2,3]
- Maximizing SVR and TSS reduction is critical to optimizing clinical outcomes as improvement in quality of life is correlated with overall survival (OS)[4,5,6]
- Novel approaches are urgently needed for MF patients who have a suboptimal response to ruxolitinib treatment

Navtemadlin Inhibits MDM2 to Restore p53 Function



- MF is characterized by overexpression of mouse double minute 2 (MDM2) in malignant CD34+ progenitor cells[7]
- MDM2 suppresses tumor protein 53 (p53) function by directly inhibiting its transcriptional activity, transporting it out of the nucleus, and tagging it for proteasomal degradation[8-10]
- Navtemadlin is a potent inhibitor of MDM2 that restores p53 function, modulates B-cell lymphoma 2 (Bcl-2) family proteins, and induces apoptosis in *TP53*^{WT} CD34+ MF progenitors by overcoming MDM2 dysregulation[11] (Figure 1)

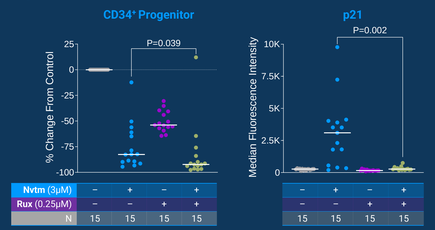
Figure 1: Navtemadlin Mechanism of Action



Synergy of Navtemadlin and Ruxolitinib

- Nonclinical data demonstrated unique CD34+ cell-killing synergy when navtemadlin was added to ruxolitinib via the suppression of p21, a critical anti-apoptotic checkpoint of p53 (Figure 2)[11]

Figure 2: Navtemadlin Added to Ruxolitinib in MF Patient Samples

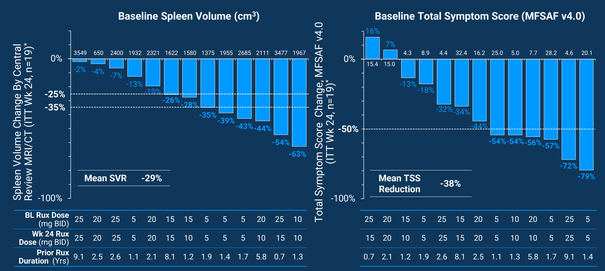


Cell survival and protein expression in MF patient samples after 72h of exposure to navtemadlin, ruxolitinib or the combination.
In vivo C_{max}: navtemadlin 2.7 μM (~240 mg QD); ruxolitinib 0.25 μM (~5 mg QD).

Proof-of-Concept for Add-On Navtemadlin to Ruxolitinib

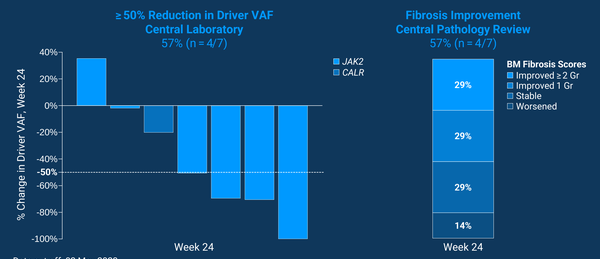
- In a Phase 1b/2 study in MF patients with a suboptimal response to ruxolitinib, add-on navtemadlin (240 mg QD *Days 1-7 / 28-day cycle*) demonstrated clinically meaningful reductions in spleen volume and improvements in quality of life[12] at Week 24 (Figure 3):
  - SVR35 of 32% and TSS50 of 32%
- Combination treatment was well tolerated with a manageable safety profile
- Marked reductions in bone marrow fibrosis, driver mutation allele burden (Figure 4), and circulating CD34+ cell counts (Figure 5) demonstrated potential disease modification
- These data provide strong rationale to further investigate this novel combination in a phase 3 study in MF patients with a suboptimal response to ruxolitinib

Figure 3: SVR and TSS Reduction at Week 24 in KRT-232-109



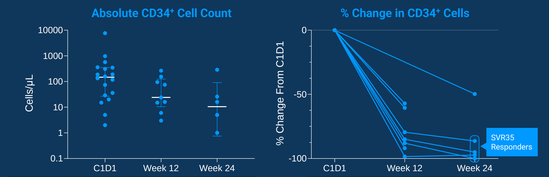
Data cut-off: 02 May 2023. Median time on ruxolitinib monotherapy was 21.6 months.
Baseline spleen volume MRI/CT scans and TSS assessments were taken while subjects were on a stable dose of ruxolitinib for ≥8 weeks (ie, no ruxolitinib wash-out). No dose increases of ruxolitinib above the stable baseline dose occurred during the 24-week assessment period. *Six patients discontinued prior to Week 24 assessment.

Figure 4: Change in Driver Mutation Allele Burden and BM Fibrosis



Data cut-off: 02 May 2023.
Evaluable patients shown at Week 24 (baseline and at least one post-baseline assessment).

Figure 5: Change in Circulating CD34+ Cells at Week 24



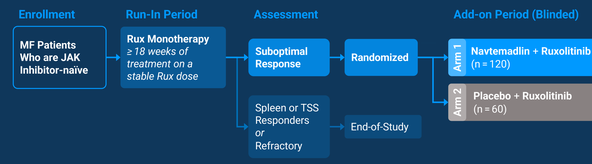
Data cut-off: 07 Apr 2023.
*One patient with a cell count of 0 at Week 24 not shown on this figure.

Methods

POIESIS Study Design

- **POIESIS** (**P**53 activation to **O**pt**I**miz**E** response**S** in Myelofibros**IS**) is a randomized, double-blind, placebo-controlled, global, phase 3 trial comparing add-on navtemadlin (240 mg QD *Days 1-7 / 28-day cycle*) versus add-on placebo to ruxolitinib in MF patients with a suboptimal response to ruxolitinib (Figure 6)
- POIESIS incorporates a novel design that aligns with clinical practice for treating JAKi-naïve MF patients (treat with add-on therapy when needed) and comprises two treatment periods:
  - Run-in Period: JAKi-naïve patients treated with ruxolitinib monotherapy for 18 weeks to identify suboptimal responders (SVR > 0% but < 35% and TSS reduction > 0% but < 50%)
  - Add-on Period: Suboptimal responders are randomized to either add-on navtemadlin or add-on placebo
- Key eligibility criteria for each treatment period are shown in Table 1
- The co-primary endpoints are targeted SVR and TSS reduction 24 weeks after randomization
- This global study is active and enrolling (Figure 7)

Figure 6: POIESIS Study Design (NCT06479135)



Co-Primary Endpoints	Secondary Endpoints	Stratification Factors
• Targeted SVR by central review MRI/CT • Targeted TSS by MFSAF v4.0	• Overall survival • Progression-free survival • Duration of spleen response	• SVR from run-in • TSS reduction from run-in • Stable dose of ruxolitinib

Stable ruxolitinib is ≥ 5 mg BID that does not require treatment hold or dose adjustment during the eight weeks prior to add-on navtemadlin or placebo.
Note: Navtemadlin dosed at 240 mg QD *Days 1-7 / 28-day cycle*.

Table 1: Key Inclusion and Exclusion Criteria

Run-In Period	Add-On Period
Key Inclusion Criteria	**Key Inclusion Criteria**
• Primary or secondary MF by WHO criteria • Intermediate-1 / 2, or High-risk disease by IPSS • ECOG performance status ≤ 2 • Spleen volume ≥ 450 cm^3 by central review MRI/CT • Total symptom score of ≥ 10 by MFSAF v4.0 • Adequate hematologic function (ANC ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, and WBC ≤ 50 × 10^9/L)	• *TP53*^{WT} by central testing • ECOG performance status ≤ 2 • Treatment with a stable dose of ruxolitinib • Suboptimal response to ruxolitinib run-in (SVR > 0% but < 35% and TSS reduction > 0% but < 50%) • Adequate hematologic function (ANC ≥ 1.5 × 10^9/L and platelet count ≥ 100 × 10^9/L)
Key Exclusion Criteria	**Key Exclusion Criteria**
• Splenic irradiation within three months • Prior ASCT or ASCT eligible • Peripheral blood or bone marrow blast count ≥ 10% • Active serious infection or uncontrolled intercurrent illness	• WBC increase ≥ 2-fold and > 50 × 10^9/L during ruxolitinib run-in • Splenic irradiation within three months • Peripheral blood or bone marrow blast count ≥ 10% • Active serious infection or uncontrolled intercurrent illness

Figure 7: 220 Global Sites Across 19 Countries (US, Europe, and Asia-Pacific)

Country (Sites)					
United States	(64)	Australia	(11)	Belgium	(5)
Italy	(19)	South Korea	(9)	Czech Republic	(5)
France	(14)	Croatia	(7)	Greece	(5)
Germany	(14)	Austria	(6)	Romania	(5)
Poland	(12)	Georgia	(6)	Hungary	(4)
Spain	(12)	Portugal	(6)	Serbia	(4)
UK	(12)				

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Abbreviations
ANC, absolute neutrophil count; ASCT, allogeneic stem cell transplant; BID, twice daily; BL, baseline; BM, bone marrow; C1D1, cycle 1 day 1; *CALR*, calreticulin; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; Gr, grade; IPSS, International Prognostic Scoring System; ITT, intention-to-treat; JAK, Janus kinase; *JAK2*, Janus kinase 2; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MFSAF, myelofibrosis symptom assessment form; MRI, magnetic resonance imaging; Nvtm, navtemadlin; QD, once daily; Rux, ruxolitinib; SVR, spleen volume reduction; SVR35, spleen volume reduction ≥ 35%; TSS, total symptom score; TSS50, total symptom score reduction ≥ 50%; VAF, variant allele frequency; WBC, white blood cell; WHO, World Health Organization; Wk, week; WT, wild-type; Yrs, years.

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