Abstract #1000

9 December 2024

Results from the Randomized, Multicenter, Global Phase 3 Study BOREAS: Navtemadlin Versus Best Available Therapy in JAK Inhibitor Relapsed/Refractory Myelofibrosis

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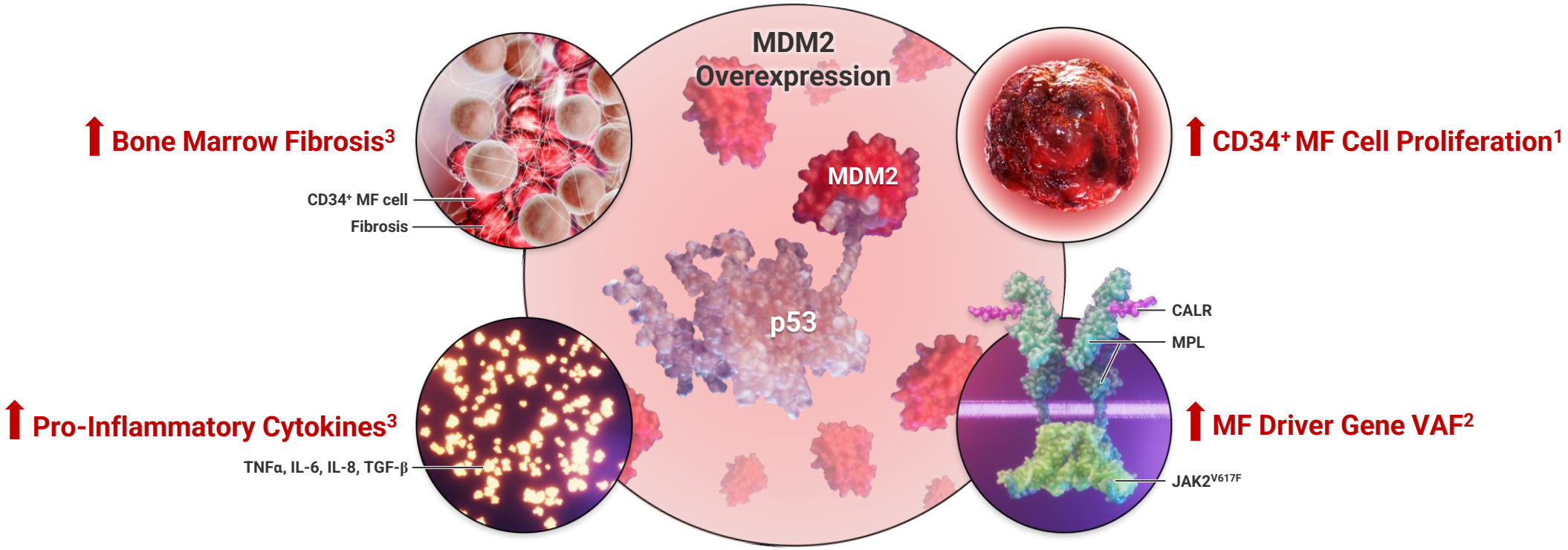
Hallmarks of Myelofibrosis

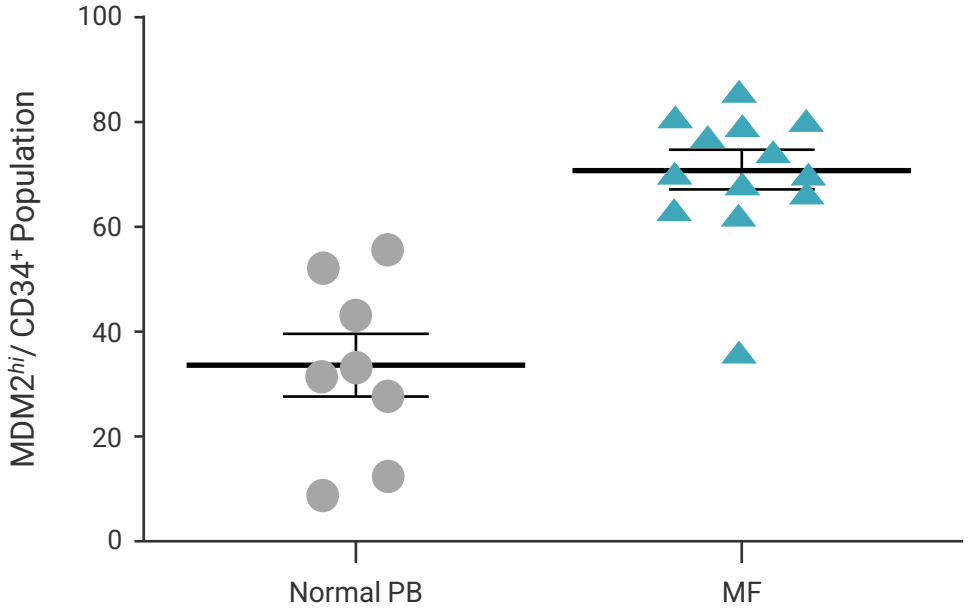
MDM2 Overexpression Prevents p53-Driven Apoptosis of CD34⁺ MF Cells



[1]Barosi G, et al. *Blood* 2001. [2] Rampal R, et al. *Blood* 2014. [3]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; TGF-β, transforming growth factor beta; TNFα, tumor necrosis factor alpha; VAF, variant allele frequency.

Navtemadlin Inhibits MDM2 to Restore p53 Function

MDM2 Overexpression in CD34⁺ MF Cells[1]



MDM2 overexpression in circulating CD34⁺ MF progenitors[2]

Navtemadlin is a Potent Inhibitor of MDM2

Navtemadlin induces apoptosis in *TP53*^{WT} CD34⁺ MF progenitors by overcoming MDM2 dysregulation[3]

Note: 95% of MF patients are *TP53*^{WT}. Binding affinity = 0.045 nM; IC50 = 9.1 nM; $t_{1/2}$ = 17 hours.
[1]Figure adapted from Lu M, et al. *Blood* 2017. [2]Nakatake M, et al. *Oncogene* 2012. [3]Clevenger T, et al. EHA 2023; 386820. Abstract P991.
Abbreviations: MDM2, mouse double minute 2; MF, myelofibrosis; PB, peripheral blood; WT, wild-type.

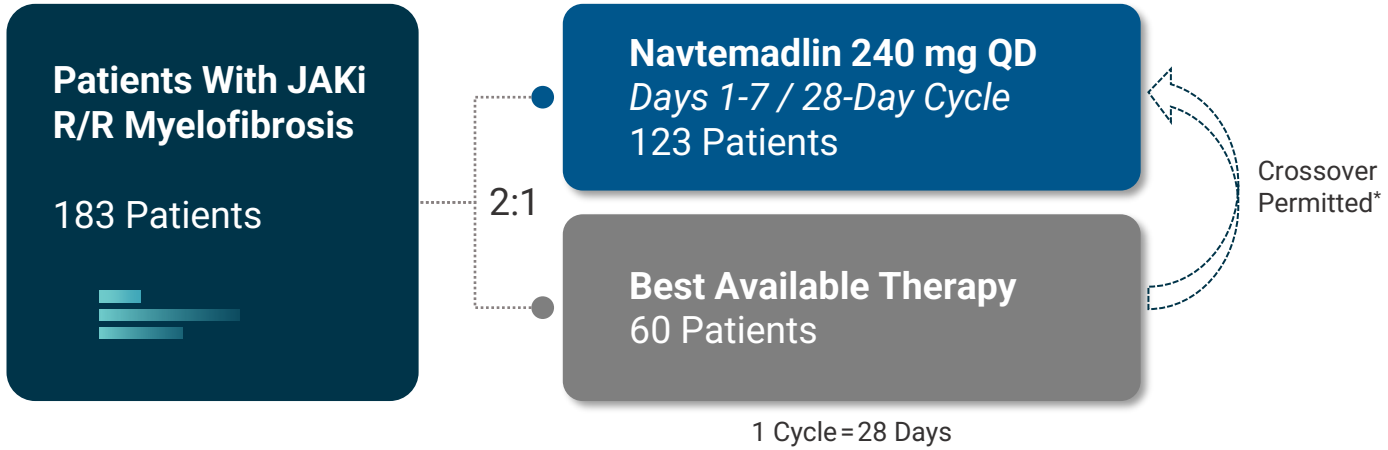
Phase 3 Study Design

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.

JAK Inhibitor Relapsed/Refractory MF

JAKi-Intolerant Patients were Not Eligible for the BOREAS Study

RELAPSED

Progressive Disease After JAKi Treatment:

≥ 100% increase in palpable distance below the LLCM (baseline splenomegaly of 5 - 10 cm)

Or

≥ 50% increase in palpable distance below the LLCM (baseline splenomegaly of > 10 cm)

Or

≥ 25% increase in spleen volume (MRI/CT from nadir)

Or

Regrowth after achieving complete response

OR

REFRACTORY

Lack of Spleen Response After ≥ 12 Weeks JAKi Treatment:

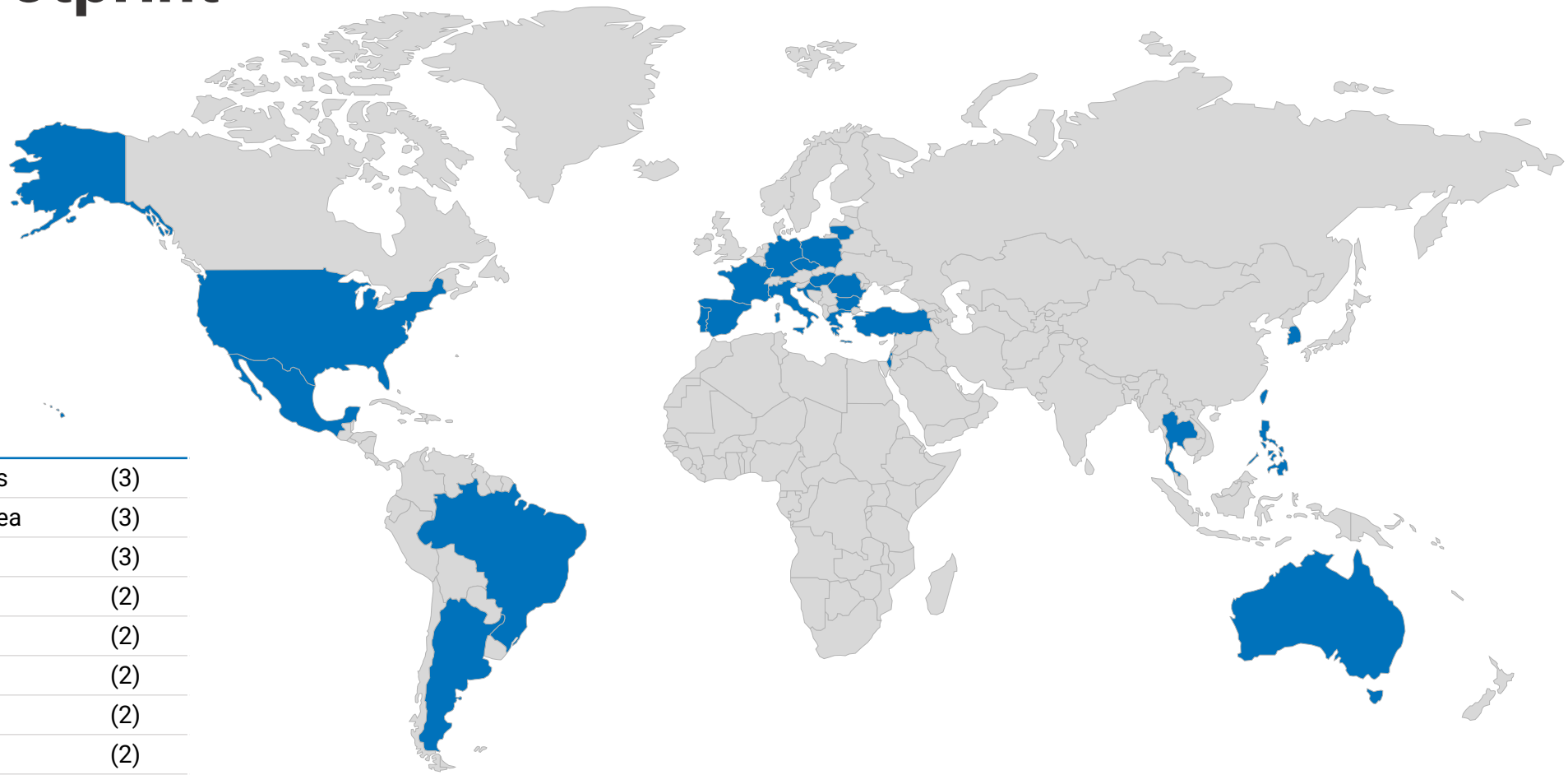
< 10% spleen volume reduction by MRI/CT

Or

< 30% decrease from baseline in spleen length by palpation

Note: TSS eligibility: A minimum of two symptoms with a score of at least one each on the MFSAF v4.0 required.
Abbreviations: CT, computed tomography; JAK, Janus kinase; JAKi, Janus kinase inhibitor; LLCM, lower left costal margin; MRI, magnetic resonance imaging.

Global Site Footprint

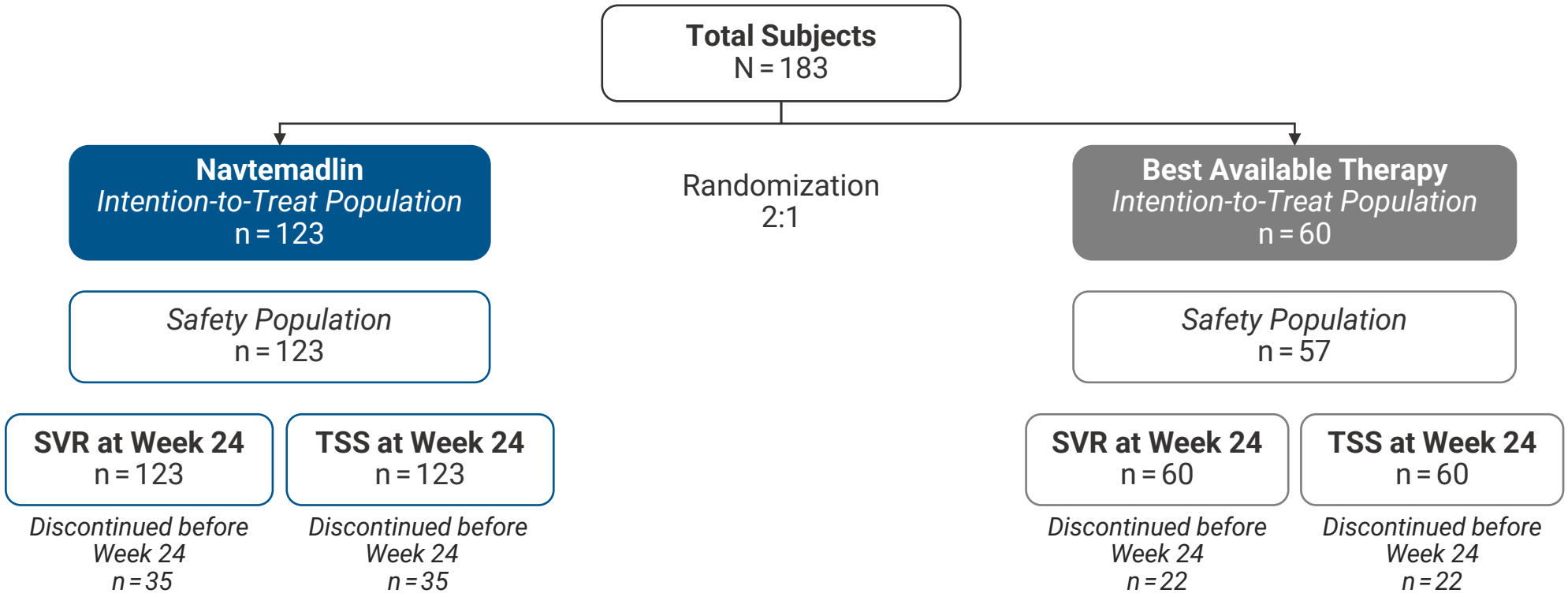


92 Global Sites

US, Europe, and Asia-Pacific

Country (Sites)			
Italy	(10)	Philippines	(3)
United States	(10)	South Korea	(3)
Spain	(9)	Thailand	(3)
Brazil	(7)	Argentina	(2)
Poland	(5)	Australia	(2)
Romania	(5)	Bulgaria	(2)
Turkey	(5)	Mexico	(2)
France	(4)	Portugal	(2)
Hungary	(4)	Taiwan	(2)
Croatia	(3)	Czech Republic	(1)
Germany	(3)	Greece	(1)
Israel	(3)	Lithuania	(1)

Patient Disposition



Data cut-off: 30 Sep 2024.
Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle). Intention-to-treat population is all randomized subjects. BOREAS enrollment was closed at 183 subjects. Safety population is all subjects who received ≥1 dose of study treatment. Three subjects randomized to the BAT arm were not treated.
Abbreviations: BAT, best available therapy; SVR, spleen volume reduction; TSS, total symptom score.

Baseline Characteristics

	Navtemadlin n = 123	Best Available Therapy n = 60[1]
Characteristic		
Male, n (%)	70 (57)	35 (58)
ECOG (0 - 1 / 2), n (%)	112 (91) / 11 (9)	51 (85) / 9 (15)
MF Subtype (Primary / Secondary), n (%)	72 (59) / 51 (42)	35 (58) / 25 (42)
DIPSS (Int-1 / Int-2 / High), n (%)	44 (36) / 60 (49) / 19 (15)	19 (32) / 32 (53) / 9 (15)
JAKi Relapsed/Refractory, n (%)	45 (37) / 78 (63)	21 (35) / 39 (65)
Prior JAKi Exposure (months), Median (range)	22.7 (2, 116)	18.3 (3, 202)
Prior Therapy, Median (range)	1 (1, 6)	1 (1, 5)
Platelet Count ($x10^9$ / L), Median (range)[2] < 100, n (%)	142 (19, 1829) 38 (31)	125 (23, 722) 20 (33)
Hgb, Median (range) Hgb < 10 g / dL, n (%)	10.1 (4, 16.1) 59 (48)	9.8 (4.9, 16.4) 31 (52)
Transfusion Dependent, n (%)	26 (21)	11 (18)
TSS, Median (range) TSS > 10, n (%)	20.8 (1.7, 64.3) 94 (76)	20.1 (0, 63.8) 46 (77)
Spleen Volume (cm^3), Median (range)	2321 (184, 5210)[3]	2242 (516, 6002)

Data cut-off: 30 Sep 2024.
Note: Navtemadlin dosed at 240 mg QD (Days 1-7 / 28-day cycle).
[1]One subject randomized to BAT, first cycle was navtemadlin. [2]Platelet values at screening. [3]One subject with baseline spleen volume < 450 cm^3 had palpable spleen ≥ 5 cm LLCM.
Abbreviations: BAT, best available therapy; DIPSS, Dynamic International Prognostic Scoring System; ECOG, Eastern Cooperative Oncology Group; JAKi, Janus kinase inhibitor; Hgb, hemoglobin; Int, Intermediate; MF, myelofibrosis; QD, once daily; TSS, total symptom score.

Baseline Characteristics (continued)

Characteristic	Navtemadlin n = 123	Best Available Therapy n = 60[1]
Median Time From Initial Diagnosis, Months (range)	48.1 (0.4, 368.3)	45.2 (5, 292.3)
< 6 months, n (%)	3 (2)	1 (2)
≥ 6-12 months	12 (10)	8 (13)
> 12-24 months	26 (21)	9 (15)
> 24 months	82 (67)	42 (70)
Prior Therapy, Median (range)	1 (1, 6)	1 (1, 5)
Ruxolitinib, n (%)	122 (99)	60 (100)
Fedratinib	5 (4)	1 (2)
Pacritinib	3 (2)	–
Momelotinib	–	1 (2)
Baricitinib	1 (1)	–
Driver Mutations, n (%)		
JAK2^{V617F}	89 (72)	39 (65)
CALR	22 (18)	16 (27)
MPL	5 (4)	1 (2)
Triple Negative	7 (6)	4 (7)
High Molecular Risk Mutations, n (%)[2]		
≥1	76 (62)	41 (68)
≥2	29 (24)	14 (23)
Bone Marrow Fibrosis Score, n (%)[3]		
Grade 1	11 (9)	6 (10)
Grade 2	43 (35)	21 (35)
Grade 3	57 (46)	22 (37)

Data cut-off: 30 Sep 2024.
Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle).
[1]One subject randomized to BAT, first cycle was navtemadlin. [2]HMR included *ASXL1*, *EZH2*, *IDH1/2*, *SRSF2*, *U2AF1* with level of detection of 3%. [3]Samples assessed by central lab (Navtemadlin: n=111, BAT: n=49).
Abbreviations: BAT, best available therapy; *CALR*, calreticulin; *JAK2*, Janus kinase 2; *MPL*, myeloproliferative leukemia virus oncogene; QD, once daily.

Treatment Disposition

	Navtemadlin n = 123[1]	Best Available Therapy n = 60[1,2]
Randomized Not Treated	–	3 (5)
On Treatment	37 (30)	3 (5)
Discontinued	86 (70)	54 (90)
Withdrawal of Consent	30 (24)	7 (12)
Adverse Event	14 (11)	4 (7)
Disease Progression	11 (9)	6 (10)
Death	9 (7)	4 (7)
Investigator Decision	18 (15)	17 (28)
Other*	4 (3)	16 (27)

Median time on study, months (range): Navtemadlin 15.6 (0.23, 39.9); BAT 6.5 (0.03, 30.5)

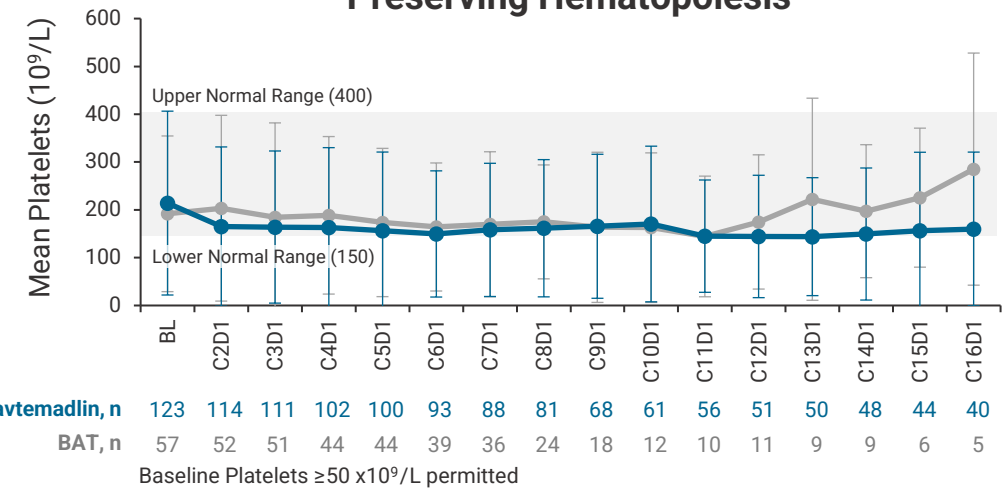
Data cut-off: 30 Sep 2024.
Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle). *Other, navtemadlin: clinical progression (n=1), drug interruption >8 weeks (n=1), lost to follow-up (n=1), refusal to return to the site (n=1).
BAT: crossed over to navtemadlin (n=11), sponsor decision (n=2), suspicious mammography finding (n=1), transformation to AML (n=1), moved out of state (n=1).
[1]Randomized data set. [2]One subject randomized to BAT, first cycle was navtemadlin.
Abbreviations: BAT, best available therapy; QD, once daily.

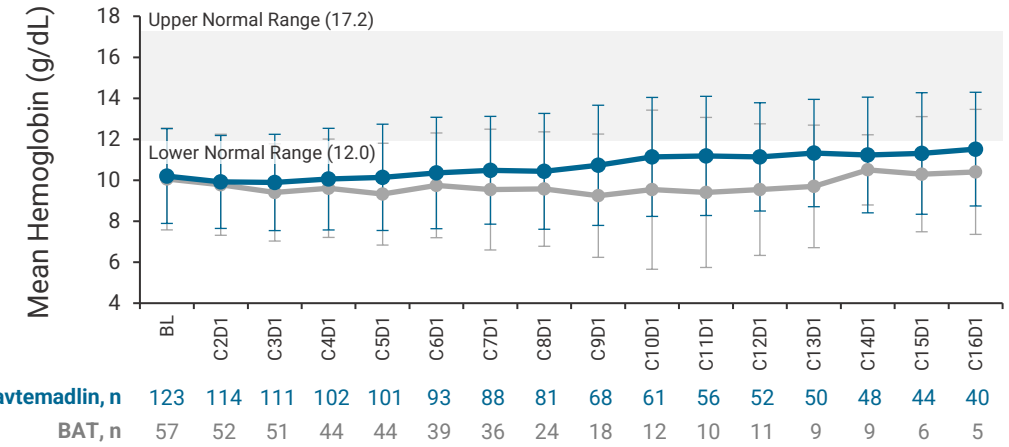
Treatment-Emergent Adverse Events

	Navtemadlin n = 123[1]		Best Available Therapy n = 57[1,2]	
Preferred Term, n (%)	**All Grade**	**Grade 3/4**	**All Grade**	**Grade 3/4**
TEAE Occurring in ≥10%[1]				
Thrombocytopenia[3]	57 (46)	45 (37)	18 (32)	14 (25)
Nausea	52 (42)	5 (4)	3 (5)	–
Diarrhea	50 (41)	7 (6)	9 (16)	1 (2)
Anemia	44 (36)	35 (29)	16 (28)	16 (28)
Neutropenia[4]	37 (30)	31 (25)	10 (18)	7 (12)
Constipation	25 (20)	1 (1)	2 (4)	–
Vomiting	31 (25)	3 (2)	1 (2)	–
Decreased Appetite	22 (18)	–	4 (7)	1 (2)
Fatigue	19 (15)	4 (3)	7 (12)	2 (4)
Peripheral Edema	15 (12)	–	7 (12)	1 (2)
Asthenia	16 (13)	2 (2)	5 (9)	1 (2)
Abdominal Pain, Upper	13 (11)	2 (2)	1 (2)	–
Pruritus	7 (6)	–	6 (11)	–

Median time on study, months (range): Navtemadlin 15.6 (0.23, 39.9); BAT 6.5 (0.03, 30.5)

Preserving Hematopoiesis





Data cut-off: 30 Sep 2024.
Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle).
[1]Safety dataset is all subjects who received ≥1 dose of study treatment. [2]One subject randomized to BAT, first cycle was navtemadlin. [3]Combined terms: thrombocytopenia and platelet count decrease.
[4]Combined terms: neutropenia and neutrophil count decrease. Abbreviations: BAT, best available therapy; BL, baseline; C, cycle; D, day; QD, once daily; TEAE, treatment-emergent adverse event.

Adverse Events of Interest

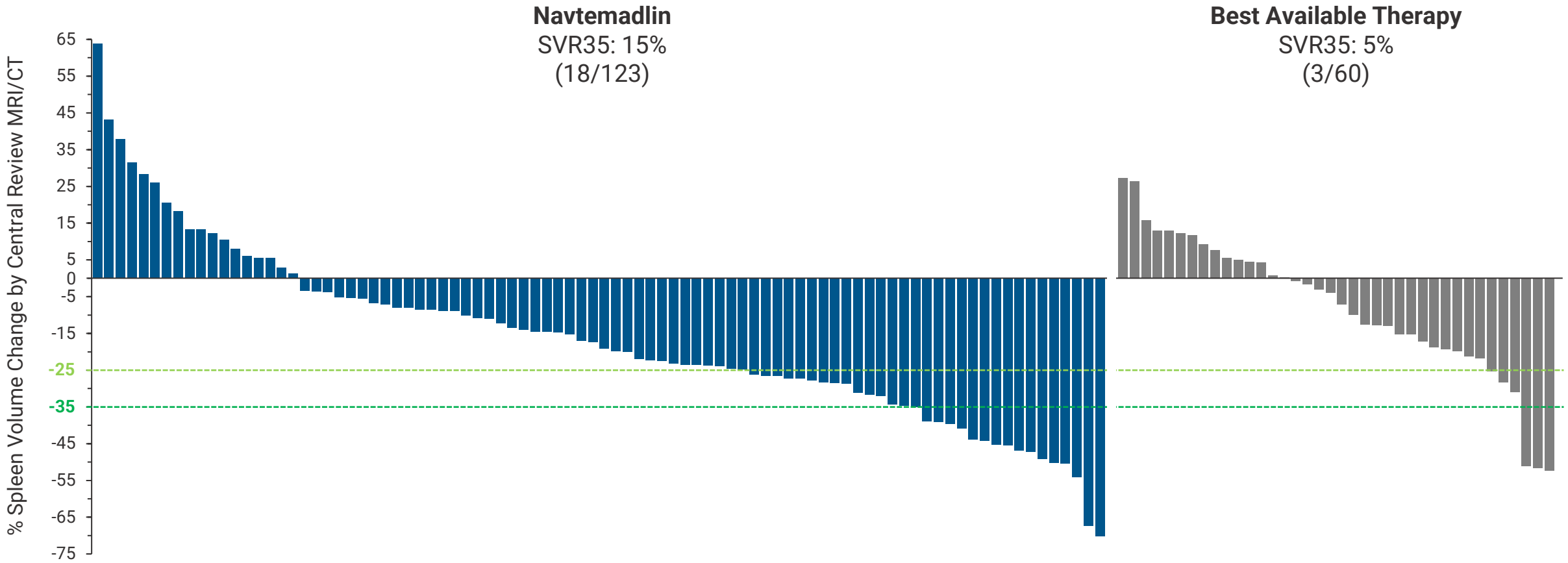
	Navtemadlin n = 123[1]					
TEAE Preferred Term, n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Time to Onset (days), Median (range)**	**Time to Resolution (days), Median (range)**
Gastrointestinal						
Nausea	21 (17)	26 (21)	5 (4)	–	4 (1, 530)	9 (1, 348[2])
Vomiting	16 (13)	12 (10)	3 (2)	–	30 (1, 477)	4 (1, 24[2])
Diarrhea	22 (18)	21 (17)	7 (6)	–	8 (1, 384)	7 (1, 338[2])
Hematologic						
Anemia	–	9 (7)	27 (22)	8 (7)	30 (1, 289)	8 (1, 369)
Neutropenia[3]	1 (1)	5 (4)	13 (11)	18 (15)	29 (8, 176)	4 (1, 24)
Thrombocytopenia[4]	2 (16)	10 (8)	14 (11)	31 (25)	29 (8, 253)	14 (1, 387)

AML Transformation, n (%)	**Navtemadlin n = 123**	**Best Available Therapy n = 60**
Progression to AML	2 (1.6)	2 (3.3)

Data cut-off: 30 Sep 2024.
Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle). Median time on study, months (range): Navtemadlin 15.6 (0.23, 39.9); BAT 6.5 (0.03, 30.5).
[1]Safety dataset is all subjects who received ≥1 dose of study treatment. [2]Duration of events includes TEAEs of intermittent nausea, diarrhea, vomiting reported as ongoing at time of data cut-off. [3]Includes terms neutropenia + neutrophil count decrease. [4]Includes terms thrombocytopenia + platelet count decrease.
Abbreviations: AML, acute myeloid leukemia; MUT, mutated; TEAE, treatment-emergent adverse event; VAF, variant allele frequency; WT, wild-type.

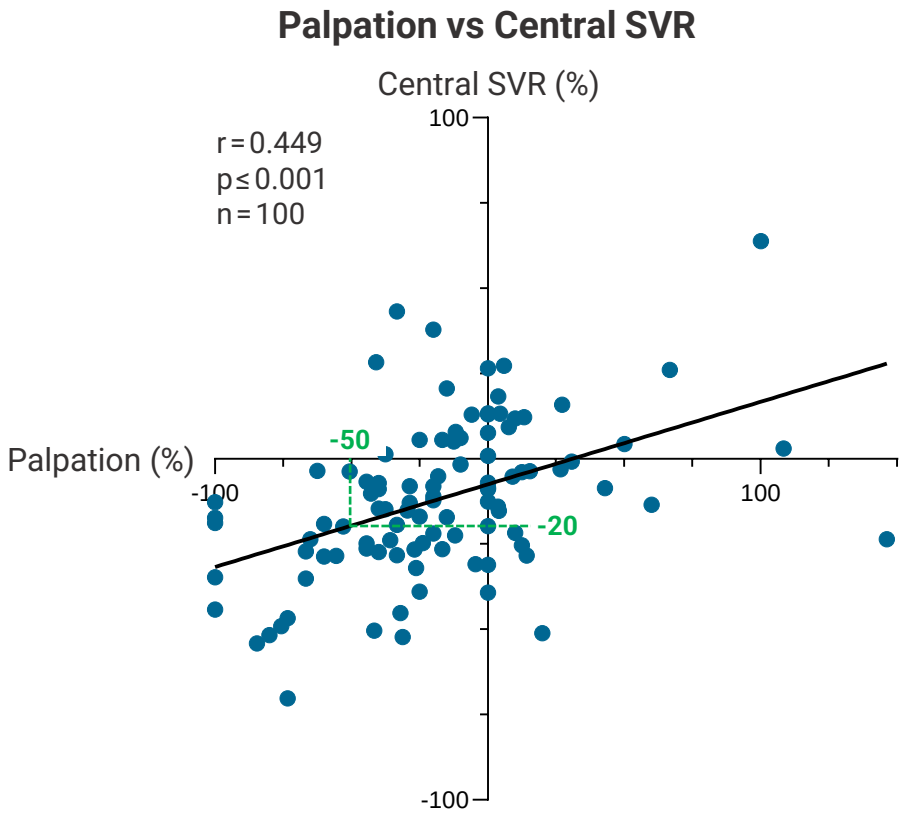
SVR35 at Week 24 (ITT Population)

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%.

Correlation of Spleen Length by Palpation and SVR by Central Review

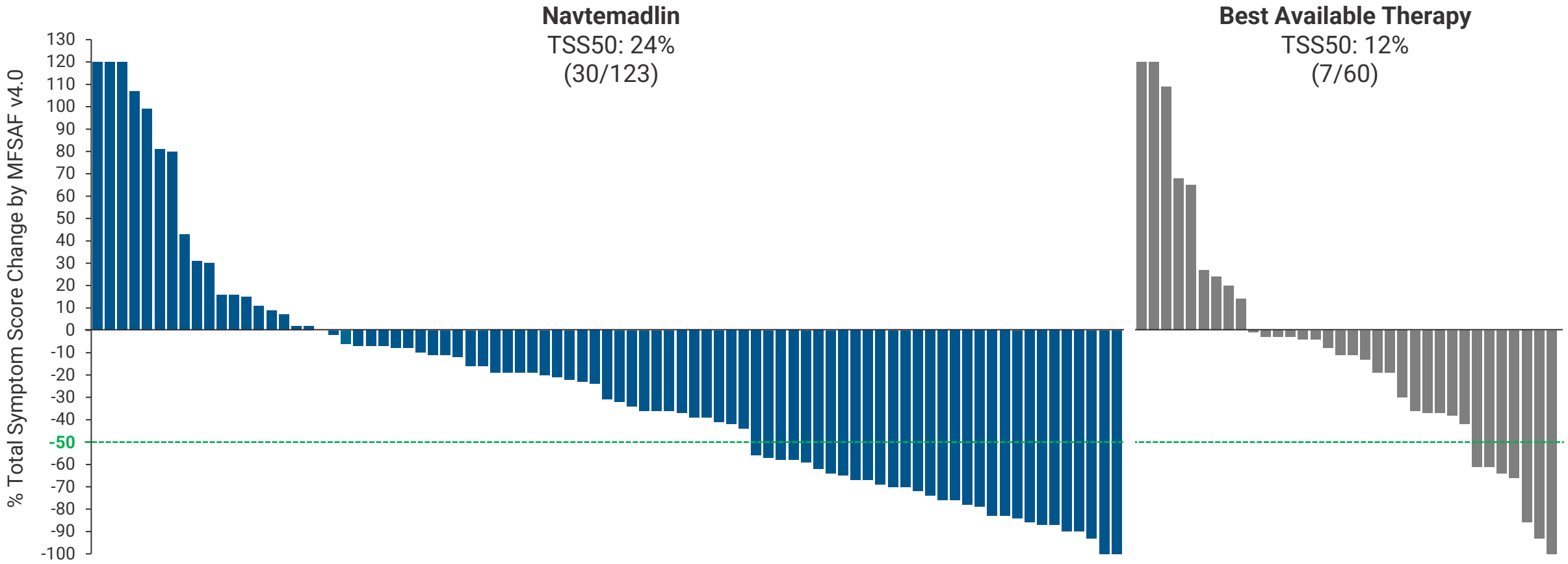


50% reduction of spleen length by Palpation is equivalent to 20% SVR by Central Review

Note: SVR measured by MRI/CT.
Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; SVR, spleen volume reduction.

TSS50 at Week 24 (ITT Population)

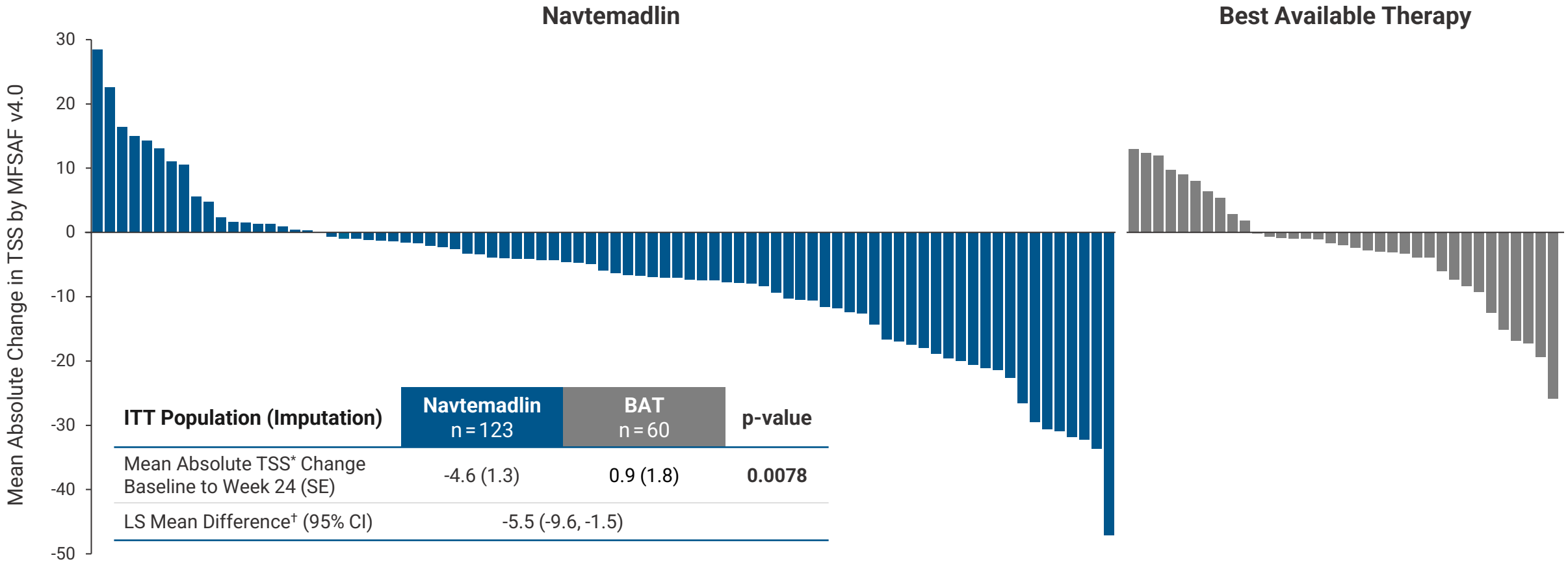
Total Symptom Score Reduction by MFSAF v4.0 – Baseline to Week 24



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=0.0507.
Week 24 TSS assessment includes Week 23 scores for subjects who stopped TSS at the start of Week 24 (n=2).
Abbreviations: BAT, best available therapy; ITT, intention-to-treat; MFSAF, myelofibrosis symptom assessment form; TSS, total symptom score; TSS50, total symptom score reduction ≥50%.

Absolute Change in TSS at Week 24 (ITT Population)

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

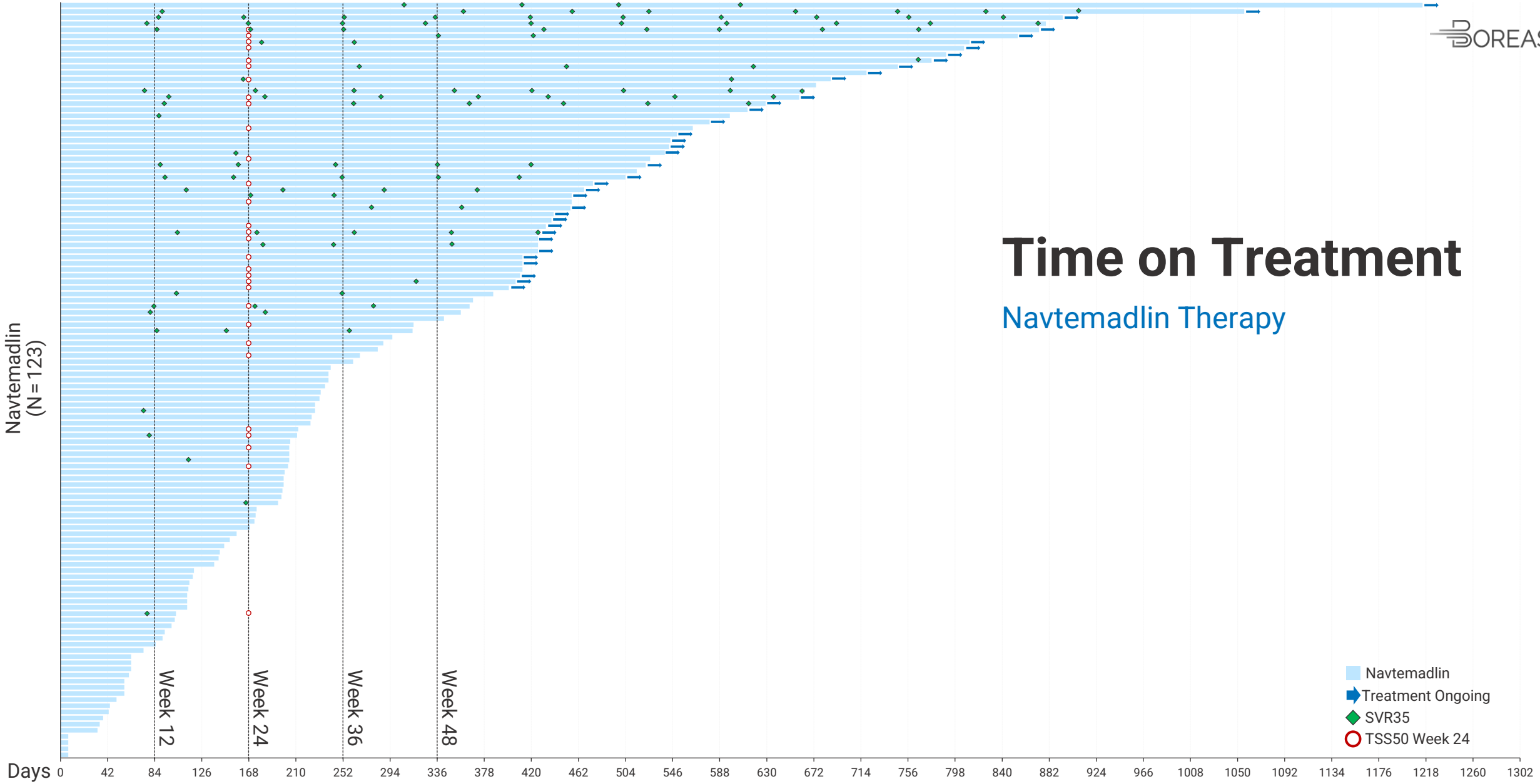


ITT Population (Imputation)	Navtemadlin n = 123	BAT n = 60	p-value
Mean Absolute TSS* Change Baseline to Week 24 (SE)	-4.6 (1.3)	0.9 (1.8)	**0.0078**
LS Mean Difference† (95% CI)	-5.5 (-9.6, -1.5)		

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.

Time on Treatment

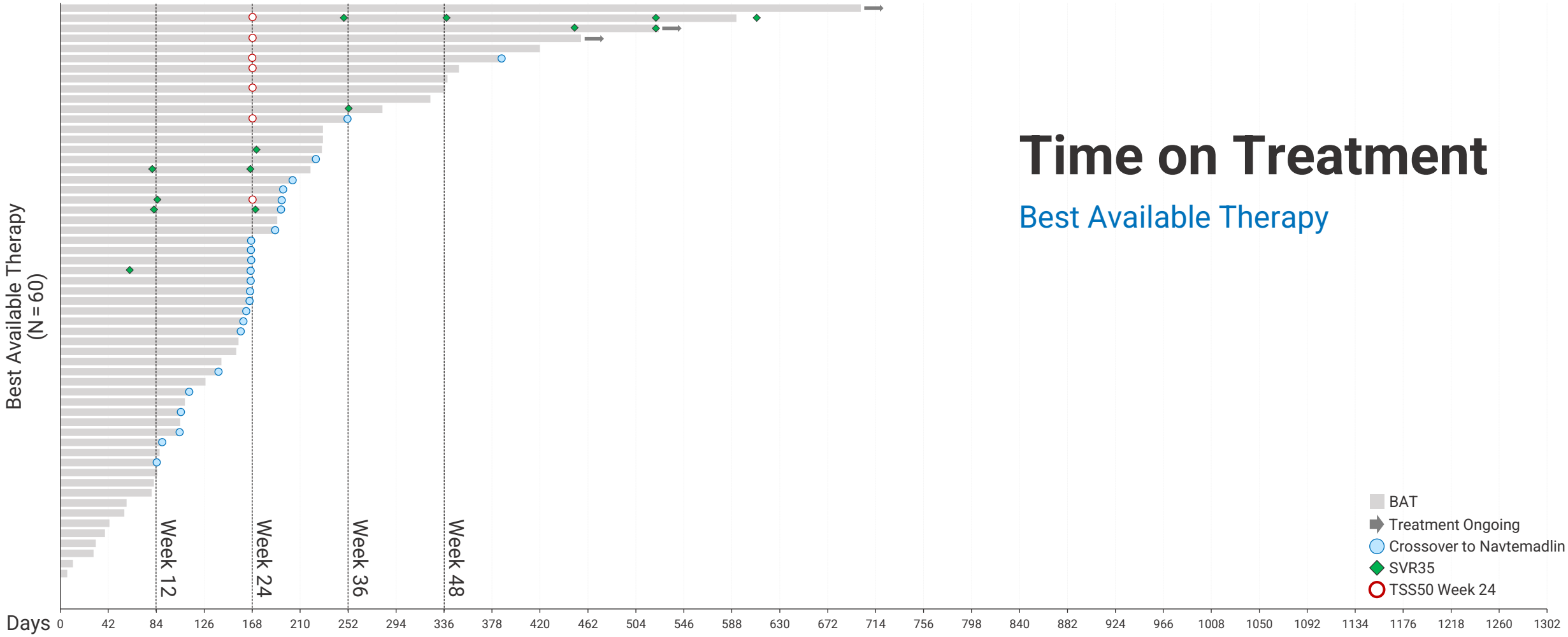
Navtemadlin Therapy



Data cut-off: 30 Sep 2024. Abbreviations: Nvtm, navtemadlin; SVR35, spleen volume reduction ≥ 35%; TSS50, total symptom score reduction ≥ 50%.

Time on Treatment

Best Available Therapy

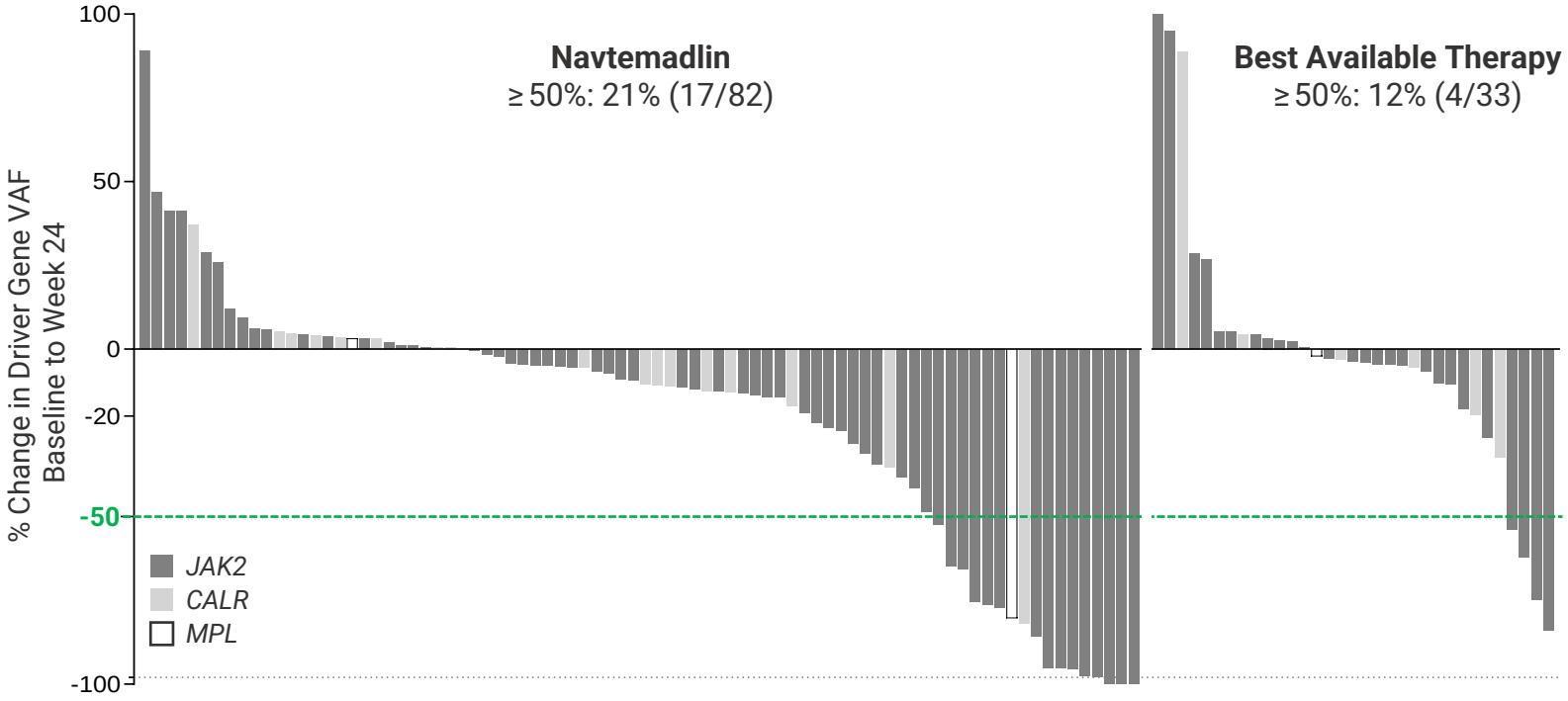


Data cut-off: 30 Sep 2024. Crossover in the BAT arm permitted after disease progression or at Week 24.
Abbreviations: BAT, best available therapy; SVR35, spleen volume reduction ≥ 35%; TSS50, total symptom score reduction ≥ 50%.

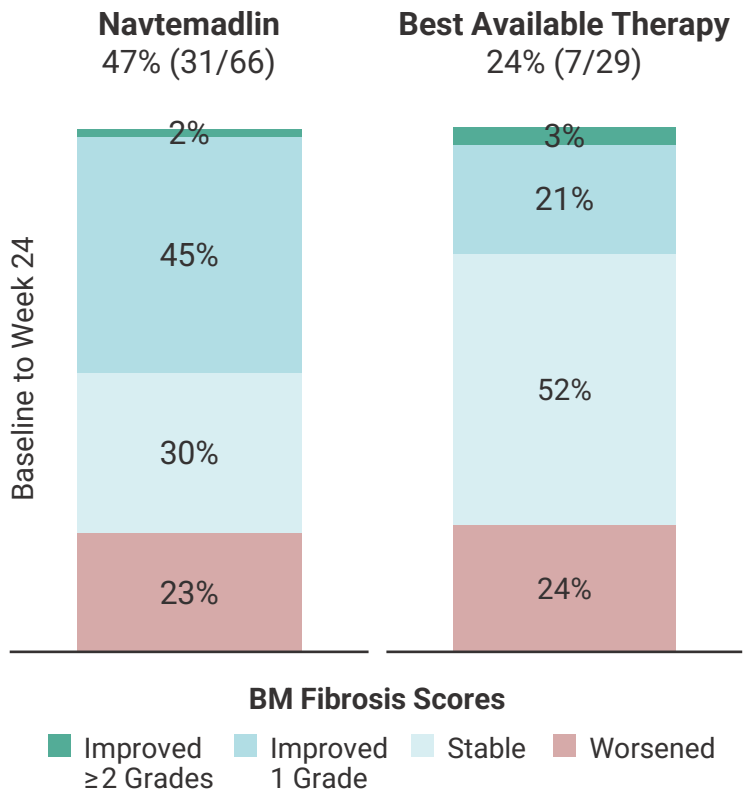
Potential for Disease Modification

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

Driver Gene VAF
by Central Laboratory



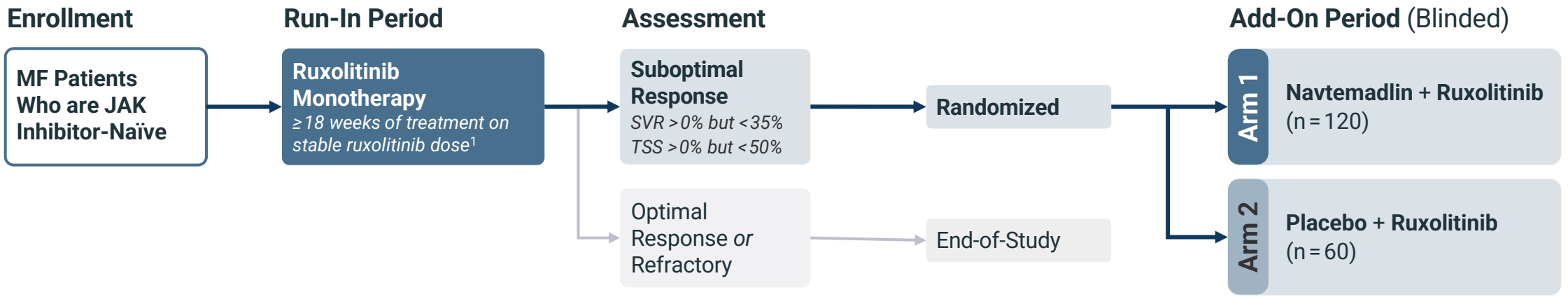
Bone Marrow Fibrosis
by Central Pathology Review



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 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

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 220 sites across 19 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; JAK, Janus kinase; MF, myelofibrosis; TSS, total symptom score; WHO, World Health Organization; WT, wild-type.

Conclusion

- BOREAS is the first global phase 3 study conducted solely in patients with myelofibrosis who are R/R to JAKi treatment to report results
- Navtemadlin demonstrated clinically relevant efficacy with an acceptable safety profile and the potential for disease modification
- The rate of SVR35 and TSS50 at Week 24 was three-fold and two-fold higher with navtemadlin vs BAT, validating the novel approach of MDM2 inhibition in patients with myelofibrosis
- Further studies with navtemadlin are warranted, including as add-on therapy to ruxolitinib in JAKi-naïve myelofibrosis patients who have a suboptimal response to ruxolitinib treatment (POIESIS; NCT06479135)

Abbreviations: BAT, best available therapy; JAKi, Janus kinase inhibitor; MDM2, mouse double minute 2; R/R, relapsed/refractory; SVR35, spleen volume reduction ≥35%; TSS50, total symptom score reduction ≥50%.

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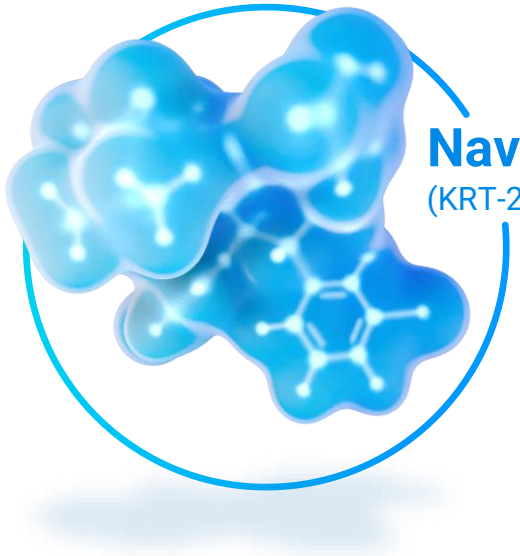

Navtemadlin
(KRT-232)

Navtemadlin data also presented in
Oral Abstract #483
TiP Poster #1808.2

Abbreviations: MDM2, mouse double minute 2.