Clinical Trial Protocol

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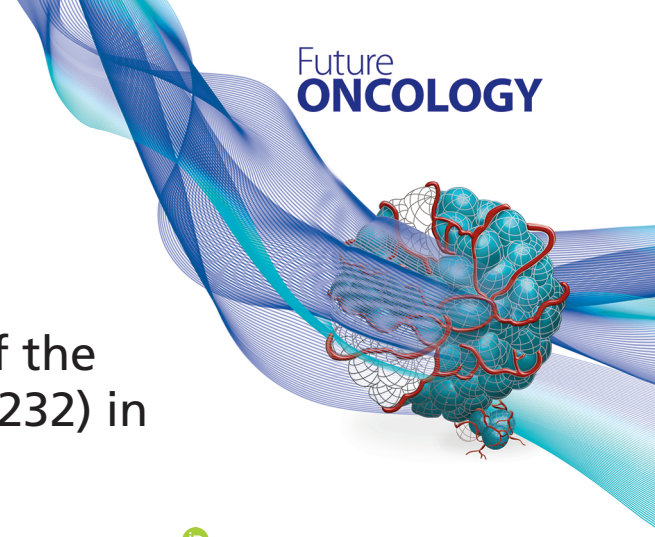

BOREAS: a global, phase III study of the MDM2 inhibitor navtemadlin (KRT-232) in relapsed/refractory myelofibrosis

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Patients with myelofibrosis (MF) who discontinue ruxolitinib due to progression/resistance have poor prognoses. JAK inhibitors control symptoms and reduce spleen volumes with limited impact on underlying disease pathophysiology. Murine double minute 2 (MDM2), a negative regulator of p53, is overexpressed in circulating malignant CD34$^+$ MF cells. The oral MDM2 inhibitor navtemadlin (KRT-232) restores p53 activity to drive apoptosis of wild-type *TP53* tumor cells by inducing expression of pro-apoptotic Bcl-2 family proteins. Navtemadlin demonstrated promising clinical and disease-modifying activity and acceptable safety in a phase II study in patients with relapsed/refractory MF. The randomized phase III BOREAS study compares the efficacy and safety of navtemadlin to best available therapy in patients with MF that is relapsed/refractory to JAK inhibitor treatment (NCT03662126).

Clinical Trial Registration: NCT03662126 (ClinicalTrials.gov)

Plain language summary: Myelofibrosis (MF) is a rare blood cancer that disrupts normal blood cell production and causes fibrosis (tissue thickening/scarring) in bone marrow, reduced red blood cells in the circulation, and an enlarged spleen. Although currently approved treatments can help relieve some effects, they have limited impact on the underlying cause of the disease. Navtemadlin is a new therapy that inhibits a protein frequently overexpressed in cancer cells found in MF patients called murine double minute 2 (MDM2), which regulates a common tumor suppressor protein called p53. By inhibiting MDM2, navtemadlin restores normal p53 function and its ability to kill MF cancer cells. BOREAS is a large clinical study of navtemadlin for MF patients whose disease is not responding to current therapy.

Tweetable abstract: Navtemadlin (KRT-232), a potent, selective and orally available MDM2 inhibitor is being explored in the global phase III BOREAS trial in #myelofibrosis patients who are relapsed or refractory to JAK-inhibitor treatment #MPNSM.

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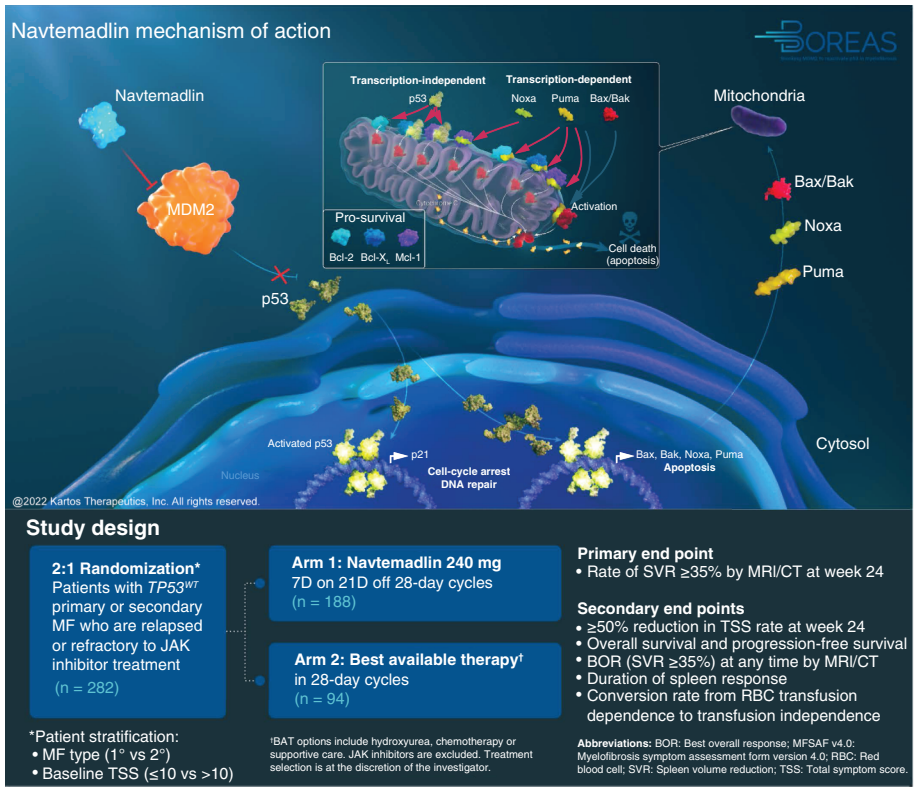
Graphical abstract:



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Keywords: MDM2 inhibitor • myelofibrosis • myeloproliferative neoplasms • navtemadlin • p53

Trial

BOREAS is a randomized, open-label, global, phase III study that evaluates the efficacy and safety of navtemadlin versus best available therapy (BAT) for the treatment of primary or secondary myelofibrosis (MF) in patients who have relapsed or are refractory (R/R) to Janus kinase (JAK) inhibitor treatment (NCT03662126) [1]. This trial has been named BOREAS (**B**l**O**cking MDM2 to **REA**ctivate p53 in Myelofibrosi**S**) after the Greek god of the powerful North Wind. Just as winds can signal changes in weather patterns, the name BOREAS is metaphorically signaling that a potential change is coming for the treatment of MF.

Background & rationale

Unmet medical need in MF

MF is a chronic myeloproliferative neoplasm, with an annual incidence of approximately 1/100,000 and an estimated prevalence of 4–6/100,000 in USA [2]. The disease is characterized by clonal proliferation of myeloid cells resulting in extramedullary hematopoiesis, hepatosplenomegaly, constitutional symptoms and cytopenias, along with bone marrow fibrosis, and an increased risk for transformation into acute myeloid leukemia (AML) [3–5]. Overproduction and dysregulation of inflammatory cytokines, particularly from monocytes or precursors of macrophages and dendritic cells, play an important role in the etiology and distinct clinical features of MF [6]. Circulating inflammatory cytokine levels, such as TNFα, IL-6, IL-8 and IL-10, are elevated in MF and may serve as prognostic markers for disease progression or poor outcomes [6,7]. TNFα is known to promote clonal dominance of malignant cells, whereas high IL-6 and IL-8 are associated with severity of constitutional symptoms [7] and elevated IL-8 is also with increased leukocytosis and higher-grade fibrosis [8]. IL-2, IL-6, IL-8, and beta-2 microglobulin, an important component for antigen presentation, have also been associated with blast transformation [7].

Although the exact cause of MF is unknown, the pathophysiology in most patients is characterized by the acquisition of driver mutations that deregulate the JAK/signal transducers and activators of transcription (STAT) signaling pathway [9,10]. Aberrant pro-survival signaling through growth factor and cytokine receptors increases the proliferation rate of malignant myeloid cells [11]. Somatic mutations in three genes in this pathway, *JAK2*, *MPL* (thrombopoietin receptor), and/or *CALR*, have been shown to drive the development of MF [9,12]. The gain-of-function *JAK2* mutation (*V617F*) has been identified in 40–75% of patients with primary MF (PMF) and can lead to the constitutive activation of downstream signaling through STAT, resulting in uncontrolled myeloproliferation [9,12]. Similarly, frame-shift mutations in the *CALR* gene and gain-of-function mutations in the *MPL* gene, which are found in 20–30% and less than 10% of patients with PMF, respectively [9,12], can lead to JAK/STAT activation. Approximately 10% of patients have no reported driver mutations; this triple-negative mutation status is associated with poor prognosis in patients with MF [9,12]. In addition, mutations in several high molecular risk (HMR) genes involved in epigenetic regulation (*ASXL1*, *EZH2*, *IDH1/2*) and RNA splicing (*SRSF2*) were identified as poor prognostic factors for overall survival and leukemia-free survival in patients with PMF [13].

Although transplantation provides a potentially curative treatment option for high- to very high-risk patients with MF, the high morbidity and mortality associated with this approach limits its adoption to younger patients with good performance status [5,14]. As a result, JAK inhibitors are currently the standard-of-care for MF based on their ability to provide symptom control and reduce spleen volumes [15]. The four main JAK inhibitors currently being studied include ruxolitinib, fedratinib, pacritinib and momelotinib, the first three of which are approved by the US FDA for the treatment of myelofibrosis [15,16]. Although these agents mediate spleen volume reduction (SVR) and improvements in total symptom score (TSS), currently published data reports only a modest impact on bone marrow fibrosis and their disease-modifying effects are limited [15]. Even with recent approvals of novel JAK-inhibitors, the prognosis for patients who are R/R to JAK inhibitors is particularly poor [3,17]. Median overall survival in patients who discontinue ruxolitinib is 13–16 months, highlighting the need for novel therapies that target alternative pathways [17,18].

Overview of MDM2 & navtemadlin mechanism of action

p53 is a tumor suppressor protein that regulates cellular proliferation and apoptosis [19,20]. Murine double minute 2 (MDM2), the primary negative regulator of p53 plays a key role in maintaining low p53 levels in unstressed mammalian cells. In response to cellular stressors like DNA damage, hypoxia or oncogene activity, p53 initiates the transcription of various genes that culminate in either cell cycle arrest or apoptosis [20–24]. Reparable damage to cells induces low levels of p53 that mediate cell cycle arrest, whereas stressors that irreparably damage cells induce high levels of p53, inducing the intrinsic (mitochondrial) apoptosis pathway (Figure 1) [20–26].

More specifically, activated p53 upregulates selected pro-apoptotic Bcl-2 proteins (including Puma, Noxa and Bim) to overcome the effects of pro-survival Bcl-2 proteins (including Bcl-2, Bcl-X_L and Mcl-1) to initiate cell death through the pore forming effectors (including Bax, Bak and Bok), which mediate the release of cytochrome c and induction of caspase-9 [22,24].

As the key negative regulator of p53, MDM2 binds to and modulates the function of p53 by inhibiting its downstream transcriptional activity, promoting its transport out of the nucleus, and ubiquitinating the protein for proteasomal degradation [19]. In non-malignant cells, activated MDM2 plays an important role in maintaining p53 at low levels. Inactivating mutations in *TP53* or overexpression of MDM2 can overcome p53-driven cell killing, promoting oncogenic transformation and conferring a strong survival advantage [20]. Although inactivating *TP53* mutations are infrequent in MPNs (<5%), p53 activity is often suppressed by constitutive JAK2-mediated signaling in $CD34^+$ cells, leading to the upregulation of the La antigen and MDM2 overexpression [27–29].

Navtemadlin (KRT-232) is a potent, selective, orally available MDM2 inhibitor that restores p53 activity to drive apoptosis in *TP53* wild-type ($TP53^{WT}$) malignancies, including reductions in malignant $CD34^+$ cells in MF (Figure 1) [30–32]. In $TP53^{WT}$ tumor cell lines, navtemadlin treatment increased protein levels of p53, p21, MDM2 and Puma in a dose-dependent manner; similar effects were observed on mRNA levels of these proteins *in vivo* [31]. Further studies in murine $TP53^{WT}$ xenograft models demonstrated that oral navtemadlin treatment resulted in significant inhibition of tumor growth and was associated with dose- and time-dependent induction of p21 mRNA in tumor samples, as well as increased apoptosis [31].

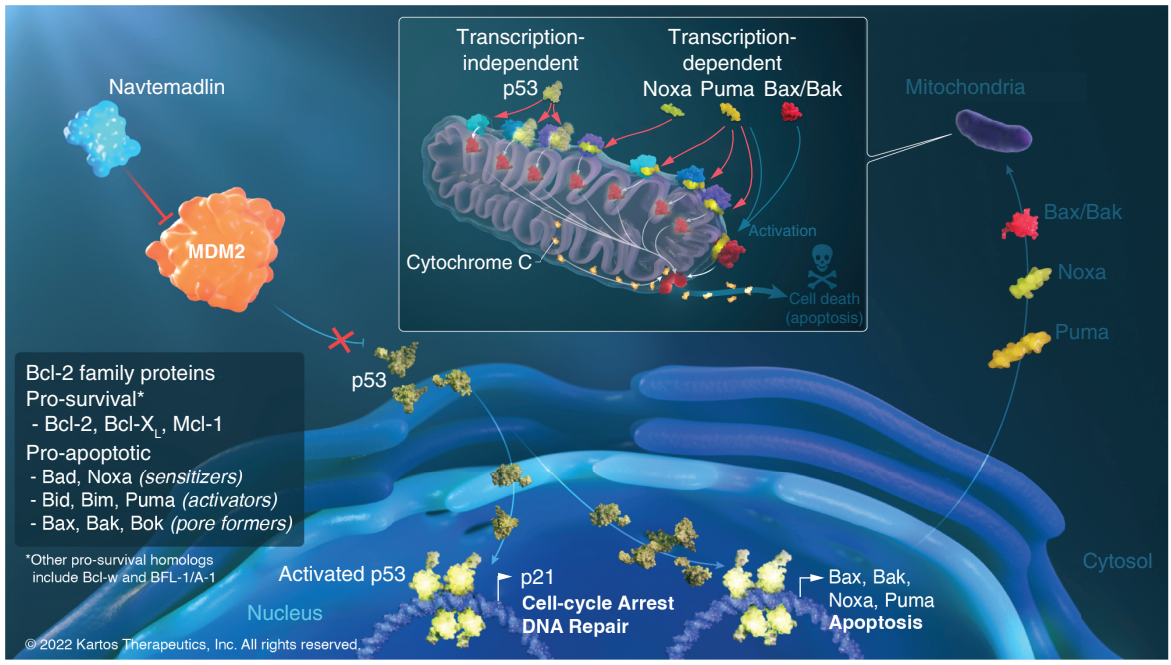

Figure 1. Navtemadlin (KRT-232) mechanism of action. p53 induces apoptosis by shifting the balance between pro-survival and pro-apoptotic Bcl-2 family members. MDM2 is the primary negative regulator of p53 cellular functions. MDM2 inhibition via navtemadlin (KRT-232) restores p53 activity to drive apoptosis of myelofibrosis cells harboring wild-type *TP53*.

Navtemadlin clinical & disease-modifying activity in MF

Preclinical studies provided the basis for further evaluation of navtemadlin in phase I/II studies of patients with MF and other *TP53*^{WT} hematologic malignancies and solid tumors [33–36]. Phase I studies demonstrated navtemadlin's dose proportional pharmacokinetic and pharmacodynamic profile, helped to characterize the optimal dose and schedule for future study, and provided early signals of antitumor activity among patients with *TP53*^{WT} malignancies [33,35]. Consistent with the established mechanism of action, navtemadlin induced gene expression of several p53 pathway members in the bone marrow, including *TP53*, *Bax*, *Puma*, *p21*, and *MDM2*.

Following these early studies, a proof-of-concept, two-part phase II study (KRT-232-101) was designed to identify the recommended phase II dose and schedule of navtemadlin for patients with MF who were R/R to JAK inhibitor treatment [34,37]. Patients were randomly assigned to 1 of 3 arms: 120 mg or 240 mg once daily (q.d.) on days 1–7 of 21-day cycles or 240 mg q.d. on days 1–7 of 28-day cycles. JAK inhibitor treatment washout was not required prior to initiation of navtemadlin. Phase II results showed promising activity of navtemadlin at a dose of 240 mg q.d. given days 1–7/28 with a best SVR ≥35% of 16% in 25 evaluable patients, best TSS response ≥50% in 30% of patients, and median reduction in peripheral blood CD34$^+$ cell counts at week 24 of 87% (Figure 2) [34,37]. Navtemadlin also demonstrated a tolerable safety profile; the most frequently reported adverse events of any grade and regardless of causality were gastrointestinal (e.g., diarrhea, nausea, vomiting) and hematologic (e.g., thrombocytopenia, anemia, neutropenia). Gastrointestinal adverse events were managed in part with the use of prophylaxis for nausea and vomiting.

Spleen responses were superior in patients who were off ruxolitinib prior to their baseline MRI/CT scan versus those who remained on ruxolitinib therapy at the time of their baseline scan (best SVR ≥35%: 29% vs 0%) [34,37]. This effect may be attributed to ruxolitinib discontinuation syndrome, which occurs within 21 days of cessation of treatment and is characterized by an acute relapse of disease symptoms, including accelerated splenomegaly and worsening cytopenias [38]. Although JAK inhibitor washout was not required prior to initiating navtemadlin treatment [34]; the spleen flare that may have resulted from ruxolitinib discontinuation is likely to have confounded the reported overall SVRs in this study.

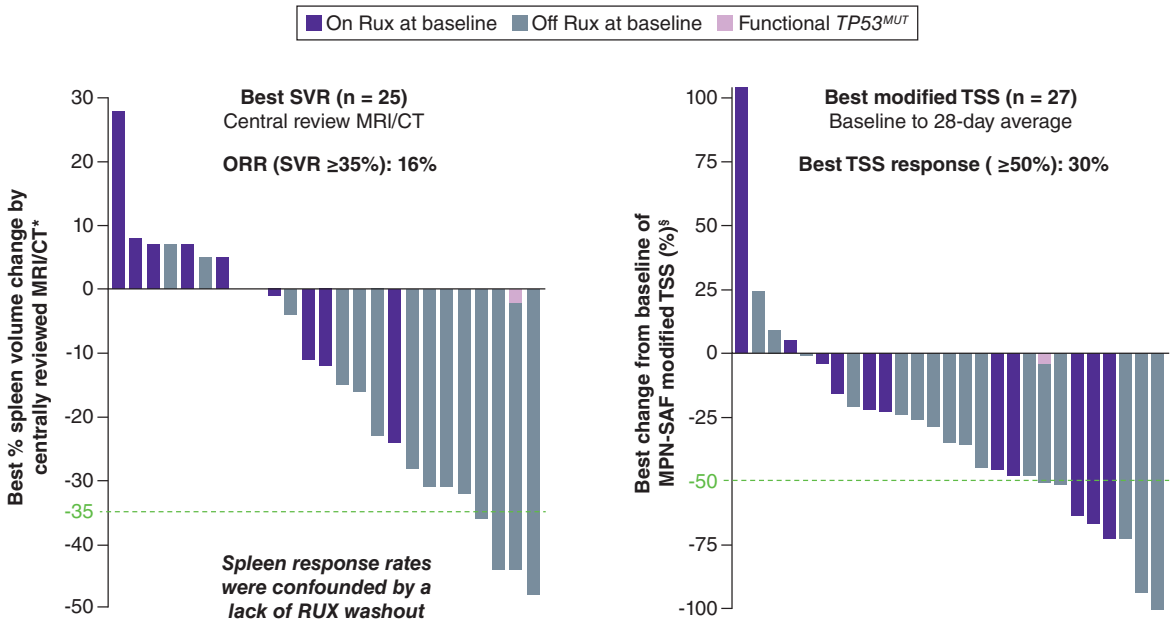

Figure 2. Clinical proof-of-concept for navtemadlin (240 mg q.d., D1–7/28) in relapsed/refractory myelofibrosis.
*SVR evaluable: patients must have baseline and at least one pre-planned post-baseline spleen MRI/CT (week 12, 24, 36).
§ TSS evaluable: requires patients to have a baseline TSS and >20-days within a 28-day period reported for post-baseline assessments.
Best Modified TSS: Best change from baseline to trailing 28-day average at end of week 4, 8, 12, 16, 20, 24, etc.
Modified MPN-SAF TSS includes early satiety, abdominal discomfort, night sweats, itching, bone pain and rib pain.
CT: Computed tomography; MPN-SAF: Myeloproliferative Neoplasm Symptom Assessment Form; ORR: Overall response rate; Rux: Ruxolitinib; SVR: Spleen volume response; *TP53* ^{MUT} : Mutated tumor protein p53; TSS: Total symptom score.

A subsequent correlative analysis of data from the same study showed that navtemadlin treatment resulted in clinically relevant changes in measures reflective of disease modification [32]. An analysis of reductions in variant allele frequency (VAF) of driver- or HMR-gene following navtemadlin treatment demonstrated that among patients with evaluable samples, a best driver gene reduction ≥20% was observed in 34% patients, and 29% showed a complete reduction in high-molecular risk or driver genes. Reduction in driver VAF at any time on study significantly correlated with SVR responses, which were higher in patients with ≥20% versus <20% decreases in driver VAFs (32% vs 5%; p = 0.0072). Bone marrow biopsies collected after 24 weeks of treatment showed that 27% of navtemadlin-treated patients had an improved fibrosis score of ≥1 grade and 51% had stable fibrosis scores as assessed by central pathology review. Navtemadlin-treated patients also demonstrated a significant decrease in serum TNFα levels (median best decrease of 41% from baseline), which significantly correlated with improvements in TSS and SVR. Demonstrating the correlation between clinical and biologic responses to navtemadlin treatment, spleen volume responses correlated with decreased peripheral $CD34^+$ cell counts, improved fibrosis scores, and reduction of myeloproliferative neoplasm (MPN)-driver mutation burden. These results suggest that changes in biomarkers of disease burden were associated with clinical benefit and support further exploration of navtemadlin's disease-modifying effects in MF.

The BOREAS phase III study design

Based on the promising activity reported in the phase II study, the phase III BOREAS study has been initiated to evaluate the efficacy and safety of navtemadlin versus BAT for patients with primary or secondary MF who are R/R to JAK inhibitor treatment (NCT03662126).

Eligibility criteria

Adults with confirmed *TP53*^{WT} primary or secondary MF (including PMF, post-polycythemia vera [PV] MF, or post-essential thrombocythemia [ET] MF according to WHO criteria [39]) are being enrolled in the study. Patients

Table 1. Key eligibility criteria.

Inclusion criteria

• Age ≥18 years
• Confirmed diagnosis of PMF, post-PV MF, or post-ET MF (WHO criteria [39])
• *TP53*^{WT} status by central laboratory testing
• High-risk, intermediate-2 risk or intermediate-1 risk (defined by DIPSS [40])
• Relapsed/refractory to prior treatment with JAK inhibitor defined as:
  ◦ Relapsed patients are those with progressive disease after JAK inhibitor treatment, defined by one of the following:
  ▪ Increase in spleen volume by ≥25% by radiographic imaging from nadir
  ▪ ≥100% increase in palpable distance below LLCM for baseline splenomegaly of 5 to 10 cm
  ▪ ≥50% increase in palpable distance below LLCM for baseline splenomegaly of >10 cm
  ▪ Regrowth after achieving complete response
  ◦ Refractory patients are those with a lack of spleen response after ≥12 weeks of JAK inhibitor treatment, defined by either:
  ▪ <10% spleen volume reduction by radiographic imaging
  ▪ <30% decrease from baseline in spleen size by palpation
• ECOG PS ≤2

Exclusion criteria
• Prior splenectomy • Splenic irradiation within 3 months prior to randomization • History of major hemorrhage or intracranial hemorrhage within 6 months prior to randomization • History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to randomization • Prior MDM2 inhibitor therapy or p53-directed therapy • Prior allogeneic stem cell transplant or plans for allogeneic stem cell transplant • History of major organ transplant • Grade 2 or higher QTc prolongation (>480 milliseconds per NCI-CTCAE v5.0)

ANC: Absolute neutrophil count; CT: Computed tomography; DIPSS: Dynamic International Prognostic Scoring System; ECOG PS: Eastern Cooperative Oncology Group performance status; JAK: Janus kinase; LLCM: Left lower costal margin; MDM2: Murine double minute 2; MF: Myelofibrosis; MFSAF v4.0: Myelofibrosis Symptom Assessment Form version 4.0; NCI-CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0; PMF: Primary MF; Post-ET MF: Post-essential thrombocythemia MF; Post-PV MF: Post-polycythemia vera MF; QTc: Corrected QT interval; *TP53*^{WT}: Wild-type tumor protein p53 gene; TSS: Total symptom score; WHO: World Health Organization.

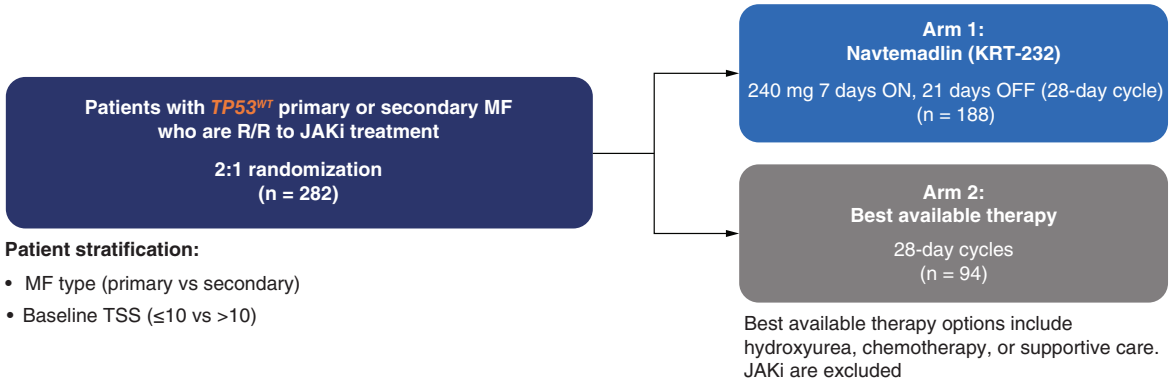

Figure 3. BOREAS phase III study design. *Treatment selection is at the discretion of the investigator. Patients with documented disease progression at any time or those who complete week-24 assessments may crossover to the navtemadlin arm.
D: Day; MF: Myelofibrosis; R/R: Relapsed/refractory; TSS: Total symptom score.

must have intermediate-1, intermediate-2, or high-risk disease (defined by Dynamic International Prognostic Scoring System [DIPSS] [40]); Eastern Cooperative Oncology Group performance status (ECOG-PS) ≤2; and have adequate hematologic function (Table 1). Patients must be R/R to prior JAK inhibitor treatment. Key exclusion criteria include prior MDM2 inhibitor or p53-directed therapy, JAK inhibitor treatment within 28 days prior to screening MRI/CT, JAK inhibitor intolerance, and allogeneic stem-cell transplant.

Study design

Approximately 282 eligible patients are randomized in a 2:1 ratio to navtemadlin (Arm 1: 188 patients) or BAT (Arm 2: 94 patients). Patients are stratified by primary versus secondary MF (PMF vs post-PV-MF or post-ET-MF) and baseline TSS (≤10 vs >10). Navtemadlin treatment is given at a dose of 240 mg orally once daily on days 1–7 in 28-day treatment cycles (Figure 3) based on the dose and schedule established in the phase II study [34]. Patients randomized to BAT will receive one of the following treatment options at the discretion of the investigator in

Table 2. Study end points.

Primary end point	• Spleen volume reduction (SVR) ≥35% at week 24 by MRI/CT (central review)
Key secondary end points	• ≥50% reduction in TSS rate at week 24 (per MFSAF v4.0) • Overall survival • Progression-free survival • Overall SVR ≥35% at any time by MRI/CT (central review) • Spleen response duration • Rate of conversion from red blood cell transfusion dependence to independence at week 24 • Safety

CT: Computed tomography; MFSAF v4.0: Myelofibrosis Symptom Assessment Form version 4.0; SVR: Spleen volume reduction; TSS: Total symptom score.

28-day cycles: anti-cancer therapy, including hydroxyurea, thalidomide, lenalidomide, pomalidomide, cladribine, busulfan, methotrexate, interferon or supportive care, including the erythropoiesis-stimulating agent, danazol, red blood cell (RBC) transfusion, corticosteroids, anagrelide, low-dose aspirin or granulocyte-colony stimulating factor. JAK inhibitors are not permitted. BAT may be given sequentially or in combination as per local treatment guidelines and regional standard of care. Patients who receive BAT with documented disease progression at any time or who complete week 24 assessments may crossover to the navtemadlin arm. Patients will be treated until disease progression, unacceptable toxicity, death, or withdrawal of consent. Patients who discontinue study treatment for any reason will be monitored in long-term follow-up for survival and subsequent anticancer therapy.

All patients receive anti-emetic prophylaxis for nausea/vomiting 30 min prior to and 8 h after each navtemadlin dose on days 1–7 of the treatment cycle when navtemadlin is administered. Anti-diarrheal prophylaxis is given on each day that navtemadlin is taken for at least the first two cycles of therapy.

Study end points & outcome measures

The primary end point is the proportion of patients achieving an SVR ≥35% at week 24 by MRI/CT (central review; Table 2). Key secondary end points include the proportion of patients with ≥50% reduction in TSS (per Myelofibrosis Symptom Assessment Form version 4.0 [MFSAF v4.0] [41]) from baseline to week 24, overall survival (OS), progression-free survival (PFS), overall SVR ≥35% at any time by MRI/CT, spleen response duration (time from initial SVR ≥35% by MRI/CT to first occurrence of disease progression), rate of conversion from RBC transfusion dependence to independence at week 24, and safety.

BOREAS will be considered complete 2 years after the last patient is enrolled, at which time patients who remain on study treatment may be eligible to enroll in a rollover study. Presently, the estimated study completion date is 31 December 2025. A list of trial locations across the globe is available on the BOREAS trial website: www.boreas-trial.com.

Conclusion

The BOREAS study will evaluate the safety and efficacy of navtemadlin versus BAT for the treatment of patients with MF whose disease is R/R to standard of care JAK inhibitor treatment. Patients with $TP53^{WT}$ may also be recruited for the open-label, multicenter phase Ib/II study of navtemadlin combined with ruxolitinib in patients who have shown a suboptimal response following ≥18 week of ruxolitinib treatment (NCT04485260) [42]. The BOREAS study has the potential to establish navtemadlin as a novel therapeutic approach for MF patients who are R/R to JAK inhibitor treatment and would otherwise have limited treatment options.

Supplementary data

An infographic accompanies this paper. To view or download this infographic in your browser please click here: https://www.futuremedicine.com/doi/suppl/10.2217/fon-2022-0901

Author contributions

All the authors were involved in the design and/or conduct of the study. All authors have contributed to the preparation and writing of the manuscript and approved the final manuscript.

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Ethical conduct of research

Signed informed consent is required by patients prior to study initiation. The BOREAS study protocol is approved by the institutional ethics review board of each participating study site. The study is being performed in accordance with the ethical principles of the Declaration of Helsinki and conducted in line with the International Conference for Harmonisation Guidelines for GCP and region-specific laws and regulations.

Data sharing statement

Queries about the ongoing trial can be addressed to boreas-trial@kartosthera.com.

Executive summary

Myelofibrosis

- Myelofibrosis (MF) is a progressive, myeloproliferative neoplasm (MPN) characterized by ineffective clonal hematopoiesis, splenomegaly, progressive bone marrow fibrosis, profound cytopenia and a propensity for transformation into acute myeloid leukemia.
- Although the exact cause of MF is unknown, the pathophysiology of MF in most patients is characterized by driver mutations that dysregulate the Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway.
- JAK inhibitors are the standard of care for MF. Although therapies targeting the JAK/STAT pathway provide symptom control and reduce spleen volumes, they have limited impact on the underlying pathophysiology of the disease.
- There remains an unmet medical need for novel therapeutic approaches with disease-modifying effects in MF, especially for patients who have failed JAK inhibitor treatment.

Navtemadlin (KRT-232)

- Navtemadlin is a potent, selective, orally available murine double minute 2 (MDM2) inhibitor that restores p53 activity to drive apoptosis in *TP53* wild-type MF.
- Elevated circulating $CD34^+$ cells that overexpress MDM2 are a characteristic feature of MF.
- By inhibiting MDM2, navtemadlin restores p53 activity, which regulates Bcl-2 family proteins to induce apoptosis.
- Navtemadlin has demonstrated a manageable safety profile and promising clinical activity, including reductions in spleen volume and improvements in symptom burden in a phase II study, and has the potential for disease-modifying effects in MF patients who are relapsed/refractory (R/R) to JAK inhibitor treatment.
  - Spleen volume responses correlated with decreased peripheral $CD34^+$ cell counts and TNFα levels, improved fibrosis scores, and reduction of MPN driver mutation burden.

BOREAS phase III study

- BOREAS is an open-label, phase III randomized, controlled study of navtemadlin versus best available therapy (BAT) in patients with PMF, post-PV MF, or post-ET MF who are R/R to JAK inhibitor treatment.
- Eligible patients will be randomized 2:1 to receive oral navtemadlin 240 mg once daily on days 1–7 of 28-day treatment cycles or BAT.
- The primary end point is the proportion of patients with a spleen volume reduction ≥35% at week 24.
- Secondary end points will include the proportion of patients with ≥50% reduction in total symptom score, overall and progression-free survival, spleen response duration, red blood cell transfusion dependency conversion and safety.

Conclusion

- The BOREAS phase III study has the potential to establish navtemadlin as a novel treatment for patients with MF whose disease is R/R to JAK inhibitor treatment.

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