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UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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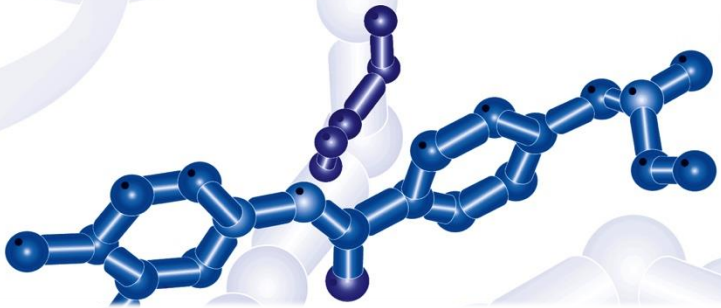

New Drugs in Hematology

President: Pier Luigi Zinzani

Bologna,
Royal Hotel Carlton
May 18-19-20, 2026

Epigenetic modifiers and pro-apoptotic agents in myelofibrosis

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Disclosures of Pankit Vachhani

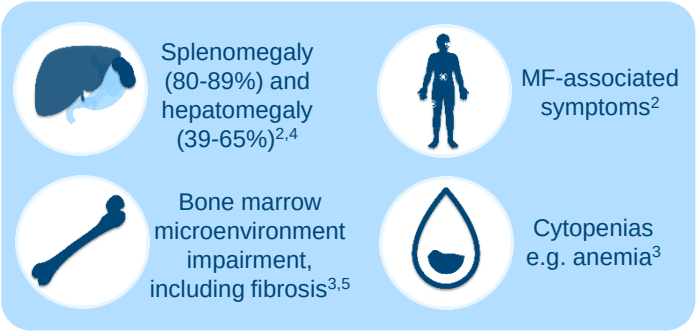
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Blueprint Medicines, Bristol Myers Squibb, Cogent Biosciences, Incyte, Sobi, Geron, GlaxoSmith Kline, Stemline, Servier, Syndax, Takeda.						●	
DISC medicine, Kartos, Karyopharm, Merck, Prelude Therapeutics, Silence Therapeutics			●				
Alabama Cancer Congress							●

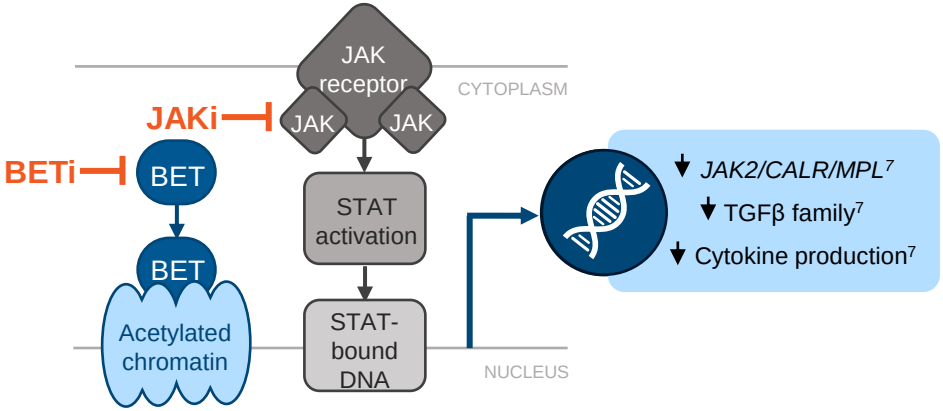
Epigenetic therapies

- Hypomethylating agents: azacitidine, decitabine
- BET Inhibitors: **pelabresib**, INCB-057643, others
- Histone Deacetylase Inhibitors: givinostat, pracinostat, others
- LSD1 Inhibitors: bomedemstat

Rational combination strategies are needed to target the underlying disease biology and further improve clinical outcomes in MF

- Myelofibrosis (MF) is a chronic and progressive blood cancer characterized by splenomegaly, MF-associated symptoms, cytopenias and impairment of the bone marrow microenvironment[1-3]





- JAK inhibitor monotherapy is the standard of care in intermediate- and high-risk MF[6]. However, there remains an unmet need for new rational combination approaches which address the underlying disease biology and improve treatment depth and duration[5]
- Pelabresib (DAK539) is an investigational oral small molecule inhibitor of BET proteins that targets inflammatory pathways involved in MF[8-10]

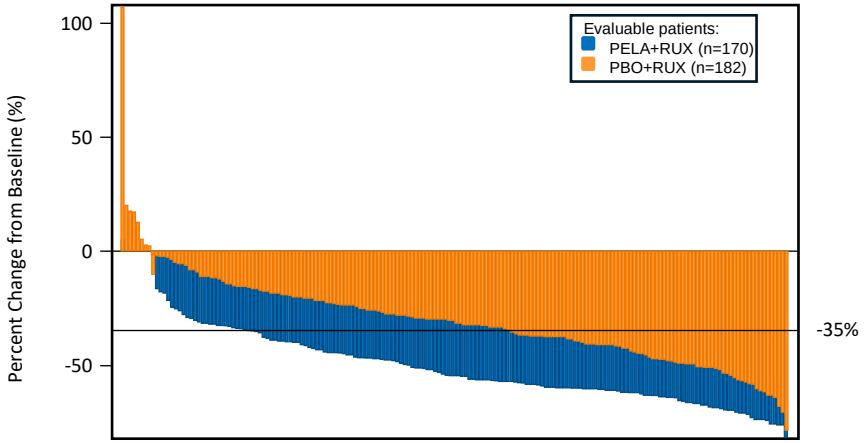
Both BET and JAK/STAT signalling pathways drive MF progression.[7]
Dual inhibition of BET and JAK/STAT signalling pathways represent a combination treatment strategy that has the potential to achieve deeper responses and disease modification in JAKi-naïve patients with MF[9]

1. Koschmieder S, *HemaSphere.* 2024;8:e70056; 2. Mughal TI, et al. *Int J Gen Med.* 2014;7:89-101; 3. Naymagon L, Mascarenhas J. *Hemasphere.* 2017;1(1):e1; 4. Cervantes F, et al. *Blood.* 2009;113(13):2895-2901; 5. Harrison CN, et al. *Cancer.* 2024;130(12):2091-2097; 6. Tefferi A, et al. *Am J Hematol.* 2023;98(5): 801-821; 7. Mascarenhas J, et al. *Leukemia.* 2021;35:3361-3363; 8. Blum KA, et al. *Cancer Res Commun.* 2022;2(8):795-805; 9. Mascarenhas J, et al. *J Clin Oncol.* 2023;41(32):4993-5004; 10. Rampal RK, et al. *Nat Med.* 2025;31:1531-1538.
BET, bromodomain and extraterminal domain; JAK, Janus kinase; MF, myelofibrosis; STAT, signal transducer and activator of transcription.

Oral 910 presented at: American Society of Hematology (ASH) Annual Meeting; December 6 - 9, 2025; Orlando, Florida

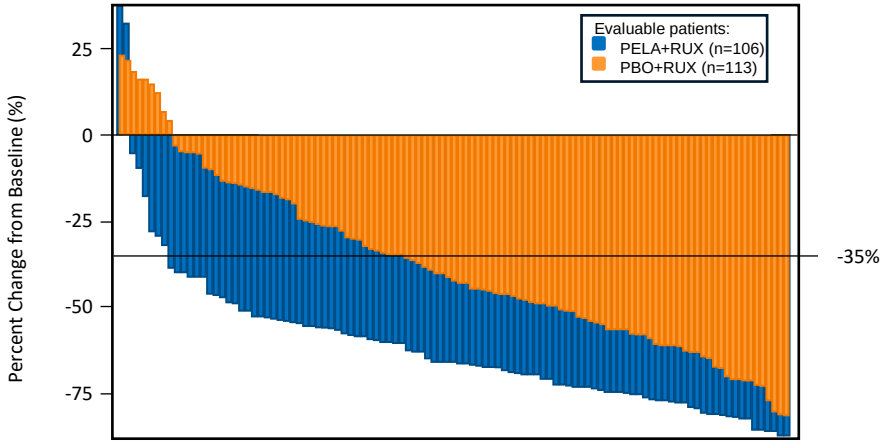
Significant reductions in spleen volume persisted from Week 24 to Week 96 with PELA+RUX compared with PBO+RUX

Week 24



	PELA+RUX (N=214)	PBO+RUX (N=216)
SVR35 response at Week 24 in **evaluable patients**	82.9% (141/170)	41.8% (76/182)
Difference	41.1%	
SVR35 response at Week 24 in **ITT population**	65.9% (141/214)	35.2% (76/216)
Difference† (95% CI)	30.4% (21.6-39.3)	

Week 96



	PELA+RUX (N=214)	PBO+RUX (N=216)
SVR35 response at Week 96 in **evaluable patients**	91.5% (97/106)	57.5% (65/113)
Difference	34.0%	
SVR35 response at Week 96 in **ITT population**	45.3% (97/214)	30.1% (65/216)
Difference† (95% CI)	14.9% (6.1-23.8)	

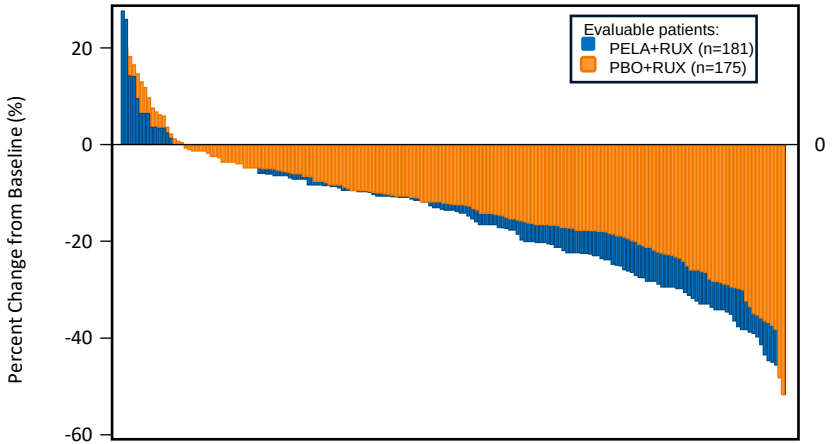
Deep reductions in spleen volume were maintained at Week 96 with PELA+RUX vs PBO+RUX

Data cutoff date: March 02, 2025.
Spleen volume assessed by central read.
Waterfall plots represent evaluable patients who have baseline and Week 24 or Week 96 data. †Calculated by stratified Cochran-Mantel-Haenszel test.
CI, confidence interval; ITT, intent-to-treat; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib; SVR35, ≥35% reduction in spleen volume from baseline.

Oral 910 presented at: American Society of Hematology (ASH) Annual Meeting; December 6 - 9, 2025; Orlando, Florida

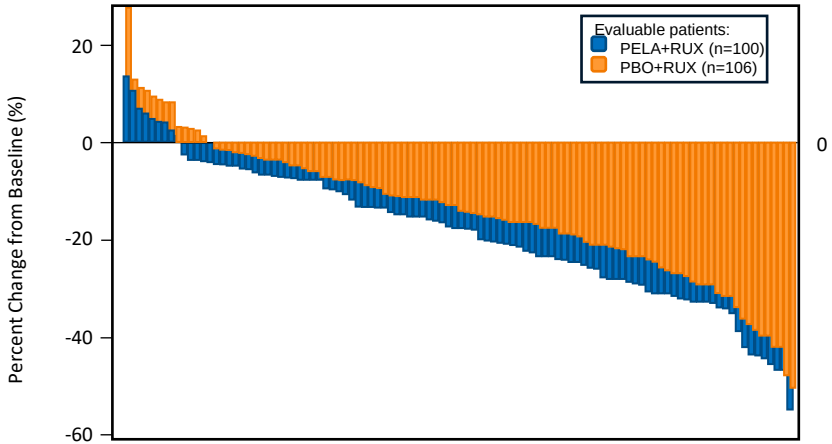
Improvements in absolute TSS at Week 24 were sustained through Week 96 with PELA+RUX vs PBO+RUX

Week 24



	PELA+RUX (N=214)	PBO+RUX (N=216)
TSS change from baseline at Week 24 in the **ITT population,** LMS	-15.08	-13.12
Difference (95% CI)	**-1.96 (-4.11, 0.18)**	

Week 96



	PELA+RUX (N=214)	PBO+RUX (N=216)
TSS change from baseline at Week 96 in the **ITT population,** LMS	-15.07	-12.48
Difference (95% CI)	**-2.59 (-5.23, 0.05)**	

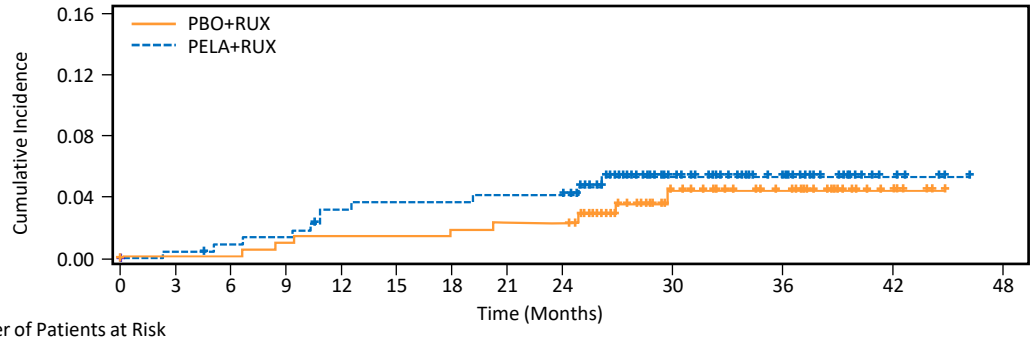
A greater decrease in absolute change in TSS from baseline to Week 96 was observed with PELA+RUX vs PBO+RUX

Data cutoff date: March 02, 2025.
Waterfall plots represent evaluable patients who have baseline and Week 24 or Week 96 data. TSS assessed by MFSAF v4.0 and using an MMRM analysis of absolute change from baseline TSS.
CI, confidence interval; ITT, intent-to-treat; LSM, least squares mean; MFSAF, Myelofibrosis Symptom Assessment Form; MMRM, mixed model for repeated measures; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib; TSS, total symptom score.

Oral 910 presented at: American Society of Hematology (ASH) Annual Meeting; December 6 - 9, 2025; Orlando, Florida

Comparable rates of accelerated phase and blast phase progression were observed between treatment arms at the Week 96 data cutoff

- Leukemic transformation cases as of March 2, 2025, Week 96 data cutoff*



	PELA+RUX†	PBO+RUX
Accelerated phase, % (n/N)	2.3 (5/216)	1.9 (4/214)
Blast phase, % (n/N)	5.1 (11/216)	3.7 (8/214)

- Cases of leukemic transformation have remained stable with PELA+RUX since the Week 48 data cutoff; PBO+RUX cases increased from 0.9% (2/214) at Week 48[1] to 3.7% (8/214) at Week 96
- The early imbalance in leukemic transformation cases decreased over time, and cases of leukemic transformation continue to be in line with the previously observed frequency seen in MF[2-3]
- In MANIFEST[4], no leukemic transformations were observed in Arm 3, a setting similar to MANIFEST-2, within the first 12 months after start of study treatment
- All leukemic transformation cases were adjudicated by an external medical expert committee

Data cutoff date: March 02, 2025.
Assessment based on local laboratory results, adverse events, and documented disease progression. Leukemic transformation confirmed by a bone marrow blast count of ≥20% or a peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1×10^9/L that lasts for ≥2 weeks. * Minimum of 96 weeks of leukemia-free survival follow-up. The last adjudication in March 2025, with the cutoff as of March 2, 2025, showed a ratio of 11:8. † The denominator of 216 for PELA+RUX includes 4 patients who crossed over from PBO+RUX.
MF, myelofibrosis; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib.
1. Vannucchi AM, et al. Presented at EHA 2025 [Oral S223]; 2. Verstovsek S, et al. *N Engl J Med.* 2012;366(9):799-807; 3. Mesa RA, et al. *J Clin Oncol.* 2017;35(34):3844-3850; 4. Mascarenhas J, et al. *J Clin Oncol.* 2023;41(32):4993-5004.

Oral 910 presented at: American Society of Hematology (ASH) Annual Meeting; December 6 - 9, 2025; Orlando, Florida

OBJECTIVE

- MANIFEST-3 (NCT07357727) is a Phase III study designed to evaluate the efficacy and safety of PELA+RUX versus PBO+RUX in JAKi-naive patients with MF, including a pre-specified, highly symptomatic patient subgroup (baseline total symptom score [TSS] ≥25)

MANIFEST-3 STUDY DESIGN AND SITES

- MANIFEST-3 is a randomized, double-blind, multicenter Phase III study that plans to enroll 460 JAKi-naive patients with primary or secondary (post-polycythemia vera [PV]/essential thrombocytopenia [ET]) MF, across 242 sites globally (**Figure 2**)
- The study is designed to explore whether adding PELA to standard therapy can further support symptom and spleen improvement across a broad range of patients, including those experiencing a substantial symptom burden (baseline TSS ≥25)
- Patients will be randomized 1:1 to PELA or placebo (PBO) once daily on Days 1-14 of a 21-day cycle, in combination with RUX twice daily throughout the cycle (**Figure 3**)
  - Randomization will be stratified by Dynamic International Prognostic Scoring System (DIPSS) (int-1 vs int-2 vs high-risk), baseline platelet count (>200 vs 100-200 x 10^9/L), and TSS (<25 vs ≥25)
  - After end of treatment and the 30-day safety follow-up visit, patients will enter either an efficacy follow-up (if no documented progression for either splenomegaly or leukemic transformation and no new treatment started for MF), or a survival follow-up (if disease progression is documented or new treatment for MF started)

Figure 2. Study Sites

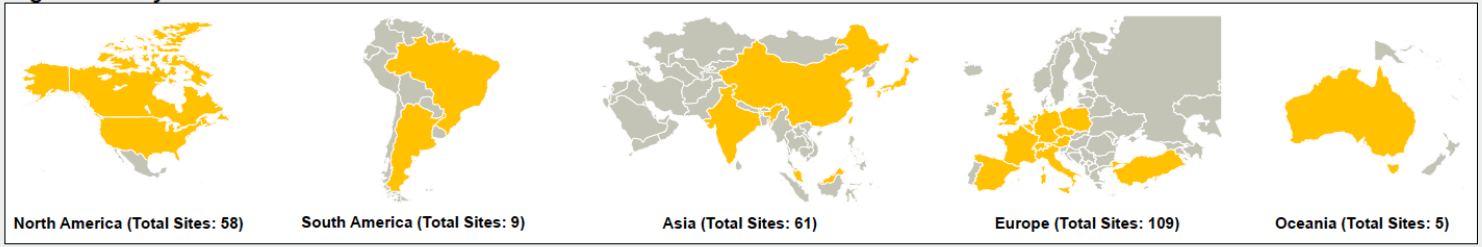
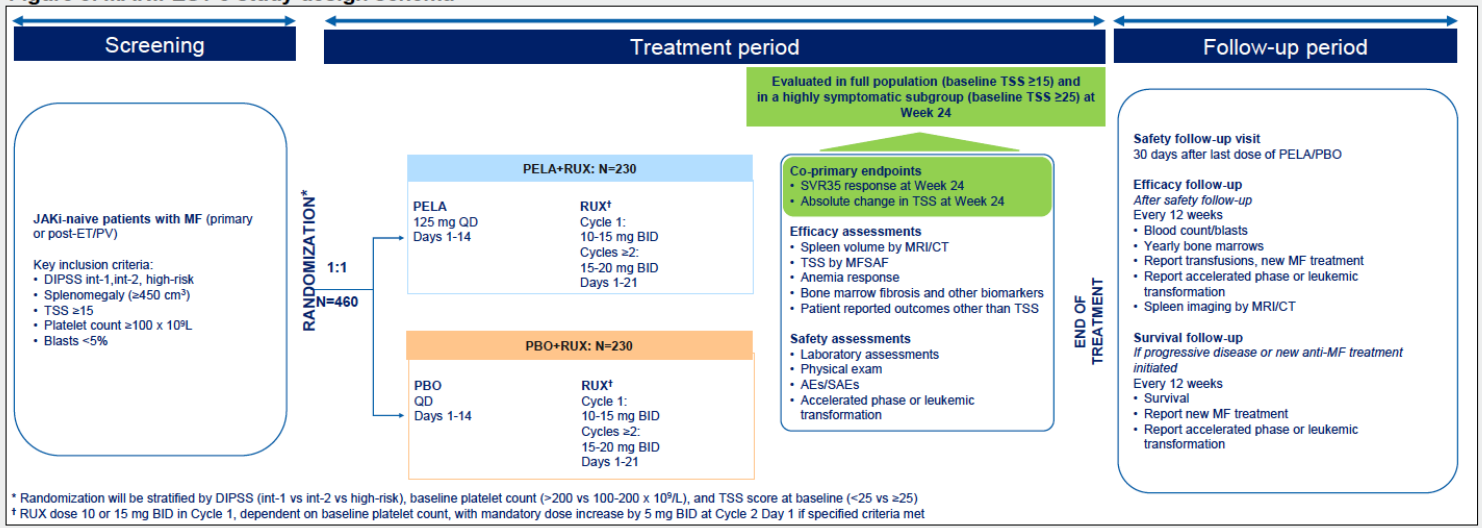


Figure 3. MANIFEST-3 study design schema



* Randomization will be stratified by DIPSS (int-1 vs int-2 vs high-risk), baseline platelet count (>200 vs 100-200 x 10^9/L), and TSS score at baseline (<25 vs ≥25)
† RUX dose 10 or 15 mg BID in Cycle 1, dependent on baseline platelet count, with mandatory dose increase by 5 mg BID at Cycle 2 Day 1 if specified criteria met

Pro-apoptotic therapies in MPN

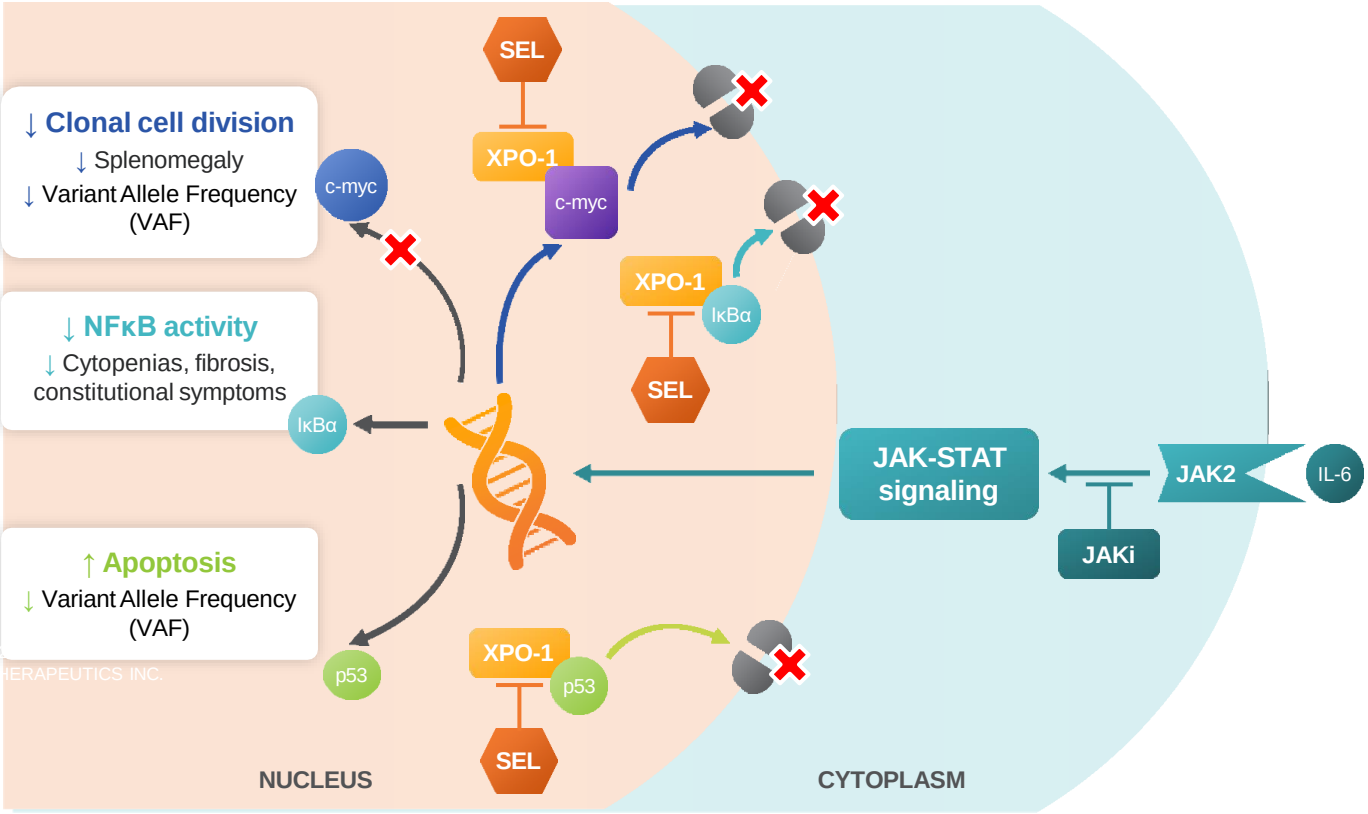
XPO1 inhibitor

- Selinexor

MDM2 inhibitors

- Idasanutlin in PV
- Siremadlin in MF (ADORE)
- **Navtemadlin in MF**
  - KRT-232-101A
  - BOREAS
  - POIESIS

XPO1 Inhibition is a Multifaceted Approach to Inhibiting the Drivers of Myelofibrosis[1-9]



1. Yan D et al. *Clin Cancer Res*. 2019;25(7):2323-2335. 2. Kashyap T et al. *Oncotarget*. 2016;7(48):78883-78895. 3. Walker CJ et al. *Blood*. 2013;122(17):3034-3044. 4. Cheng Y et al. *Mol Cancer Ther*. 2014;13(3): 675-686. 5. Argueta C et al. *Oncotarget*. 2018;9(39);25529-25544. 6. Gandhi UH et al. *Clin Lymphoma Myeloma Leukemia*. 2018;18(5):335-345. 7. Garg M et al. *Oncotarget*. 2017;8(5):7521-7532. 8. Tan M et al. *Am J Physiol Renal Physiol*. 2014;307(11): F1179-1186. 9. Turner JG et al. *Oncotarget*. 2016;7(48):78896-78909.

Rapid and Sustained Improvement in SVR35 Rates Observed with the Combination Relative to Ruxolitinib Alone

Spleen Volume Reduction

Rapid SVR35 at week 12 of 49% compared to 20% with ruxolitinib monotherapy

Sustained SVR35 at week 36 of 47% compared to 23% with ruxolitinib monotherapy

Selinexor has not been approved by the U.S. FDA or any other regulatory authority for use in myelofibrosis.

	Selinexor + Ruxolitinib (N = 235)	Placebo + Ruxolitinib (N = 118)
SVR35 at Week 12, n (%)	116 (49.4)	24 (20.3)
SVR35 at Week 24, n (%)	117 (49.8)	33 (28.0)
Patients Who Completed Week 36 or Discontinued Prior to Week 36	207	100
SVR35 at Week 36, n (%) [1]	97 (46.9)	23 (23.0)
SVR35 at Any Timepoint, n (%)	159 (67.7)	53 (44.9)
Exact 95% CI	(61.3, 73.6)	(35.7, 54.3)
Cochran-Mantel-Haenszel Test (Selinexor vs. Placebo)		
Odds Ratio (95% CI)	2.59 (1.64, 4.10)	
Nominal One-Sided P-value	**<.0001**	

Data Cutoff Date: 2026-02-20

CI=Confidence Interval; SVR35=Spleen Volume Reduction of >=35%

Note: SVR35 at Week 12 and 24 allows +/- 21-day window. SVR35 at Week 36 and 48 allows +/- 28-day window. Note: SVR35 at any timepoint is defined as proportion of patients with a >=35% reduction in spleen volume from baseline to any post-baseline assessments regardless of visit window before new anti-MF therapy or disease progression. Note: Cochran-Mantel-Haenszel test is stratified by randomization factors.

[1] Denominator is the number of patients who completed the spleen assessment or discontinued the study prior to the specific timepoint.

Symptom Benefit at Week 24 was Comparable Across the Two Arms with Similar Symptom Improvement Relative to Baseline

Symptom Improvement

Similar levels of absolute TSS improvement from baseline in the selinexor plus ruxolitinib arm compared to ruxolitinib

These differences were not statistically significant

Selinexor has not been approved by the U.S. FDA or any other regulatory authority for use in myelofibrosis.

	Selinexor + Ruxolitinib (N = 235)	Placebo + Ruxolitinib (N = 118)
Baseline		
n	235	117
Median	21.71	19.57
Mean	22.74 (11.877)	22.23 (13.031)
Mean (STD)	2.1 , 53.9	3.0 , 58.3
Week 24		
Adjusted Absolute Mean Change from Baseline (95% CI)	-9.89 (-11.19, -8.59)	-10.86 (-12.58, -9.14)
Adjusted Mean Difference (Selinexor vs. Placebo) (95% CI)	0.97 (-1.07, 3.02)	
One-sided P-value	0.8246	

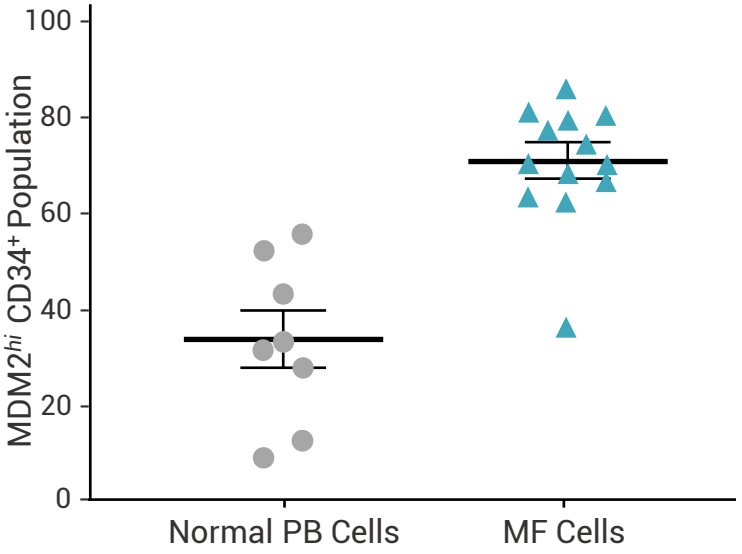
Data Cutoff Date: 2026-02-20

CI=Confidence Interval; TSS=Total Symptom Score
Note: TSS is the sum of the 6 individual symptom scores included in the MFSAF v4.0, excluding fatigue. Each individual symptom score is on the 0-10 scale, and the TSS ranges from 0 to 60. A higher TSS indicates a higher disease burden and thus a worse outcome.
Note: Adjusted absolute mean change from baseline, adjusted mean difference, 95% CI and p-value are based upon mixed-effects model for repeated measures (MMRM) adjusted for randomization stratification factors, sex and baseline TSS.
Note: n is the number of patients with TSS available.

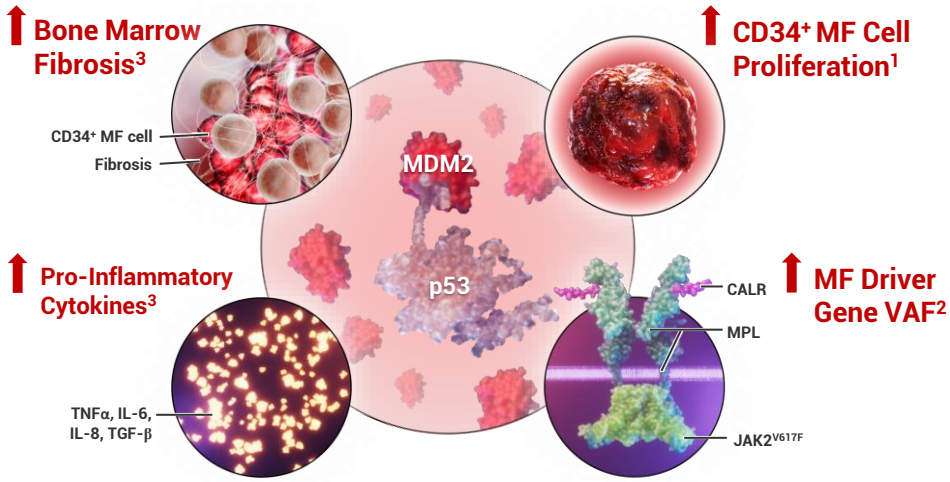
Hallmarks of Myelofibrosis

MDM2 Overexpression Prevents p53-Driven Apoptosis of CD34⁺ MF Cells

MDM2 Overexpression in MF CD34⁺ Cells[1]



MDM2 Overexpression



Note: 95% of MF patients are *TP53*^{WT}.
[1]Figure adapted from Lu M, et al. *Blood* 2017; [2]Barosi G, et al. *Blood* 2001. [3]Rampal R, et al. *Blood* 2014. [4]Verstovsek S, et al. *NEJM* 2010.
Abbreviations: CALR, calreticulin; IL, interleukin; JAK2, Janus kinase 2; MDM2, mouse double minute 2; MF, myelofibrosis; MPL, myeloproliferative leukemia virus oncogene; PB, peripheral blood; TGF-β, transforming growth factor beta; TNFα, tumor necrosis factor alpha; VAF, variant allele frequency.

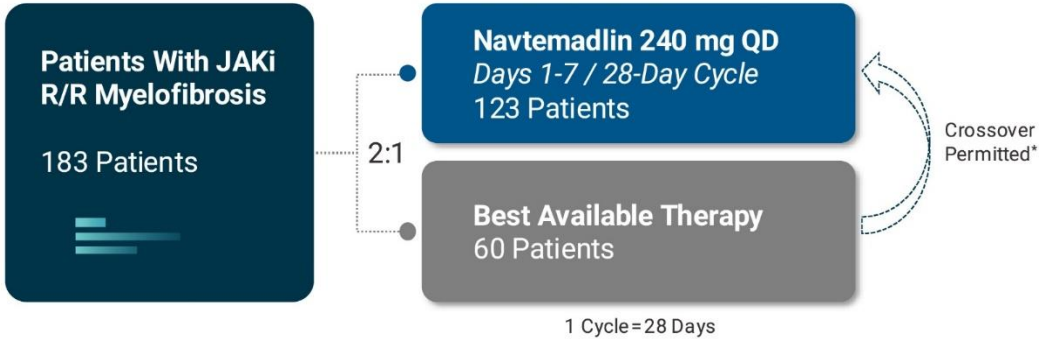
Phase 3 Study Design

A Randomized, Open-Label, Global Phase 3 Study of Navtemadlin in *TP53*^{WT} Patients With Myelofibrosis Who Are Relapsed or Refractory to JAK Inhibitor Treatment

BOREAS
Blocking MDM2 to reactivate p53 in myelofibrosis

Stratification Factors:
- Primary MF vs Secondary MF
- Baseline TSS (≤ 10 vs >10)

Physician's Choice (BAT):
- Hydroxyurea
- Peginterferon
- IMiDs
- Supportive care

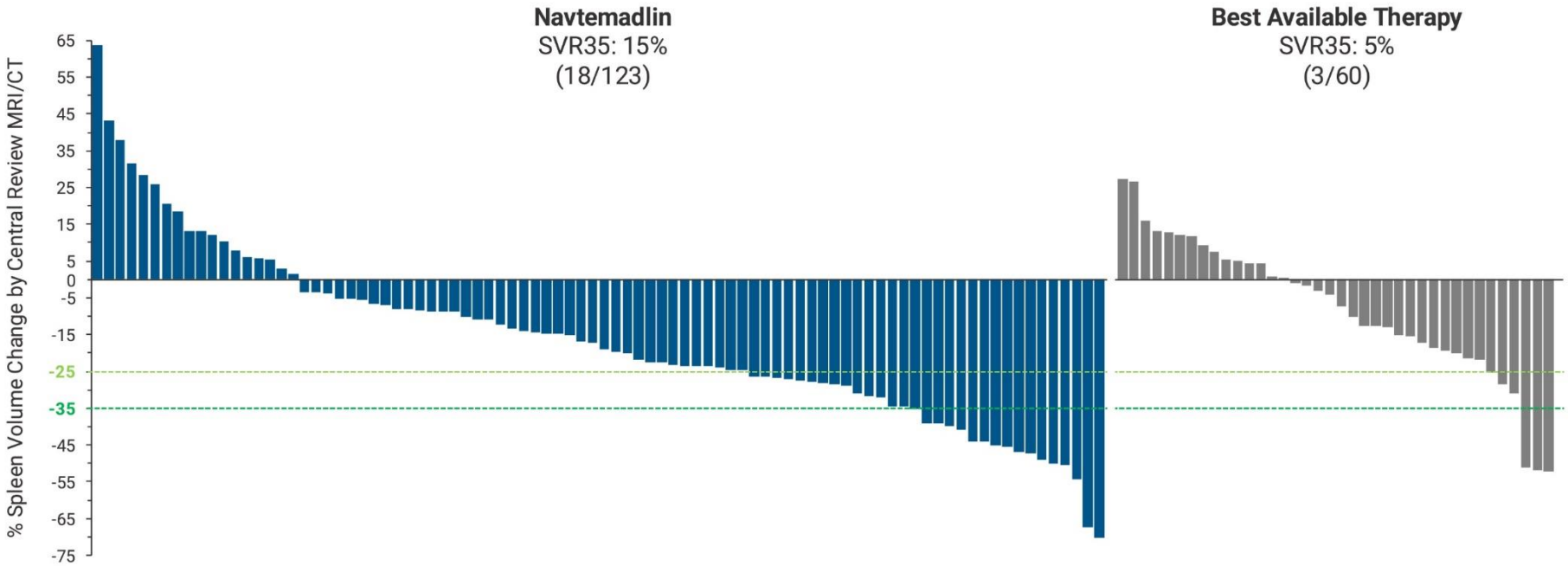


PRIMARY ENDPOINT	KEY SECONDARY ENDPOINT	KEY PHASE 3 STUDY NOTES
• SVR35 Week 24 by MRI/CT Central Review	• TSS50 Week 24 by MFSAF v4.0	• 28-day JAKi wash-out prior to C1D1 • JAKi excluded in BAT arm • C1D1 occurred within 7-days of baseline MRI/CT • Diarrhea prophylaxis for first two cycles

Note: BOREAS enrollment was closed at 183 subjects.
*Crossover in the BAT arm was permitted after disease progression or at Week 24.
Abbreviations: BAT, best available therapy; C1D1, cycle 1 day 1; CT, computed tomography; IMiDs, immunomodulatory imide drugs (lenalidomide, pomalidomide); JAK, Janus kinase; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MFSAF, myelofibrosis symptoms assessment form; MRI, magnetic resonance imaging; QD, once daily; R/R, relapsed/refractory; SVR, spleen volume reduction; SVR35, spleen volume reduction ≥35%; TSS, total symptom score; TSS50, total symptom score reduction ≥50%; WT, wild-type.

SVR35 at Week 24 (ITT Population)

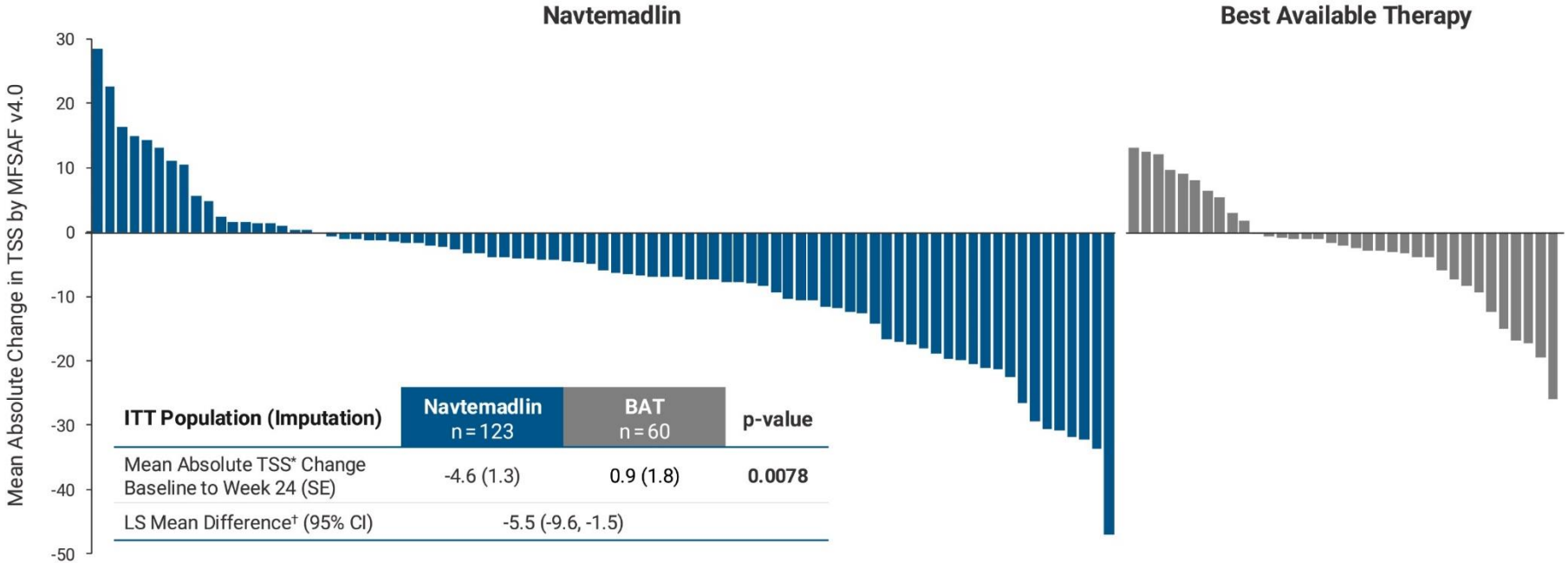
Spleen Volume Reduction by Central Review MRI/CT – Baseline to Week 24



Data cut-off: 30 Sep 2024.
Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle). ITT is all randomized subjects. Figure represents subjects with baseline and Week 24 data.
Navtemadlin vs BAT, p=0.0815. SVR25: Navtemadlin, 27% (33/123); BAT, 10% (6/60). BAT SVR35 responders received hydroxyurea (2) and lenalidomide (1).
Abbreviations: BAT, best available therapy; CT, computed tomography; ITT, intention-to-treat; MRI, magnetic resonance imaging; SVR35, spleen volume reduction ≥ 35%.

Absolute Change in TSS at Week 24 (ITT Population)

Total Symptom Score Reduction by MFSAF v4.0 – Baseline to Week 24

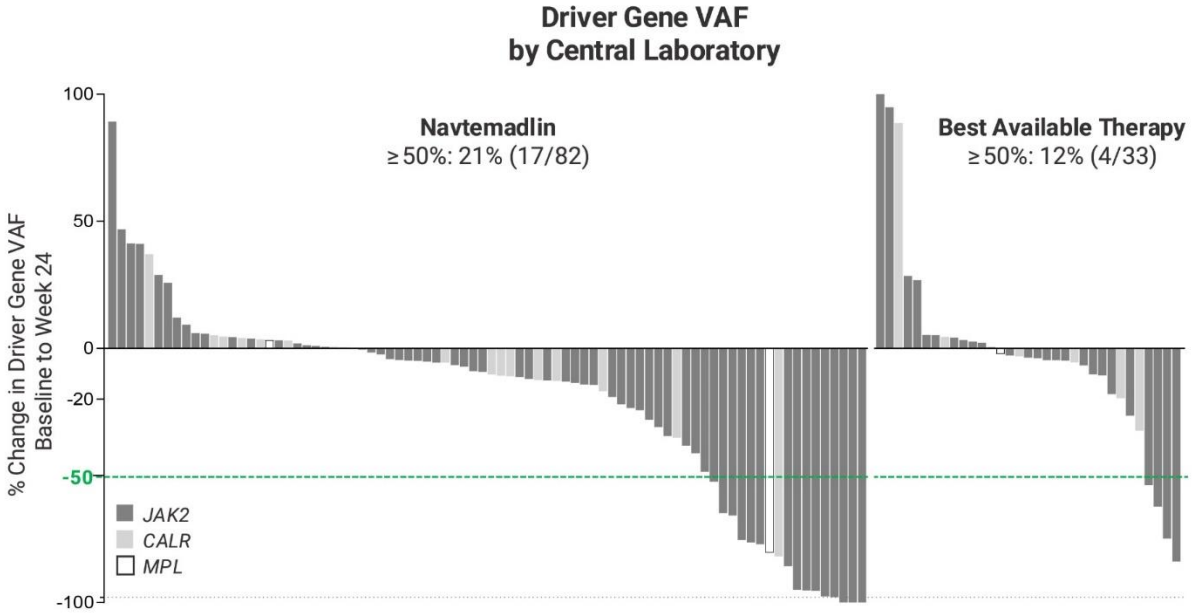


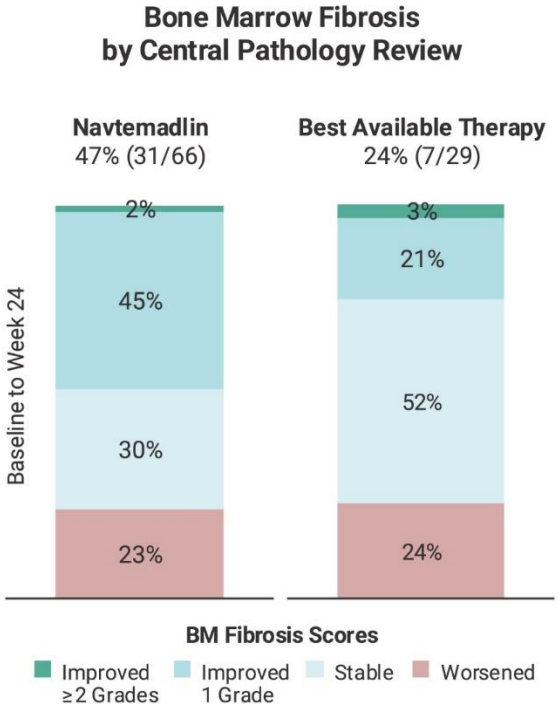
ITT Population (Imputation)	Navtemadlin n = 123	BAT n = 60	p-value
Mean Absolute TSS* Change Baseline to Week 24 (SE)	-4.6 (1.3)	0.9 (1.8)	**0.0078**
LS Mean Difference† (95% CI)	-5.5 (-9.6, -1.5)		

Data cut-off: 30 Sep 2024. Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle). ITT is all randomized subjects. Figure represents subjects with baseline and Week 24 data.
Week 24 TSS assessment includes Week 23 scores for subjects who stopped TSS at the start of Week 24 (n = 2).
*Sensitivity analysis determined by ANCOVA model using multiple imputation. †Least square mean difference from ANCOVA model adjusting for MF subtype and baseline TSS.
Abbreviations: ANCOVA, analysis of covariance; BAT, best available therapy; CI, confidence interval; MF, myelofibrosis; MFSAF, myelofibrosis symptom assessment form; SE, standard error; TSS, total symptom score.

Potential for Disease Modification

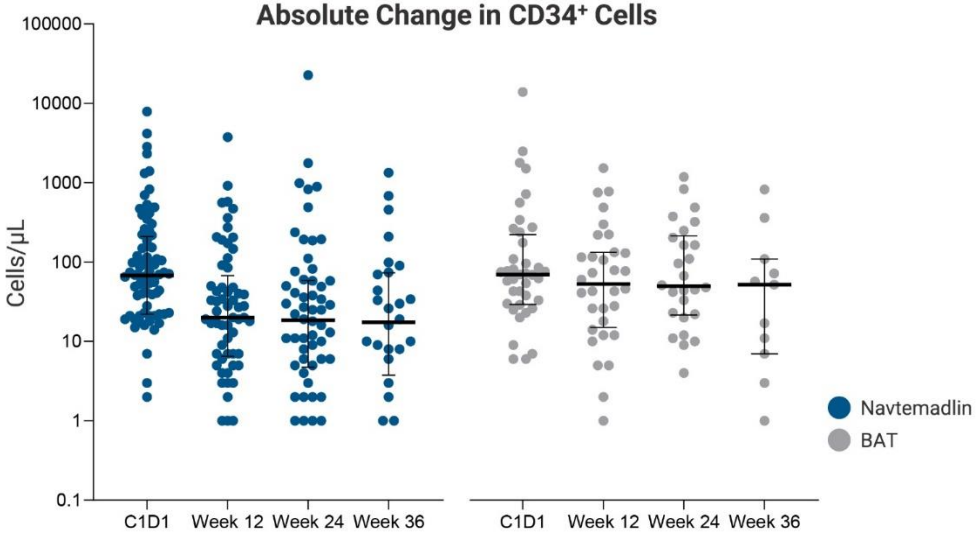
Driver Gene VAF Reduction and Bone Marrow Fibrosis Improvement – Baseline to Week 24





Data cut-off: 30 Sep 2024.
Note: Week 24 evaluable subjects shown.
Abbreviations: BM, bone marrow; *CALR*, calreticulin; *JAK2*, Janus kinase 2; *MPL*, myeloproliferative leukemia virus oncogene; VAF, variant allele frequency.

Navtemadlin Reduces Circulating CD34⁺ Cells



	Navtemadlin				BAT			
Median (cells/µL)	68	20	19	19	70	60	50	52
N	80	61	58	27	38	33	26	11

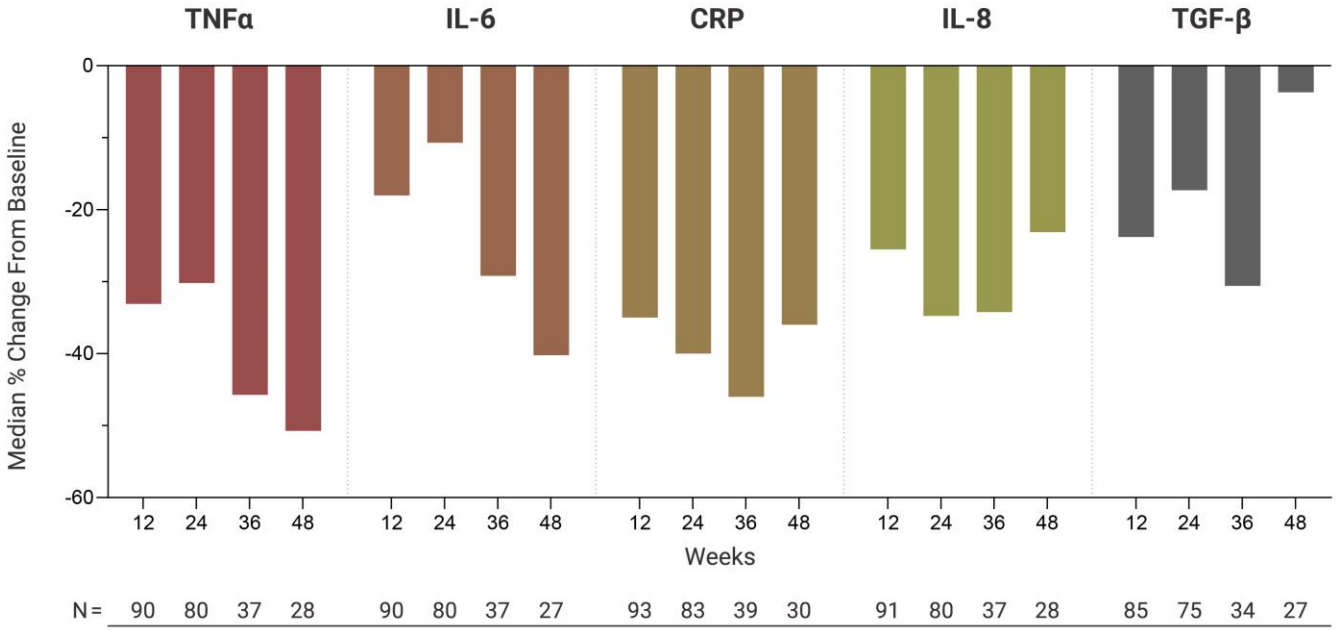
Median % Change CD34⁺ Cells (Baseline Paired)[1]

Median % Change	Navtemadlin	BAT
Week 12	-68% n = 50	-52% n = 25
Week 24	-70% n = 48	-38% n = 19
Week 36	-76% n = 21	-33% n = 9

Data cut-off: 30 Sep 2024.
Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle). Peripheral blood CD34⁺ cells normal range ≤7 cells/µL.
[1]Required to have a baseline and a second timepoint.
Abbreviations: BAT, best available therapy; C1D1, cycle 1 day 1.

Reductions in Pro-Inflammatory Markers

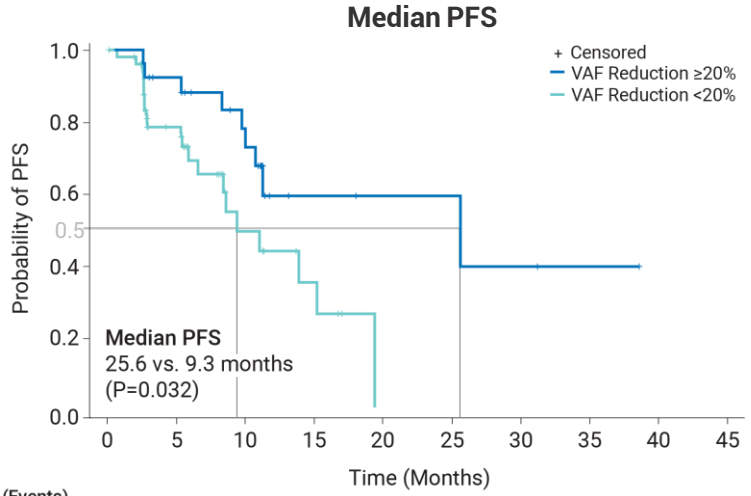
Navtemadlin Reduces Serum Cytokine Levels Over Time



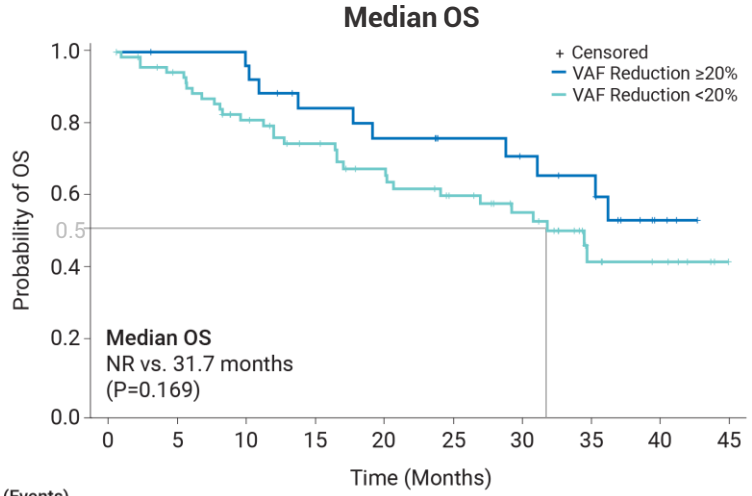
Data cut-off: 30 Sep 2024.
Abbreviations: CRP, C-reactive protein; IL, interleukin; TGF-β, transforming growth factor beta; TNFα, tumor necrosis factor alpha.

Navtemadlin in JAKi R/R MF, Driver Gene VAF Reduction Correlates With PFS and OS in All Cohorts

Driver Gene VAF Reduction*, ≥20% or <20%



# at risk (Events)									
VAF Reduction ≥20%	27 (0)	22 (2)	14 (6)	4 (8)	3 (8)	3 (8)	2 (9)	1 (9)	0 (0)
VAF Reduction <20%	72 (0)	29 (10)	9 (17)	4 (19)	0 (21)				

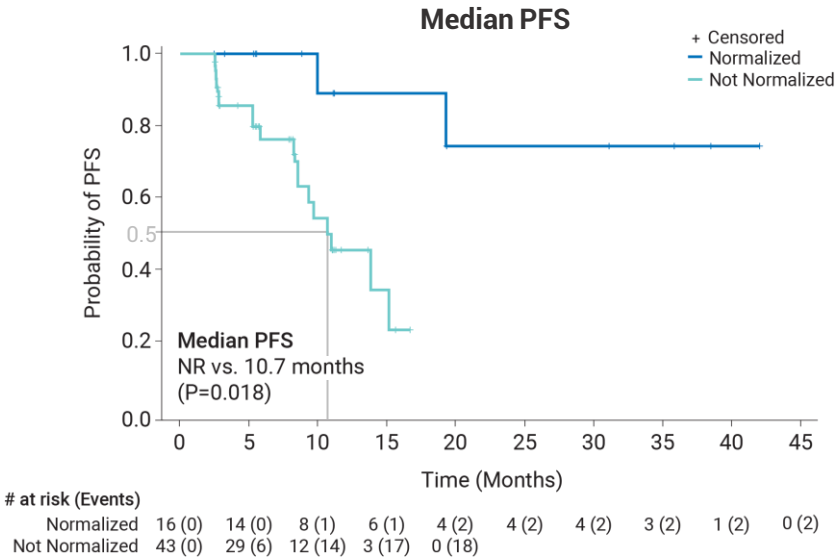


# at risk (Events)										
VAF Reduction ≥20%	27 (0)	26 (0)	24 (2)	20 (4)	18 (6)	15 (6)	13 (7)	11 (8)	3 (10)	0 (10)
VAF Reduction <20%	72 (0)	63 (5)	50 (13)	43 (17)	35 (22)	28 (25)	22 (27)	9 (31)	6 (31)	0 (31)

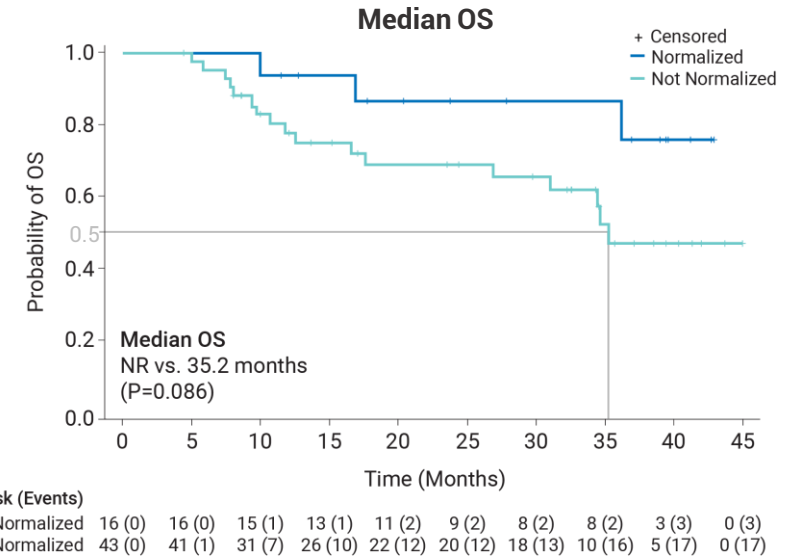
n=99

Data cut-off: 06 Jan 2023.
All Cohorts, four dose schedules at either 120 mg QD or 240 mg QD.
*Patients with paired samples (baseline, week 12, week 24) n=99. Progression free survival defined as time from start of navtemadlin treatment until progression of disease by spleen progression, transformation to accelerated phase or leukemia, or death due to any cause.
Abbreviations: OS, Overall Survival; PFS, progression free survival; VAF, variant allele frequency.

Navtemadlin in JAKi R/R MF, Normalization of Blood CD34+ Counts Correlate With PFS and OS in All Cohorts



# at risk (Events)										
Normalized	16 (0)	14 (0)	8 (1)	6 (1)	4 (2)	4 (2)	4 (2)	3 (2)	1 (2)	0 (2)
Not Normalized	43 (0)	29 (6)	12 (14)	3 (17)	0 (18)					



# at risk (Events)										
Normalized	16 (0)	16 (0)	15 (1)	13 (1)	11 (2)	9 (2)	8 (2)	8 (2)	3 (3)	0 (3)
Not Normalized	43 (0)	41 (1)	31 (7)	26 (10)	22 (12)	20 (12)	18 (13)	10 (16)	5 (17)	0 (17)

n=59

Data cut-off: 06 Jan 2023.
All Cohorts, four dose schedules at either 120 mg QD or 240 mg QD. Normalization, normal CD34+ cell count defined as <7 cells/μL.
Progression free survival defined as time from start of navtemadlin treatment until progression of disease by spleen progression, transformation to accelerated phase or leukemia, or death due to any cause.
Abbreviation: NR, not reached; OS, overall survival; PFS, progression-free survival.

Phase 1b/2 Study Design for KRT-232-109

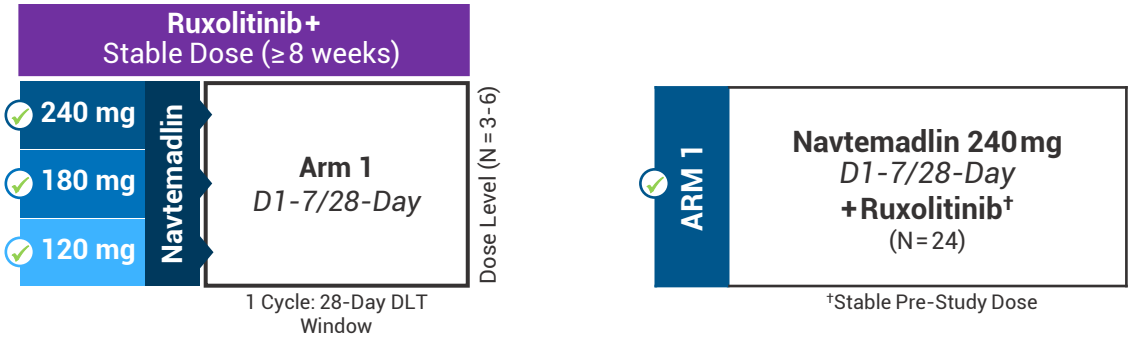
A Global, Open-Label, Multicenter Phase 1/2 Study of the Safety and Efficacy of Navtemadlin Combined With Ruxolitinib in Patients With Primary Myelofibrosis, Post–Polycythemia Vera Myelofibrosis, or Post–Essential Thrombocythemia Myelofibrosis Who Have Suboptimal Response to Ruxolitinib Treatment

ENROLLMENT → **PHASE 1 (DOSE ESCALATION)** → **PHASE 2 (DOSE EXPANSION)**

Patients with suboptimal response to ruxolitinib after ≥18 weeks of treatment

No evidence of response or progression on ruxolitinib*

≥100×10^9/L platelets



PRIMARY ENDPOINT

- Phase 1: **Navtemadlin RP2D in Combination With Ruxolitinib**
- Phase 2: **Spleen Response Rate at Week 24**
  SVR ≥35% by MRI/CT Central Review

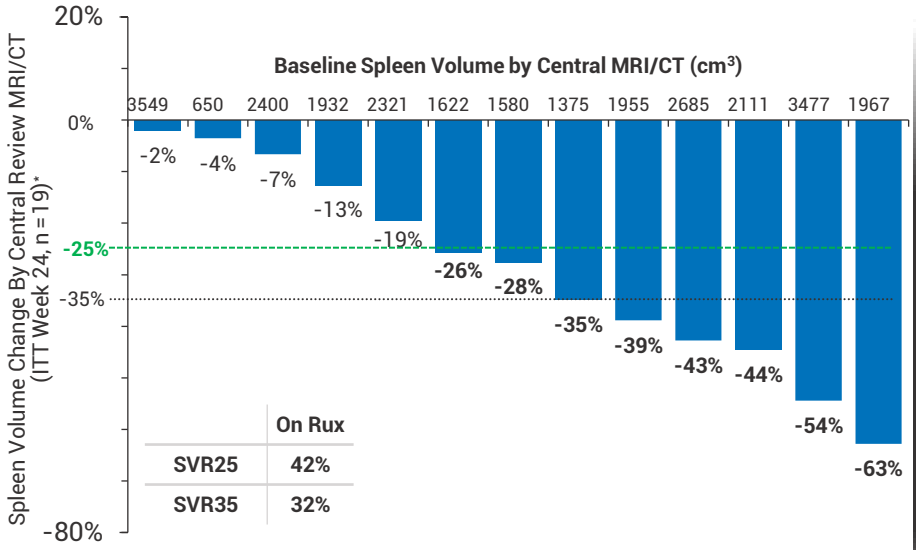
KEY SECONDARY ENDPOINTS

- **Improvement of MFSAF v4.0 TSS ≥50% at Week 24**
- Spleen response duration
- RBC transfusion independence
- Spleen response rate at any time point from baseline

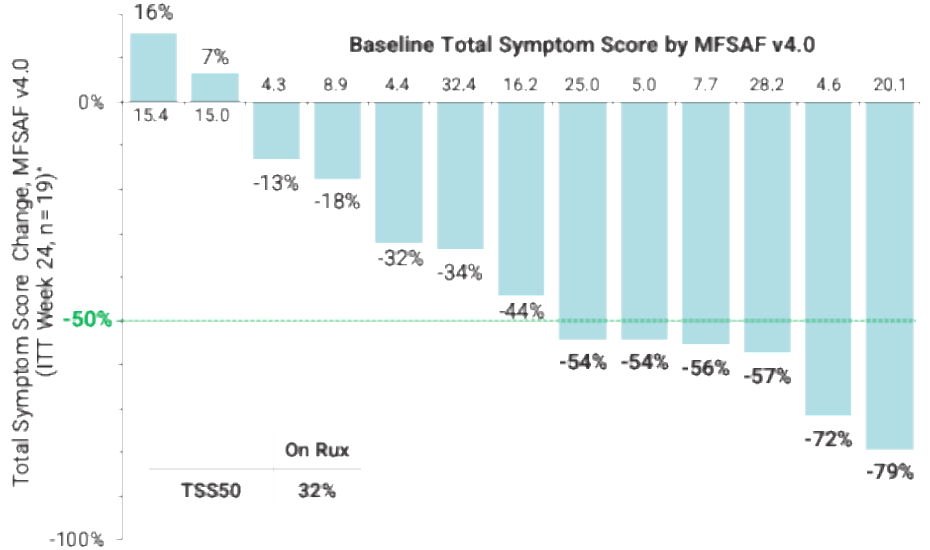
Note: *Patients have neither achieved a spleen response by International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria, nor have had evidence of progression in spleen or symptoms while on a stable dose of ruxolitinib. Abbreviations: CT, computed tomography; D, day; DLT, dose-limiting toxicity; MFSAF v4.0, myelofibrosis symptom assessment form version 4.0; MRI, magnetic resonance imaging; RBC, red blood cell; RP2D, recommended phase 2 dose; SVR, spleen volume reduction; TSS, total symptom score.
Mascarenhas J, et al. *Hemasphere* 2023.

Navtemadlin Added to Ruxolitinib in Suboptimal Responders

SVR and TSS After Navtemadlin is Added to Stable Dose of Ruxolitinib in KRT-232-109 (ITT Analysis Set)



Baseline Rux Dose (mg BID)	25	20	25	5	20	15	15	5	5	5	20	25	10
Week 24 Rux Dose (mg BID)	25	20	25	5	20	15	10	5	5	5	10	15	10
Prior Rux Duration (Yrs)	9.1	2.5	2.6	1.1	2.1	8.1	1.2	1.9	1.4	1.7	5.8	0.7	1.3



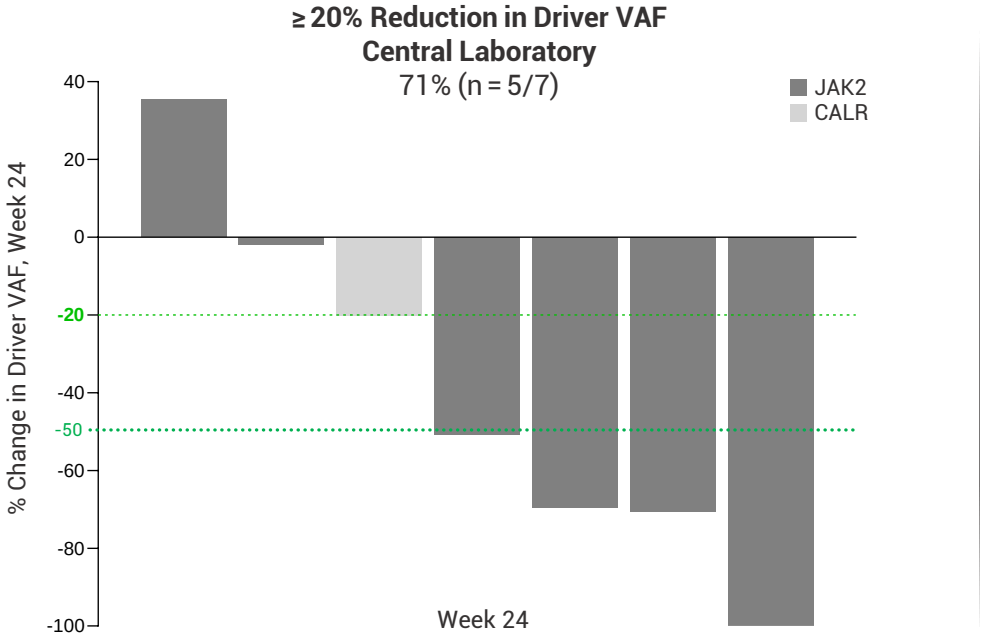
Baseline Rux Dose (mg BID)	25	20	15	5	25	15	20	5	10	20	5	25	5
Week 24 Rux Dose (mg BID)	15	20	10	5	25	15	20	5	10	10	5	25	5
Prior Rux Duration (Yrs)	0.7	2.1	1.2	1.9	2.6	8.1	2.5	1.1	1.3	5.8	1.7	9.1	1.4

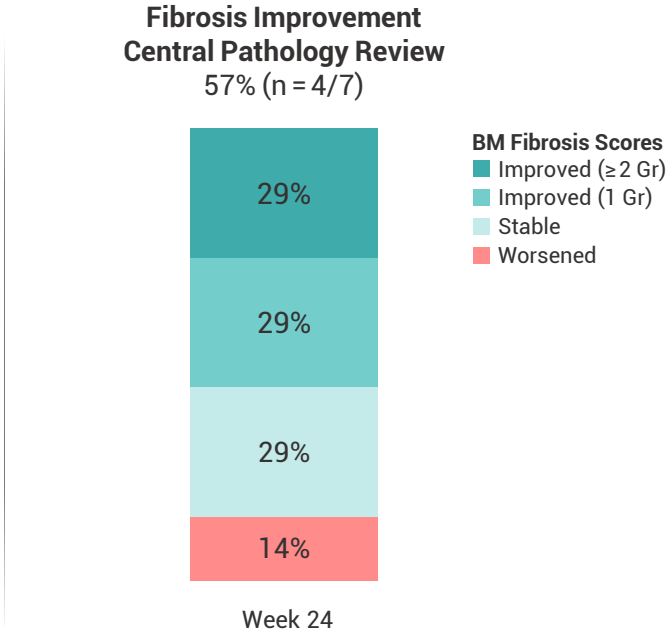
No Dose Increases of Rux Above the Stable Baseline Dose Occurred during the 24-Week Assessment Period

Note: 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).
*Six patients discontinued prior to Week 24 assessment. Abbreviations: BID, twice-a-day; CT, computed tomography; ITT, intention-to-treat (all randomized subjects); MFSAF v4.0, myelofibrosis symptom assessment form version 4.0; MRI, magnetic resonance imaging; Rux, ruxolitinib; SVR, spleen volume reduction; TSS, total symptom score; Yrs, years.
Mascarenhas J, et al. *Hemasphere.* 2023.Data cut-off: 02 May2023.

Potential for Disease Modification

Improvement ≥ 1 Grade in Bone Marrow Fibrosis at Week 24 was 57% of the Evaluable Patients

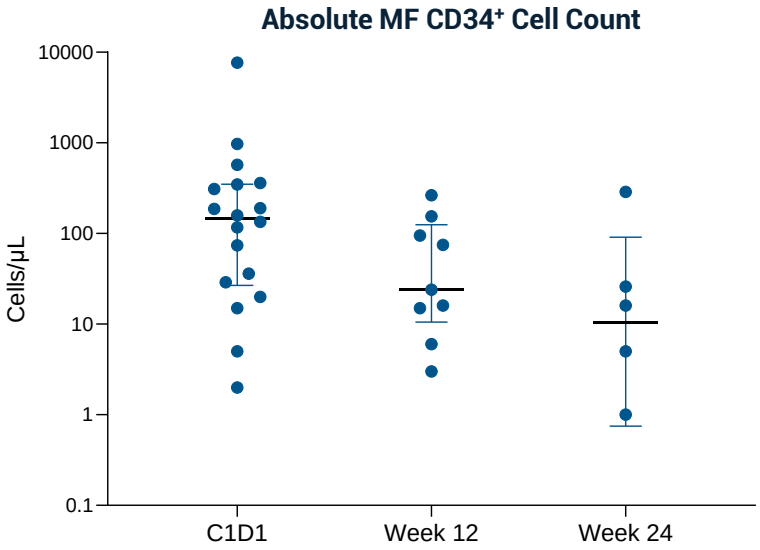




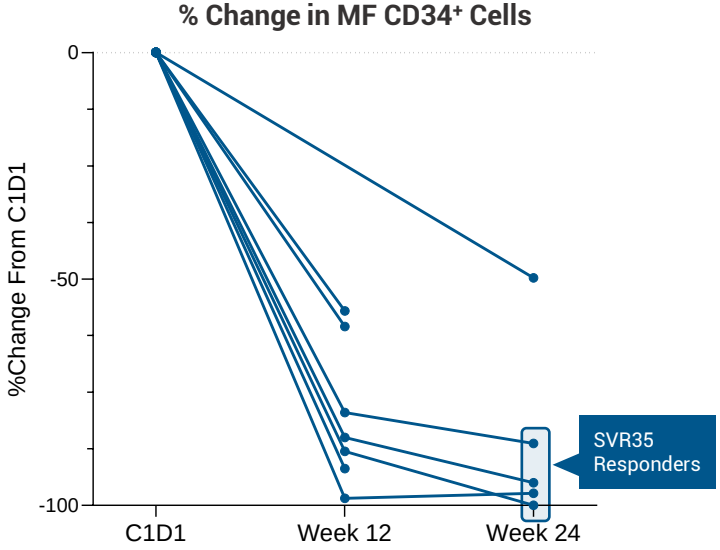
Mascarenhas J, et al. *Hemasphere* 2023. Data cut-off: 02 May2023.
Evaluable patients shown at Week 24 (baseline and at least one post baseline assessment).
Abbreviations: BM, bone marrow; CALR, calreticulin; D, day; JAK2, Janus kinase 2; MF, myelofibrosis; QD, once-a-day; VAF, variant allele frequency.

Change in Peripheral Blood MF CD34⁺ Cells

Reduction in MF CD34⁺ Cells – Baseline to Week 24



	C1D1	Week 12	Week 24
Median (cells)	146	24	10
Mean (cells)	621	73	56
N	18	9	6*

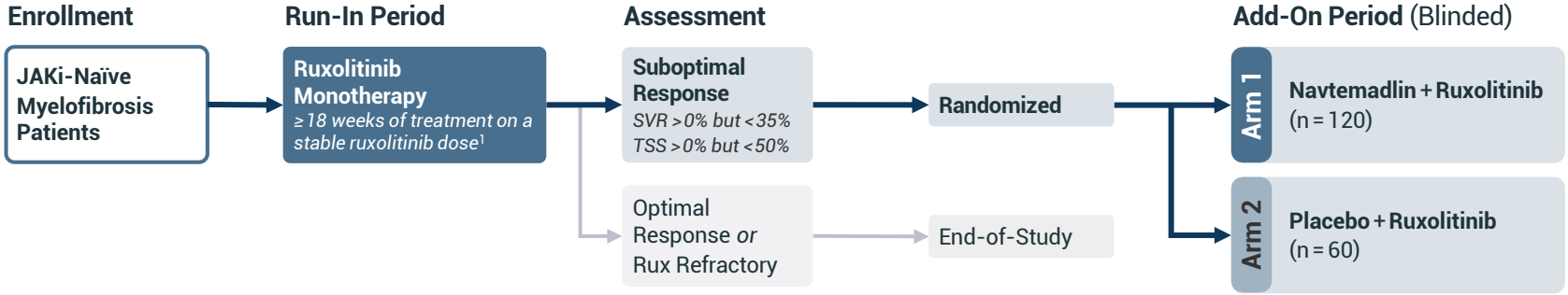


	C1D1	Week 12	Week 24
Median (%)		-85	-95
Mean (%)		-80	-86
N		7	5

Mascarenhas J, et al. *Hemasphere* 2023. Data cut-off: 07 Apr2023.
*One patient represented at "0" not seen on this graph.
Abbreviations: C1D1, cycle 1 day 1; D, day; µL, micro-liter; SVR35, spleen volume reduction ≥35%; Wk, week.

Phase 3 Study in Suboptimal Responders to Ruxolitinib

A Phase 3 Randomized, Double-Blind, Add-On Study Evaluating the Safety and Efficacy of Navtemadlin and Ruxolitinib vs Placebo and Ruxolitinib in JAK Inhibitor-Naïve Patients With Myelofibrosis Who Have a Suboptimal Response to Ruxolitinib Treatment



Run-In Period (N = 600)

Key Inclusion Criteria

- Primary or secondary MF by WHO criteria
- Int-1, Int-2, or High-risk disease by IPSS
- Spleen volume ≥450 cm^3
- Platelet count ≥100 x 10^9/L

Add-On Period (N = 180)

Key Inclusion Criteria

- *TP53*^{WT} by central testing
- Treatment with a stable dose of ruxolitinib
- Suboptimal response to ruxolitinib run-in

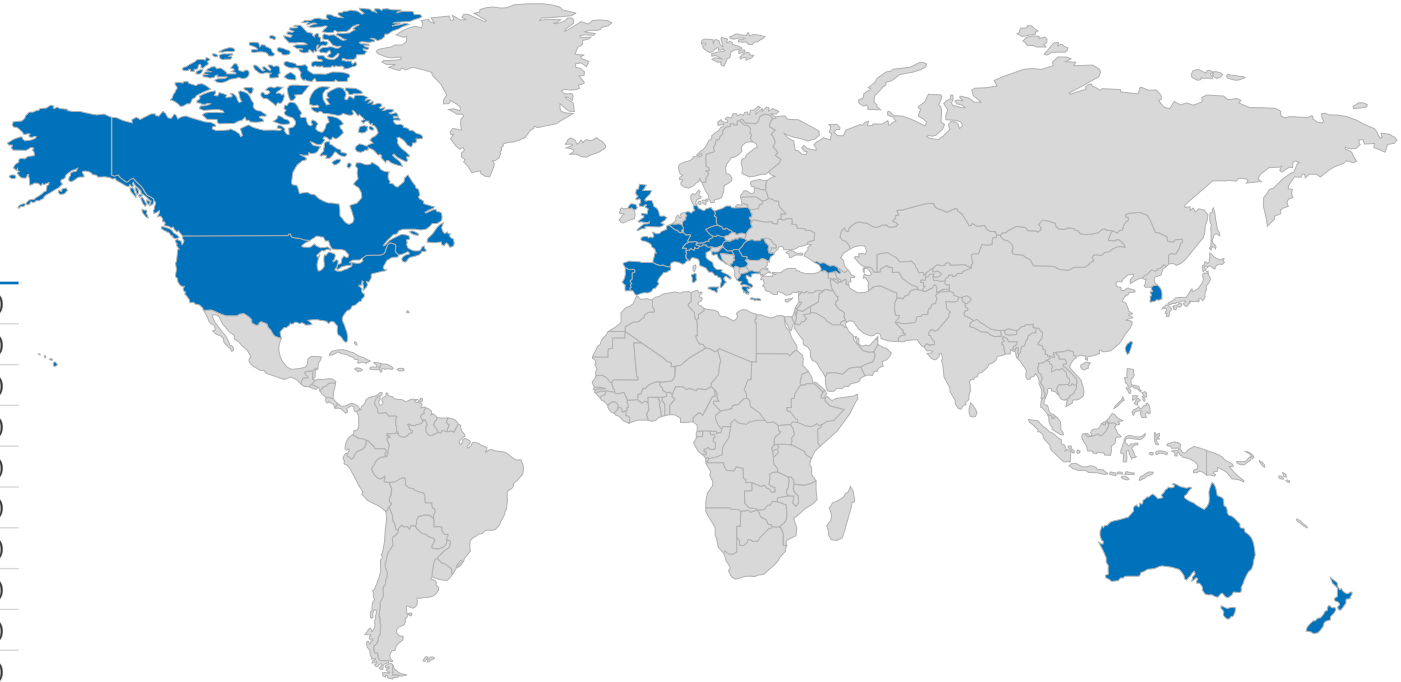
Endpoints

Multi-Component Co-Primary Endpoints

- Targeted SVR and TSS reduction 24 weeks after randomization

Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle). Target enrollment from 254 sites across 23 countries.
[1]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.
Abbreviations: BID, twice daily; Int, intermediate; IPSS, International Prognostic Scoring System; JAKi, Janus kinase inhibitor; Rux, ruxolitinib; TSS, total symptom score; WHO, World Health Organization; WT, wild-type.

Global Site Footprint



254 Global Sites

North America, Europe & Asia-Pacific

Country (Sites)			
United States	(64)	Canada	(6)
Italy	(20)	Georgia	(6)
France	(15)	Portugal	(6)
Germany	(15)	Belgium	(5)
Poland	(15)	Czech Republic	(5)
UK	(14)	Greece	(5)
Spain	(13)	New Zealand	(5)
Australia	(12)	Romania	(5)
South Korea	(9)	Taiwan	(5)
Austria	(7)	Hungary	(4)
Croatia	(7)	Serbia	(4)
Switzerland	(7)		