Title: A two-tiered, phase II, rule-based, intra-patient dose escalation study to investigate safety and feasibility of vactosertib (TEW-7197) as monotherapy or in combination with ruxolitinib for the treatment of anemic patients with Philadelphia chromosome-negative Myeloproliferative Neoplasms (Ph-neg MPNs)

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Statement of Compliance

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
ddPCR	Droplet Digital Polymerase Chain Reaction
DL	Dose Level
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
EPO	Erythropoietin
ESA	Erythropoiesis Stimulating Agent
ET	Essential Thrombocythemia
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HSPC	Hematopoietic Stem and Progenitor Cells
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research
MF	Myelofibrosis
MFI	Mean Fluorescence Intensity
MPNs	Myeloproliferative Neoplasms
MTD	Maximum Tolerated Dose
NOAEL	No Observed Adverse-Effect-Level
Ph-neg	Philadelphia Chromosome Negative
PHI	Protected Health Information
PV	Polycythemia Vera
PI	Principal Investigator
REDCap	Research Electronic Data Capture
RCM	Red Cell Mass
SAE	Serious Adverse Event
SOC	Standard of care
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAP	Unanticipated Problem
VAF	Variant Allelic Frequency
WB	Whole Blood
WCM	Weill Cornell Medicine
WHO	World Health Organization

1. Protocol Summary

Full Title: A two-tiered, phase II, rule-based, intra-patient dose escalation study to investigate safety and feasibility of vactosertib (TEW-7197 for the treatment of anemic patients with Philadelphia chromosome-negative Myeloproliferative Neoplasms (Ph-neg MPNs)

Short Title: TGFβR1 inhibition in Ph-neg MPNs

Clinical Phase: II

Principal Investigator: Joseph M Scandura, M.D., Ph.D.

Study Description: This is a two-tiered single arm Phase 2 trial of vactosertib (TEW-7197) for the treatment of anemia in Ph-neg MPNs. Both tiers use a rule-based, accelerated dose escalation scheme to efficiently assess the potential of vactosertib to safely and effectively treat anemic patients with Ph-neg MPNs. The first tier of this trial (Tier 1) is an intra-patient dose finding study in 12 patients that uses a low starting dose of vactosertib for all patients. Treatment dose is escalated according to prospectively-defined rules, and a toxicity and treatment effect algorithm (*Table 3 in section 7*) during the period of 16 weeks (4 treatment cycles). If pre-established efficacy and safety endpoints are met *(section 12.1)*, then Tier 1 of the study will be followed by a Tier 2 expansion study with an additional 25 patients for a period of 24 weeks (6 treatment cycles).

Vactosertib will be administered in combination with stable dose of current therapy. Prior to enrollmentpatients must be on a stable dose of their current therapy for 3 months prior to entering the study. For patients not receiving cytoreductive therapies (e.g., interferon, hydroxyurea, DNA hypomethylating agents or other cytotoxic chemotherapy) must be off their most recent for a period of at least 14 days or 5 half-lives, whichever is longer. Supportive care measures including packed red blood cell (PRBC) transfusions for HGB <7g/dL, or symptomatic anemia, will be permitted. Administration of erythropoiesis stimulating agents (ESAs), however, will not be permitted on the trial (patients recruited would have serum EPO >125 U/L above which the benefit of ESAs is not supported)[1].

Sample Size: Total = 37 subjects (N = 12 for Tier 1, N = 25 for Tier 2)

Enrollment: This study will enroll 37 subjects and screen up to 100 subjects**.**

Study Population: Patients of age ≥ 18 with anemia due to Ph-neg MPNs

Enrollment Period: 72 months

Study Design:

This is a two-tiered single arm Phase 2 trial of vactosertib (TEW-7197) for the treatment of anemia in Ph-neg MPNs. Both tiers use a rule-based, accelerated dose escalation scheme to efficiently assess the potential of vactosertib to safely and effectively treat anemic patients with Ph-neg MPNs. The first tier of this trial (Tier 1) is an intra-patient dose finding study in 12 patients that uses a low starting dose of vactosertib for all patients. Treatment dose is escalated according to prospectively-defined rules, and a toxicity and treatment effect algorithm (*Table 3 in section 7*) during the period of 16 weeks (4 treatment cycles). If pre-established efficacy and safety endpoints are met *(section 12.1)*, then Tier 1 of the study will be followed by a Tier 2 expansion study with an additional 25 patients for a period of 24 weeks (6 treatment cycles).

Study Duration:

24 months (4 months for tier 1, 6 months for tier 2, and follow-up after intervention (2 months for patients who come off study and 12 months for patients completing study).

Participant Duration: Approximately 18 months

Study Agent: Vactosertib

Intervention Description:
Vactosertib is given oral twice a day for 5 days followed by 2 days off. The starting DL is 50mg BID (*see Table 2 in section 6 for DLs*). A cycle is defined as 4 weeks of treatment.**Primary Objective:**

- To establish a safe and tolerable dose and schedule of vactosertib in Ph-neg MPNs as determined by the study dose escalation algorithm (Table 3 in section 7).
- To preliminarily assess efficacy of vactosertib in treating anemic patients with Ph-neg MPNs as reported by symptomatic, splenic and/or erythropoietic response (section 9.1).
- To determine the safety and tolerability of vactosertib administered alone or in combination with cytoreductive therapies for MPN (approved and standard of care).

Secondary Objectives:

- To evaluate on target molecular activity of vactosertib in anemic patients with Ph-neg MPNs as determined by the following parameters:
    - Molecular response, measured by change in blood (and/or marrow) variant allelic frequency (VAF) of MPN driver mutations (JAK2, CALR or MPL).
    - Histologic response, measured by change in bone marrow biopsy cellularity and fibrosis grade.
    - SMAD2/3 phosphorylation measured by flow cytometry of peripheral blood and/or bone marrow hematopoietic cells and/or by immunohistochemical staining of bone marrow biopsy sections.
- To identify common toxicities of vactosertib in patients with Ph-neg MPNs.

Exploratory Objectives:

To assess the stem cell directed effect of vactosertib by quantifying the VAF of MPN driver mutations in stem, progenitor and mature cell populations isolated from PB or BM samples before and after treatment with vactosertib.

Endpoints:

Primary Endpoints: (Safety and Efficacy)

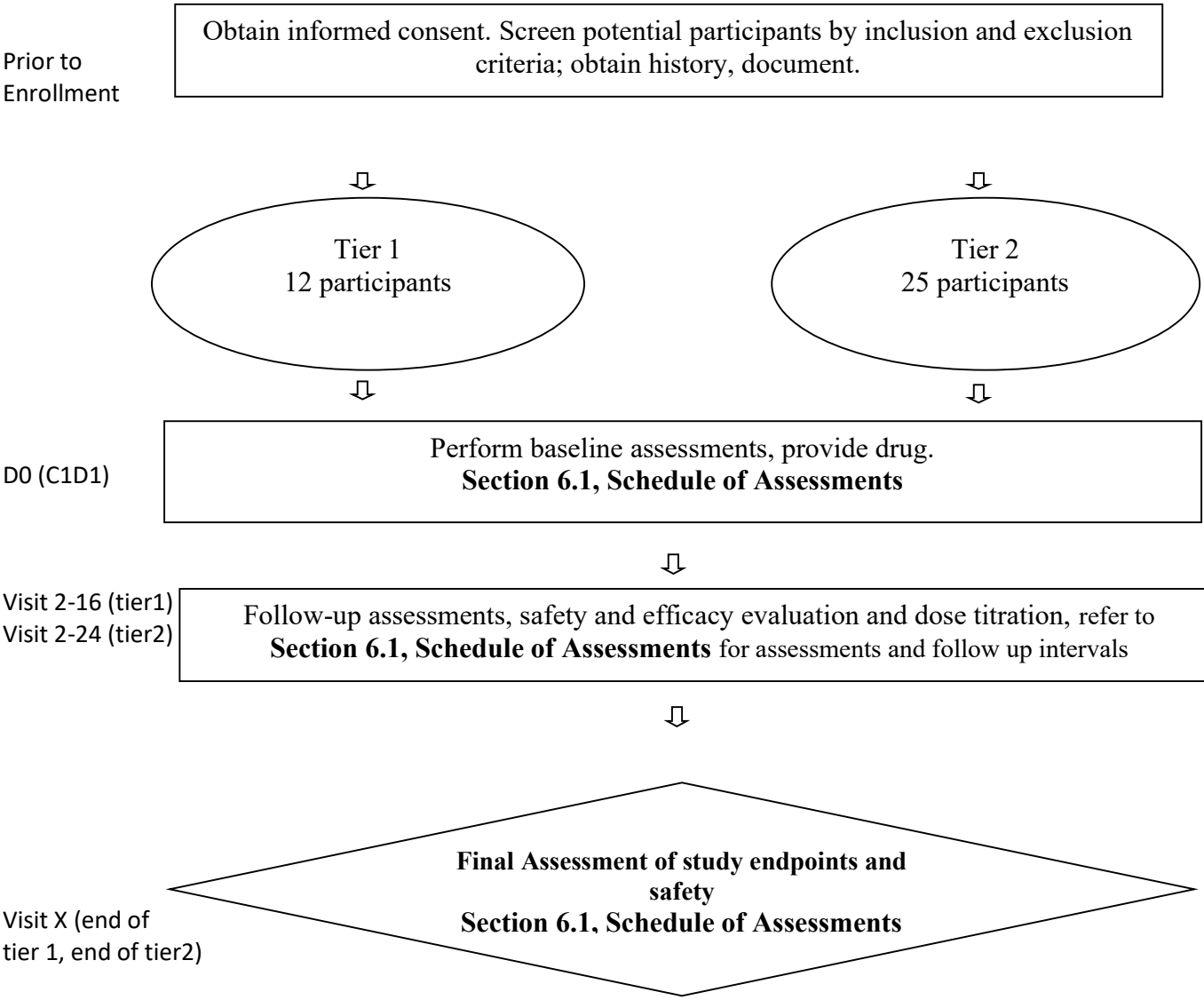
- Tier 1 (Safety endpoints):
  - Define the safest, minimally effective starting DL for Tier 2 (section 5.3.5.1).
  - Identify DLTs and, possibly the MTD of vactosertib in patients with MPN
- Tier 2 Efficacy endpoints (section 9.1):
  - Erythropoietic response as defined by the IWG-MRT criteria
  - Clinical response in symptoms as defined by IWG criteria.
  - Splenic response as defined by IWG criteria.[2,3]
- Tier 2 Safety endpoints: Identify DLT and, possibly MTD

Secondary Endpoints:

- Histologic response defined by any reduction in grade of bone marrow fibrosis by histopathologic assessment at 16 weeks.
- Molecular response defined by a decrease in VAF of MPN-driver mutations (eg. JAK2, CALR, and MPL allelic ratio) in blood and/or bone marrow cells.
- Pharmacodynamic Response defined as any of the following:
  - Reduced immunohistochemical staining for SMAD2/3 phosphorylation in bone marrow biopsy sections *(See Figure 1*).
  - Reduced mean fluorescence intensity (MFI) of SMAD2/3 phosphorylation staining in peripheral blood and/or bone marrow HSPCs or mature progeny as assessed by flow cytometry *(See Figure 2).*
- The incidence of hematologic toxicities, infections, disease progression, thrombosis events, and the probability of overall and progression free survival, will be monitored.

1.1 Schema

***Section 6.1, Schedule of Assessments**, e.g., Visit 1; Visit 2; etc.*



1.2 Study Objectives

1.2.1 Primary Objectives

- To establish a safe and tolerable dose and schedule of vactosertib in Philadelphia chromosome negative (Ph-neg) Myeloproliferative Neoplasms (MPNs).
- To preliminarily assess efficacy of vactosertib in treating anemic patients with Ph-neg MPNs as reported by symptomatic, splenic and/or erythropoietic response.
- To determine the safety and tolerability of vactosertib administered alone or in combination with available cytoreductive therapies for MPN (approved and standard of care).

1.2.2 Secondary Objectives

- To evaluate the on target molecular activity of vactosertib in anemic patients with Ph-neg MPNs. This will be determined by the following parameters:
  - Molecular response, measured by change in blood (and/or marrow) allelic ratio of MPN driver mutations (JAK2, CALR or MPL).
  - Histologic response, measured by change in bone marrow biopsy cellularity and fibrosis grade.
  - SMAD2/3 phosphorylation measured by flow cytometry of peripheral blood and/or bone marrow hematopoietic cells or by immunohistochemical staining of bone marrow biopsy sections.
- To identify common toxicities of vactosertib in patients with Ph-neg MPNs.

1.2.3 Exploratory Objectives

To assess the stem cell directed effect of vactosertib by quantifying the VAF of MPN driver mutations in stem, progenitor and mature cell populations isolated from PB or BM samples before and after treatment with vactosertib.

2. Background

2.1 Disease

Ph-neg MPNs are clonal hematologic malignancies categorized into the 3 major subtypes of Essential Thrombocythemia, Polycythemia Vera, and Primary Myelofibrosis by the WHO criteria. The Ph-neg MPNs are phenotypically diverse with very different disease course and overall survival[4]. However, a common issue across the different subtypes particularly during advanced stages is anemia and its treatment is currently limited to supportive care.

2.2 Investigational Agent/Device

(from MedPacto Investigation Brochure (IB) section 6: Summary of Data and Guidance for the Investigator)[5]

2.2.1. Pharmacology and Toxicology

Vactosertib (INN name, other names: TEW-7197, EW-7197, EW7197) is a highly selective, potent inhibitor of the protein serine/threonine kinase activity of transforming growth factor (TGF)-β receptor type 1 (TGFBR1; also known as activin receptor-like kinase 5 [ALK5]). Vactosertib inhibits the phosphorylation of the ALK5 substrates SMAD2 and SMAD3, as well as the intracellular signaling of TGFβ.

Nonclinical studies conducted to date include in vitro and in vivo pharmacology studies, and PK studies in mice, rats, and dogs. The safety of vactosertib was evaluated in an in vitro human hERG assay, in a CNS and respiratory safety study in rats, and in a cardiovascular safety study in conscious, telemetry-instrumented Beagle dogs. Vactosertib produced a concentration-dependent inhibition of hERG-mediated potassium currents from 10 to 100 µM (IC_{50} = 31.04 µM); no inhibition was observed at 1 µM. No treatment-related changes in the safety pharmacology studies on the central nervous and respiratory systems tested in rats and dogs were observed after oral administration of vactosertib at doses of up to 100 mg/kg. With respect to cardiovascular effects of vactosertib in Beagle dogs, a NOAEL of at least 100 mg/kg was established for orally administered vactosertib.

The toxicological profile of vactosertib has been evaluated in a single-dose GLP study in rats, repeated-dose non-GLP studies up to 14 days in rats and dogs, repeated-dose GLP studies up to 28 days in rats and dogs, a 13-week repeated-dose GLP study in rats, and in GLP genotoxicity studies.

Results from the single-dose toxicity study in rats suggested the NOAEL to be 100 mg/kg, the highest dose tested. Based on the results from the 4-week repeated-dose toxicity studies, the NOAEL was considered to be 20 to 50 mg/kg/day in rats. However, the MTD was considered to be less than 100 mg/kg/day when administered orally to dogs for 14 days. Genotoxicity studies did not show any potential genetic toxicity concerns. The pharmacokinetics of vactosertib was evaluated using plasma concentration data collected from patients with advanced-stage solid tumors who were enrolled in a Phase 1 study (NCT02160106; First-in-Human Dose-Escalation Study of TEW-7197 Monotherapy in Subjects with Advanced Stage Solid Tumors). The plasma concentration-time data for vactosertib were obtained from patients with advanced-stage solid tumors who orally received vactosertib tablets once or twice daily under fasted conditions for a 28-day treatment cycle (5 day on/ 2 day off regimen). After the first oral administration of vactosertib, the maximum plasma concentration (C_{max}) of vactosertib was achieved at a median time (t_{max}) ranging from 0.52 to 1.77 hours across all doses studied. Following the attainment of the C_{max}, the plasma concentrations of vactosertib declined in a multi-exponential manner with an average apparent terminal half-life of 1.86 to 5.47 hours across all doses studied. After repeated oral administrations once daily for five days, the plasma concentrations appear to reach a steady state, as supported by the short apparent terminal half- lives in the range from 0.4 hours to 18.1 hours. Following the oral administrations for 5 days, the accumulation of vactosertib was negligible with the median accumulation ratio of AUC (RAUC) ranging from 0.75 to 1.16. The AUC values of vactosertib demonstrated an increasing trend in proportion to the escalation vactosertib.

The plasma pharmacokinetic parameters for vactosertib in NCT02160106, following the first (Cycle 1, Day 1) and multiple (Cycle 1, Day 5) oral administrations are summarized in Table X below.

Table 1: Summary of the plasma pharmacokinetic parameters of vactosertib estimated in patients with advanced-stage solid tumors

Day 1								
Parameter	30 mg QD (N = 3)	60 mg QD (N = 3)	100 mg QD (N = 6)	140 mg QD (N = 4)	200 mg QD (N = 4)	260 mg QD (N = 5)	340 mg QD (N = 4)	200 mg BID (N = 6)
$AUC_{0\text{-last}}$ (h*ng/mL)	980 (59.4)	979 (40.3)	4640 (24.4)	5810 (70.3)	4910 (93.5)	10500 (59.2)	6960 (83.4)	9690 (51.1)
C_{max} (ng/mL)	327 (112.1)	437 (11.6)	1310 (63.8)	1010 (67.7)	1330 (137.8)	2950 (45.5)	1490 (35.4)	2770 (70.9)
t_{max} (h)[a]	0.52 (0.50-1.50)	1.5 (0.50-1.50)	1.11 (1.00-3.00)	1.77 (0.50-3.00)	1.24 (0.98-4.00)	1 (0.67-4.02)	1.06 (0.50-4.03)	1 (0.50-1.50)
$t_{1/2}$ (h)[b]	2.52 (0.930)	1.69 (0.814)	3.25 (1.59)	5.71 (3.91)	3.10 (1.14)	2.92 (1.01)	4.39 (1.33)	3.21 (0.563)
Day 5								
Parameter	30 mg QD (N = 3)	60 mg QD (N = 3)	100 mg QD (N = 6)	140 mg QD (N = 4)	200 mg QD (N = 4)	260 mg QD (N = 5)	340 mg QD (N = 4)	200 mg BID (N = 6)
AUC0-last (h*ng/mL)	875 (56.1)	829 (129.4)	3500 (32.9)	5340 (48.7)	4700 (44.3)	8410 (45.3)	7500 (45.4)	6570 (31.0)
Cmax (ng/mL)	318 (63.1)	481 (43.7)	866 (70.1)	1460 (39.7)	1900 (56.7)	2250 (50.7)	1840 (32.2)	2040 (43.6)
t_{max} (h)[a]	1 (1.00-3.00)	1.33 (0.50-1.50)	1.3 (0.50-2.00)	1.5 (1.00-1.55)	1.48 (1.00-1.50)	1.5 (0.62-3.95)	0.52 (0.50-2.05)	1 (0.53-1.10)
$t_{1/2}$ (h)[b]	1.99 (0.969)	1.71 (0.970)	5.46 (4.21)	2.66 (0.974)	2.23 (0.500)	4.05 (2.41)	6.92 (5.07)	3.68 (1.49)

Abbreviations: QD = once daily; BID = twice daily; $AUC_{0\text{-last}}$ = area under the concentration-time curve from hour 0 to the last measurable concentration; BID = twice daily; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration over a dosing interval; t_{max} = time of maximum plasma concentration; $t_{1/2}$ = apparent terminal elimination half-life; CV = coefficient variation..

Vactosertib PK analysis was undertaken in a prospective, open label, multicenter, dose escalation and dose expansion study in patients with low or intermediate risk myelodysplastic syndrome (NCT03074006; Phase 1/2 Study of TEW-7197 Monotherapy in Patients with Low or Intermediate Risk Myelodysplastic Syndromes (MDS)). Results are shown in Table 2 below.

Table 2: Summary of the plasma pharmacokinetic parameters of vactosertib estimated in patients with myelodysplastic syndromes.

	Day 1			Day 5		
Parameter	100 mg BID[a] (N = 3)	200 mg BID[a] (N = 3)	300 mg BID[b] (N = 3)	100 mg BID[a] (N = 3)	200 mg BID[a] (N = 3)	300 mg BID[b] (N = 3)
$AUC_{0\text{-last}}$ (h*ng/mL)	2059 (25%)	8332 (3%)	12329 (11491)	1155 (36%)	5409 (27%)	6868 (8355)
Cmax (ng/mL)	1226 (89%)	3746 (3%)	4393 (4490)	499 (92%)	2324 (9%)	4337 (5790)
t_{max} (h)	1 (0.5-2)	0.5 (0.50-2)	1 -0.96	1 (0-2)	0.4 (0.4-0.5)	0.5 0.52
$t_{1/2}$ (h)	2.1 (77%)	2.3 (23%)	2.3	2.8 (31%)	2.0 (20%)	2.6

[a] geometric mean (CV%), except Tmax shown as median (minimum-maximum).

[b] C_{max} and $AUC_{0\text{-}last}$ are expressed as arithmetic mean of 3 subjects (values of 2 subjects except 1003). $T_{1/2}$ is expressed as arithmetic mean of 2 subjects. T_{max} is shown as median of 3 subjects (median of 2 subjects except 1003).

2.2.2. Drug-Drug interactions

No formal drug interaction trials have been conducted with vactosertib. In nonclinical studies, vactosertib was shown to be a substrate for efflux transporters MDR1, BCRP, and MRP1, but not MRP2. Vactosertib does not appear to be a substrate for the uptake transporters OCT1, OCT2, NTCP, OAT1, OAT3, OATP1B1, OATP1B3, and OATP2B1. In vitro, vactosertib was a strong inducer of MDR1 at concentrations as low as 0.1 μM and induced CYP1A2, CYP2B6, CYP3A4, and UGT1A1 at concentrations as low as 1.0 μM and UGT1A4 at 10 μM. Vactosertib inhibited CYP3A4, CYP2C8, and CYP2D6 with IC_{50} values of 8.9, 21.8, and 17.9 μM, respectively, and UGT1A1 with an IC_{50} value of 13.5 μM. Vactosertib also inhibited MDR1 transport (IC_{50} 10 μM) and the uptake transporters OCT1, OCT2, OAT1, and OATP1B1 with IC_{50} values of 4, 5, 17, and 6 μM, respectively. In a non-clinical study, sorafenib did not substantially inhibit vactosertib metabolism. However, vactosertib inhibited formation of sorafenib metabolites when tested in human liver microsomes. CYP3A4 is an enzyme which is inhibited substantially by vactosertib, and CYP3A4-mediated sorafenib N-oxidation (M2), hydroxylation (M3) and desmethylation (M4) were substantially inhibited by vactosertib with IC_{50} values of 3.1, 5.4, and 3.6 μM, respectively. The potential for in vivo inhibition of human CYP3A4 was evaluated by calculating R-values, which were >1.75 and >1.80 with doses of vactosertib 100 mg and 140 mg, respectively.

For CYP450, vactosertib did not show significant inhibition of CYP1A2, 2A6, 2B6, 2C9, or 2C19 activities in human liver microsomes (IC50 > 50 μM). CYP2C8-mediated rosiglitazone hydroxylation and CYP2D6-mediated dextromethorphan O-demethylation were slightly inhibited by vactosertib, with IC50 values of 21.8 and 17.9 μM, respectively. Midazolam 1'-hydroxlyation and imatinib N-demethylation were moderately inhibited in the presence of vactosertib, with IC50 values of 13.4 and 8.9 μM, respectively.

Vactosertib appears to display competitive inhibition against midazolam 1'-hydroxylation, imatinib *N*-demethylation, and 17β-estradiol-3-glucuronidation, with estimated Ki values of 2.6, 1.4, and 8.9 μM in human liver microsomes, respectively. Considering the in vitro results, drug interactions may need to be considered when vactosertib is co-administered with CYP3A substrates with narrow therapeutic ranges.

Although no formal drug interaction trials have been conducted with vactosertib, the most likely interacting drugs are those metabolized by CYP3A, CYP2C8 or CYP2D6. Midazolam, rosiglitazone and dextromethorphan should be used with caution in patients taking vactosertib.

Major metabolites of vactosertib (EW-7332, EW-7434, and INT-EW-8) did not substantially inhibit the activities of CYPs and UGTs (IC_{50} > 50 μM) except for marginal inhibition of CYP1A2 by EW-7332. All three metabolites significantly increased mRNA expressions of CYP2B6, UGT1A1, and UGT1A4 in human hepatocytes at higher than 1 μM (> 2-fold increase) to a similar extent. The metabolites did not show any inhibitory effects on efflux transporters, P- gp, BCRP, MRP1 or MRP2 (IC_{50} > 100 μM). EW-7332 inhibited transport activities of OCT1 and OAT3 with IC_{50} values of 0.5

and 2.0 μM, respectively. EW-7434 only inhibited transport activity of OAT3 (IC_{50}, 1.9 μM). On the contrary, the metabolite INT-EW-8 showed strong inhibition of OCT1, OCT2, OAT1 and OAT3 with IC_{50} values of 0.4, 1.6, 0.7 and 1.4 μM, respectively. The activities of OATPs were slightly inhibited at 100 μM of the metabolites. Unlike the parent vactosertib, the metabolites did not affect mRNA expression levels of MDR1, BCRP, and OATP1B1 in human hepatocytes.

2.2.3. Adverse reactions

In the phase 1 study of vactosertib (NCT02160106, MP-001), 29 patients were treated with vactosertib once daily in 7 cohorts at the dose range of 30 ~340 mg and 5 patients in 200 mg twice daily cohort (Cohort 8) for 5 days with 2 days off.

In the phase 1/2 clinical trial (NCT03074006) for patients with low or intermediate risk myelodysplastic syndrome, vactosertib 200 mg BID cohort completed cycle 1 (28 days) without dose-limiting toxicity. In the 3 patients enrolled in the third cohort of vactosertib 300 mg BID, no patient experienced DLT. The safety and efficacy evaluation of vactosertib 300 mg BID is currently underway in MP-VAC-204 (NCT03724851) and GC-01 (NCT03698825) trials.

Vactosertib was safe and well tolerated, and the maximum tolerated dose was not determined. The most frequent TRAEs were mainly mild to moderate including fatigue, nausea, anorexia, and headache, while Grade 3/4 abdominal pain, ALT/AST elevation, cerebrovascular accident, and pulmonary edema were reported. One DLT of stroke was seen at 100 mg only daily (QD) in a 72-yr-old penile cancer patient who was ex-smoker and history of pulmonary thromboembolism. He developed stroke on C1D6 following 5-day 100 mg vactosertib treatment and was hospitalized with diagnosis of brain infarction with irregular plaque in both carotid arteries. After standard treatment, he recovered on C1D8 with sequelae of difficulty in fine motor movement.Adverse events incurred in MP-VAC-105 (Food Effect) clinical phase 1 study and assessed to have causal relationship with vactosertib are as follows headache, nausea, diarrhea. Serious adverse event assessed to have causal relationship with vactosertib incurred in MP-VAC-105 (Food Effect) clinical phase 1 study is presyncope. Finally, no abnormalities in echocardiography or cardiac enzyme levels were reported in this study but echocardiography with Doppler and cardiac enzyme levels should be performed to monitor cardiac valvulopathy or potential myocardium damage at the screening and every 12 weeks and at the end of the treatment. Unexpected serious adverse events that have been determined to be related to vactosertib in the ongoing Phase 1b/2a trial MP-VAC-203 were one case of interstitial lung disease and one case of lung infiltration. Unexpected serious adverse events that have been determined to be related to vactosertib in the ongoing Phase 1b/2a trial MP-VAC-204 were one case of asthma and one case of tubulointerstitial nephritis.

2.3. Rationale

Anemia and bone marrow fibrosis are prominent features of higher-risk Philadelphia chromosome negative myeloproliferative neoplasms (Ph-neg MPNs) and both portend a worse prognosis. Current therapies for this population, outside of clinical trials, is supportive and directed towards improving symptoms and reducing thrombotic risk. There is no single standard approach to treating these diseases. Supportive measures (e.g., transfusions,

erythroid stimulating agents), cytoreductive agents (e.g., hydroxyurea or interferon), ruxolitinib for symptomatic disease, and a panoply of other non-FDA approved therapies (lenalidomide/prednisone, DNA hypomethylating agents, etc…) are used to temporize symptoms or normalize blood counts. Cytoreductive therapies and ruxolitinib typically worsen anemia[6]. Even patients with myelofibrosis (MF) who have good symptom control on ruxolitinib, generally need to pursue other therapies within three years due to disease progression[7,8] . In transplant ineligible patients, there is no effective therapy for anemia nor any means to reverse marrow fibrosis, so management is primarily supportive and includes erythrocyte transfusions and erythropoiesis stimulating agents (ESAs) for symptomatic anemia[1,9]. But ESAs are often ineffective in this population and patients frequently become refractory to repeated transfusion. This is an area of unmet need where clinical trials are needed to identify new treatment approaches.

A promising approach to overcome some of the morbidities associated with advanced MPNs is therapeutic targeting of the Transforming Growth Factor beta (TGFβ) pathway. TGFβ, and members of the TGFβ superfamily, have been studied as potential regulators of erythropoiesis[10–13]. Specifically, TGFβ induces hematopoietic stem cell (HSC) quiescence, prevents progenitor cell proliferation and accelerates terminal erythroid maturation through canonical SMAD-dependent signaling pathways [14,15]. The Scandura lab has recently found that TGFβ signaling suppresses production of early erythroid committed progenitors and that blockade of TGFβ signaling can sensitize to erythropoietin. Therefore, inhibition of TGFβ could promote regeneration of normal HSCs and proliferation of erythroid progenitors to treat the underlying hypoproliferative anemia in advanced MPNs.

Inhibitors of TGFβ pathway have yielded encouraging pre-clinical results in the management of anemia due to ineffective erythropoiesis resulting from myelodysplastic syndrome (MDS)[16–18] and Fanconi anemia[19]. In MDS, a phase II clinical trial of an inhibitor of ALK5 (TGFβ receptor I, TGFBR1), Galunisertib, demonstrated hematologic improvement with reduced transfusion dependency in 10 of 38 (26%) patients with low to intermediate risk MDS [20]. Two new ligand traps (luspatercept and sotatercept) have shown promising initial results in anemic patients with MDS[18] and MPNs (clinicaltrials.gov NCT03194542 & NCT01712308) and luspatercept met its primary endpoint of hematologic efficacy in the MEDALIST phase III clinical trial (clinicaltrials.gov NCT02631070).

In MF, TGFβ is a potent inducer of fibrosis and several studies have explored its crucial role in disease pathogenesis. Indeed, MF megakaryocytes (MKs) release significantly higher levels of TGFβ compared to MKs of healthy controls, and genetic ablation or inhibition of TGFβ pathway signaling cured important features of these diseases in several murine models [21–26]. Aberrant TGFβ expression also appears to play a pathogenic role in fibrotic progression of polycythemia vera (PV), essential thrombocythemia (ET)[27] and other hematologic malignancies[28]. We have found the bone marrow of virtually all patients with MPNs have evidence of abnormal TGFβ signaling as reported by nuclear SMAD2/3 phosphorylation (Figure 1).

The rationale for TGFβ inhibition in the treatment of myelofibrosis is based on our hypothesis and extensive pre-clinical data that blocking excess TGFβ found in MPN bone marrow will release suppression of normal hematopoiesis thereby contributing to improved blood counts and reduced MPN mutation variant allele frequency (VAF) [29]. Because we have also found in

preclinical models that blockade of TGFβ can sensitize the erythropoietic response to ESAs, we also anticipate that blockade of TGFβ signaling will improve cytopenias, notably anemia, in patients with advanced MPNs. We believe the preferential advantage conferred upon normal rather than MPN hematopoietic stem and progenitor cells (HSPCs) is due to refractoriness of MPN HSPCs to the cytostatic activity of TGFβ signaling. As a potent, orally-active inhibitor of ALK5, with favorable pharmacokinetics and promising early phase results demonstrating feasibility and tolerability in cancer patients, vactosertib is an appealing test agent for treatment of anemia and fibrosis in patients with Ph-neg MPNs.

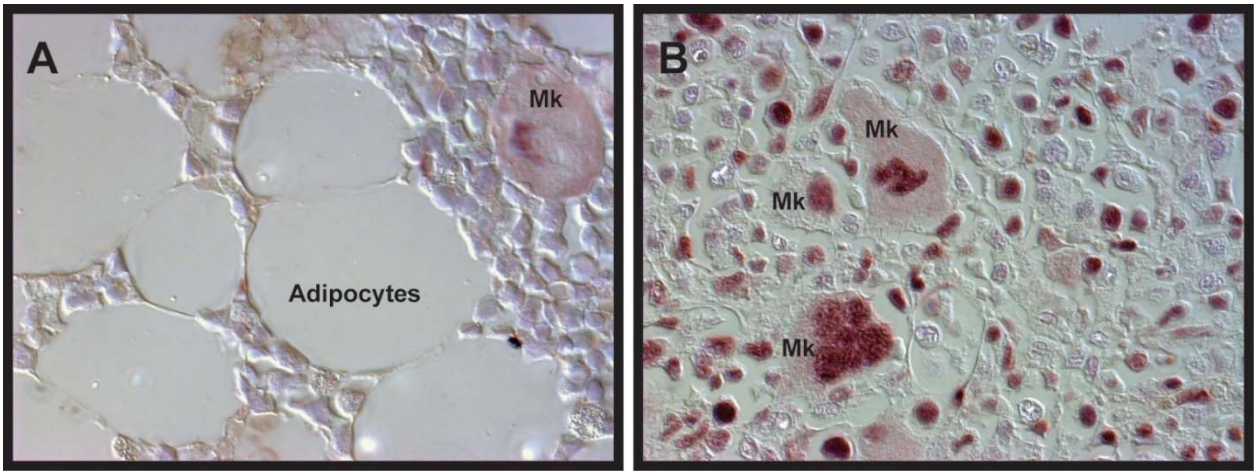


Figure 1: TGFβ Signaling Is Increased in MPN Bone Marrow: Bone marrow biopsy sections from normal (A) and patient with MPN (B) are shown. Immunohistochemsitry for SMAD2/3 phosphorylation is shown as brown nuclear signal. Megakaryocytes are indicated by Mk.

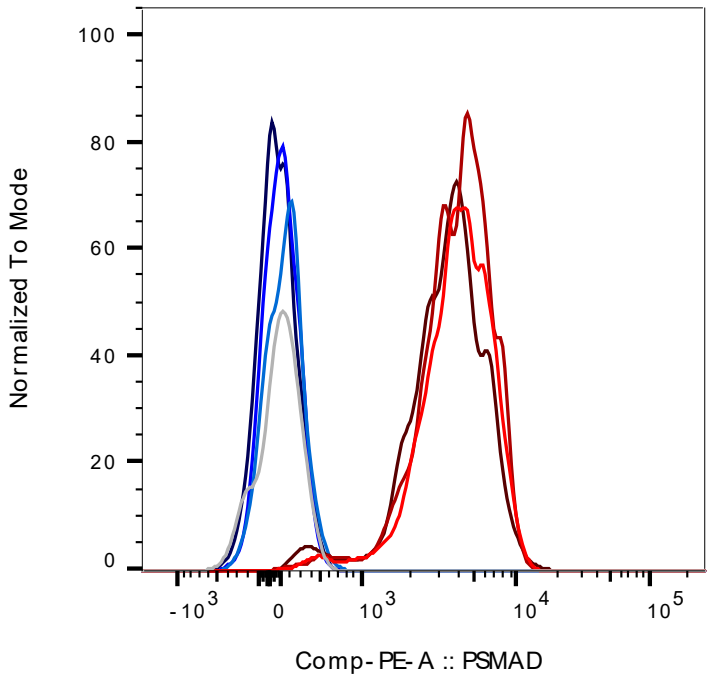


Figure 2: TGFβ Signaling Detected by Intracellular Flow Cytometry of Bone Marrow Cells: **Histograms of intracellular immunofluorescence staining of bone marrow hematopoietic stem cells are shown for normal mice (red colors) or mice with TGFβ1 knocked out (blue histograms) or for the fluorescence minus one control with no secondary antibody to detect phospho-Smad2/3. These results show the utility of intracellular flow cytometry to report TGFβ signaling in well-defined hematopoietic subpopulations.**

2.4 Risk/Benefit Assessment

Vactosertib is a potent, orally-active inhibitor of ALK5, with favorable pharmacokinetics and safety profile (*see section 2.2)*. The benefit of using vactosertib is based on the promising preclinical data of the effectiveness of TGFβ pathway inhibition in the treatment of anemia (*see section 2.3)*. This is also evidenced by the efficacy of a different TGFβ pathway inhibitor in the treatment of anemia in Myelodysplastic Syndrome (MEDALIST phase III trial, www.clinicaltrials.gov NCT02631070). An additional benefit of using vactosertib is the potential for a disease modifying effect by targeting the MPN stem cell. This is evidenced by several studies demonstrating that the TGFβ pathway is essential in the pathogenesis of MPNs and inhibiting this pathway can treat marrow fibrosis as well (*see section 2.3)*. Finding agents with stem cell directed activity is critical in the management of MPNs as there are currently no curative therapies aside from transplant. Therefore, the many potential benefits of vactosertib likely outweigh the few potential risks.

2.5 Correlative Studies Background

2.5.1. Correlating clinical endpoints with SMAD 2/3 phosphorylation.

TGFβ signals via a heterodimeric receptor pair TGFβR2 and TGFβR1 (ALK5). TGFβ binding to TGFβR2 activates TGFβR1 thereby inducing it to phosphorylate the intracellular messenger proteins SMAD2 & SMAD3. For these reasons, measuring SMAD2/3 phosphorylation is a good biochemical reporter of TGFβR1 activity. Because vactosertib is a TGFβR1 inhibitor, measuring SMAD2/3 phosphorylation (pSMAD2/3) is a way to monitor vactosertib activity in the body. Flow cytometry is a tool that allows for cell mixtures such as blood to be decorated using antibodies to identify different subpopulations of cells within the mixture. Flow cytometry can also be used to assess pSMAD2/3 phosphorylation with the signal intensity reporting the degree of pSMAD2/3 within each cell (Figure 2). In this way the pSMAD2/3 mean fluorescence intensity (MFI) can be used to report the average TGFβR1 signaling in a subpopulation of cells.

2.5.2 Correlating clinical endpoints with the VAF of hematopoietic stem, progenitor and mature cell subpopulations.

Monitoring whole blood (WB) variant allele frequency (VAF) of the MPN driver mutation is routinely done in clinical trials to measure molecular responses. Molecular responses as measured by WB VAF have a general correlative trend with hematologic response. However, the molecular response does not correlate as well with bone marrow response[30]. Therefore, WB VAF monitoring alone is a suboptimal method for determining the clinical efficacy of the investigational drug on a molecular level. This is primarily because WB is predominantly granulocytes and other mature hematopoietic cells with a <1% contribution from the stem

and progenitor cell compartment. It was found that the VAF at the level of stem and progenitor cells varies from that of the mature cells and can differ amongst MPN phenotypes[31].Since MPNs originate from hematopoietic stem cell, identifying the change in VAF in the CD34+ hematopoietic compartments is likely to be informative of a potential disease modifying activity of an investigational agent. We hypothesize that molecular responses on the level of stem and progenitor cells correlate with bone marrow responses and the correlative studies on research blood samples will determine this. The blood will be deconvoluted into immunophenotypically defined hematopoietic subpopulations using a combination of Ficoll separation, CD34+ immunomagnetic selection, and finally fluorescence-activated cell sorting (FACS). The VAF of the sorted populations will be determined by digital droplet polymerase chain reaction (ddPCR).

3. Study Design

3.1 Overall Design

- This is a two-tiered single arm phase 2 trial of vactosertib. Both tiers use a rule-based, accelerated dose titration scheme to efficiently assess the potential of vactosertib to safely and effectively treat anemic patients with Ph-neg MPNs. The two-tier design of this phase II study serves to limit exposure of subjects to vactosertib if we observe unexpected toxicity in the treatment of MPN patients in tier 1 before proceeding to the larger/ longer tier 2 portion of the study. The rule-based accelerated dose titration allows quick identification of the minimally effective dose range and therefore approximating “real world” clinical practice because it allows individualized dose adjustments.

3.2 Scientific Rationale for Study Design

The rationale for TGFβ inhibition in the treatment of myelofibrosis is based on our hypothesis and extensive pre-clinical data that blocking excess TGFβ found in MPN bone marrow will release suppression of normal hematopoiesis thereby contributing to improved blood counts and reduced MPN mutation variant allele frequency (VAF) [29]. Because we have also found in preclinical models that blockade of TGFβ can sensitize the erythropoietic response to ESAs, we also anticipate that blockade of TGFβ signaling will improve cytopenias, notably anemia, in patients with advanced MPNs, who often have elevated serum erythropoietin levels. We believe the preferential advantage conferred upon normal rather than MPN hematopoietic stem and progenitor cells (HSPCs) is due to refractoriness of MPN HSPCs to the cytostatic activity of TGFβ signaling. As a potent, orally-active inhibitor of ALK5, with favorable pharmacokinetics and promising early phase results demonstrating feasibility and tolerability in cancer patients, vactosertib is an appealing test agent for treatment of anemia and fibrosis in patients with Ph-neg MPNs.

Many approved or standard of care therapies for MPNs (e.g., hydroxyurea, JAK2-inhibitors such as ruxolitinib) are associated with variable degrees of treatment-induced cytopenias. These cytopenias often complicate therapy as caregivers balance the benefits against the cytopenias. The rationale for adding vactosertib to available therapy complicated by cytopenias is to improve blood counts while also potentially improving stem and progenitor directed activity of therapy.

3.3 Justification for Dose

Dose selection is based on the toxicology results in rats and early clinical experience in humans, since the rat appears to be the most sensitive species in the GLP toxicology studies. The dog appears to be less sensitive, tolerating higher doses (once scaled to HED) than the rat. In the non-GLP study TED-106 (14-day oral dose range in rat), the MTD was set at 80 mg/kg/day which scales to a HED of approximately 12.9 mg/kg or approximately 800 mg (based on a 60-kg body weight in humans). In the 4-week GLP dose range study in rats with 2-week recovery (TED-107), a 60 mg/kg/day dose was not associated with any mortality (HED of 9.7 mg/kg or approximately 600 mg). This dose was associated with macroscopic and/or microscopic changes in the heart (valvular fibroplasia) and in the bone (femur and sternum, consisting of growth plate dysplasia and metaphyseal hyperostosis). Other test substance-related changes were observed in kidneys, lungs, skin, stomach, liver, spleen, female genital system, and clinical chemistry and hematology. Most of these findings were reversible or partially reversible at the highest (120 mg/kg/day) dose level tested in this study. In a subsequent 4-week GLP toxicology study in rats with 4-week recovery (TED-177) which included doses up to 50 mg/kg/day (HED of approximately 8.1 mg/kg or 500 mg), there were no mortalities during the terminal or recovery phases of the study.

For the first in human study, a starting dose of 30mg/day vactosertib was selected (based on the combined pharmacology and toxicology data and using body surface area scaling) for the Phase 1 clinical trial MP-001. This dose falls into the pharmacologically active dose range in mouse xenograft models and is 1/20 of the Severely Toxic Dose in 10% of the animals (STD10) in rodents. The provisional dose escalation for this study includes an initial 100% dose escalation, followed by decreasing incremental increases of approximately 67 to 40% in subsequent doses (60, 100, 140, and 200 mg/day).

In the phase 1 study of vactosertib (NCT02160106, MP-001), 29 patients were treated with vactosertib once daily in 7 cohorts at the dose range of 30 ~340 mg and 5 patients in 200 mg twice daily cohort (Cohort 8) for 5 days with 2 days off.

In the phase 1/2 clinical trial (NCT03074006) for patients with low or intermediate risk myelodysplastic syndrome, vactosertib 200 mg BID cohort completed cycle 1 (28 days) without dose-limiting toxicity. In Tthe 3 patients enrolled in the third cohort of vactosertib 300 mg BID, is currently under DLT evaluation in this study no patient experienced DLT. The safety and efficacy evaluation of vactosertib 300 mg BID is currently underway in MP-VAC-204 (NCT03724851) and GC-01 (NCT03698825) trials.

Preliminary data indicate that vactosertib has been well tolerated with mild toxicity observed to date.

In the MP-001 study, Vactosertib was safe and well tolerated, and the maximum tolerated dose was not determined. The most frequent TRAEs were mainly mild to moderate including fatigue, nausea, anorexia, and headache, while Grade 3/4 abdominal pain, ALT/AST elevation. Serious adverse events assessed to have causal relationship with vactosertib incurred in MP-001 phase 1 clinical study are one case of cerebrovascular accident and one case of respiratory failure. One DLT of stroke was seen at 100 mg only daily (QD) in a 72-yr-old penile cancer patient who was ex-smoker and history of pulmonary thromboembolism. He developed stroke on C1D6 following 5-

day 100 mg vactosertib treatment and was hospitalized with diagnosis of brain infarction with irregular plaque in both carotid arteries. After standard treatment, he recovered on C1D8 with sequelae of difficulty in fine motor movement.

Finally, no abnormalities in echocardiography or cardiac enzyme levels were reported in this study but echocardiography with Doppler and cardiac enzyme levels should be performed to monitor cardiac valvulopathy or potential myocardium damage at the screening and every 12 weeks and at the end of the treatment.

Vactosertib monotherapy in this phase 1 clinical study with 200 mg BID of vactosertib in patients with advanced solid cancer showed good tolerability and safety. Vactosertib 300 mg BID as monotherapy in patients with MDS is currently being evaluated (NCT03074006), and vactosertib 100 mg and 200 mg BID in combination with immune check point inhibitors, cytotoxicity chemotherapeutic drugs, and target agents are also under evaluation in other sold and hematologic malignancies (NCT03698825, NCT03732274, NCT03724851, NCT03143985, NCT03666832, NCT03802084).

For patients receiving vactosertib combinations, the dose of cytoreductive treatments (e.g., hydroxyurea, ruxolitinib) is determined by the treating physician according to the package insert and clinical judgement and is maintained at a stable dose for at least 3 months prior to enrollment.

3.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the **Schedule of Assessments (SoA), Section 6.1**. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

4. Subject Selection

4.1 Study Population

Patients meeting WHO 2016 criteria for the diagnosis of Ph-neg MPN including PV, ET, MF, MDS/MPN and MPN-U [32] with anemia and meeting the inclusion criteria, but not the exclusion criteria, will be eligible.

4.2 Inclusion Criteria

- Age ≥ 18 years
- Patients meet the WHO 2016 criteria for a Ph-neg MPN (including PV, ET, MF, MDS/MPN, MPN-U).
- Patients with MF must have DIPSS+ Intermediate or High-risk MF (primary of post-PV/ET)
- Patients should be on a stable dose of current cytoreductive therapy for at least 3 months prior to C1D1.
- Anemia as defined by HGB < 10 g/dL, or transfusion of ≥ 2 packed red blood cell (PRBC) unit within the past 4 weeks with HGB ≤8.5g/dL. The anemia, in the investigator's opinion,

must be due to underlying MPN and not due to other causes such as the toxic effects of prior cytoreductive chemotherapy.

- Ineligible, unsuitable or refractoriness to ESA therapy defined as any of the following:
    - Serum erythropoietin (EPO) >125 U/L[4].
    - Proven ESA unsuitability is defined by history of any of the following:
    - Loss of erythroid hematologic improvement while receiving stable or increased ESA dose; or
    - ESA-attributed toxicity that, in the treating physician's opinion, makes ESA therapy unsuitable for subject.
    - ESA refractoriness defined by lack of erythroid hematologic improvement to ESA:[27]
        - Less than 1.5 g/dL increase in hemoglobin after at least 6 weeks of ESA therapy; or
        - Ongoing transfusion dependence that has not been reduced by > 4U over an 8-week period compared to ESA pre-treatment 8 weeks.
- ECOG Performance status ≤ 2
- Able to swallow tablets
- Able to give written informed consent
- Willing and able to comply with scheduled visits, treatment plans, tests and procedures.
- Acceptable Organ Function as defined by:
    - serum creatinine ≤ 2 mg/dL or > 50 mL/min/1.73m^2 by direct measure
    - AST(SGOT)/ALT(SGPT) ≤ 3x institutional upper limit of normal
    - Total bilirubin ≤ 2x institutional upper limit of normal

  Note: Subjects with documented diagnosis of Gilbert's Syndrome resulting in elevated total bilirubin levels will be eligible provided all other eligibility criteria are met.

  Note: Subjects with total bilirubin 2-3 mg/dL and direct (conjugated) bilirubin in the normal range will be eligible, provided all other eligibility criteria are met.
- Acceptable Cardiovascular status as defined by:
    - Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≤ 450 ms for males, and ≤ 470 ms for females on screening ECG.
    - Left ventricular ejection fraction (LVEF) greater than institutional lower limit of normal as determined by cardiac doppler echocardiogram (Echo) or cardiac magnetic resonance imaging (MRI).
    - Cardiac troponin, brain natriuretic peptide (BNP), and creatinine kinase MB isoform (CK-MB) levels that are within institutional range of normal
- Female subjects of childbearing potential must have a negative serum pregnancy test within 7 days of the first administration of study drug.

4.3 Exclusion Criteria

- Any other serious medical condition which in the Investigator's opinion would preclude safe participation in the study.
- Subjects, in the opinion of the Investigator, who are unsuitable to participate in the study.

- Known history of difficulty swallowing, malabsorption or other conditions that may reduce absorption of the product.
- Patients with history of TIA or stroke within the past 12 months are excluded.
- Subjects with significant cardiac dysfunction as defined by the following:
    - Myocardial infarction within 6 months prior to study registration;
    - Unstable angina pectoris;
    - New York Heart Association (NYHA) Class III/IV congestive heart failure;
    - Uncontrolled hypertensive urgency or emergency;
    - Cardiac conduction abnormalities (e.g., symptomatic or sustained atrial or ventricular arrhythmias, second- or third-degree atrioventricular block, complete bundle branch blocks) that, in the investigator's medical judgement, makes them unsuitable for clinical trial.
    - Moderate or severe valvular heart disease, documented by cardiac doppler echocardiogram (Echo) or cardiac MRI (CMR), that in the investigator's medical judgement, makes them unsuitable for clinical trial.
- Pregnancy or breast-feeding for the entire duration of study participation or in the 30 days following the last dose of study drug. Due to the potentially teratogenic effects of TGFβ inhibition during development, pregnant and nursing subjects may not be enrolled and pregnancy must be avoided.
- **Note:** Women of child-bearing potential—defined as sexually active woman who has not undergone hysterectomy and who has had menses any time within the preceding 24 months—must have a negative serum or urine pregnancy test 7 days prior to registration.
- Female subjects who are breastfeeding, or intend to breastfeed, during the study or in the 30 days following the last dose of study drug are excluded.
- Women and men of childbearing potential must either commit to continued abstinence from heterosexual intercourse or commit to simultaneous use of two acceptable methods of birth control—one highly effective method (e.g., IUD, tubal ligation or vasectomy) of patient or partner, and one additional effective method (e.g., latex condom, diaphragm or cervical cap) from the time of screening through 90 days following the last dose of study drug. Use of oral contraceptives is not allowed.
- Current or planned use of any of the following classes of drugs during the study period:
    - Drugs which are exclusively or primarily eliminated by cytochrome P-450 isozyme 3A4 (CYP)3A4 or by UDP glucuronyltransferase 1A1 (UGT)1A1.
    - Drugs which are substrates for the drug transporter multidrug resistance protein 1 (MDR1) and have a narrow therapeutic window; or which are strong inhibitors of drug transporter MDR1.
    - Any major surgeries within 28 days of study enrollment.

4.4 Lifestyle Considerations

- Not applicable

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not

meet the criteria for participation in this trial (screen failure) because of a modifiable factor may potentially be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

4.6 Strategies for Recruitment and Retention

- The study will be listed or otherwise included on government (clinicaltrials.gov), philanthropic (MPN-RF, CR&T) and institutional (Richard T Silver MPN Center) websites, Facebook and Twitter accounts (as applicable).

5. Registration Procedures

5.1 Subject Registration

Subjects will be registered within the WRG-CT as per the standard operating procedure for this process.

6. Study Procedures

6.1 Schedule of Assessments

Table 1a. Tier 1 schedule of trial events 6.1.1

Tier 1 Schedule of Assessments	Screening	Treatment Tier 1																
		Cycle 1				Cycle 2				Cycle 3				Cycle 4				
	Pre-study D-28 to -1	Wk1[a]	Wk2[a]	Wk3[a]	Wk4[a]	Wk5[a]	Wk6[a]	Wk7[a]	Wk8[a]	Wk9[a]	Wk10[a]	Wk11[a]	Wk12[a]	Wk13[a]	Wk14[a]	Wk15[a]	Wk16[a]	End of Tier 1 – Patients meeting composite response and toxicity endpoint may continue vactosertib
Informed Consent Form	X																	
Inclusion/Exclusion Criteria	X																X	
Enrollment	X																	
Demographics	X																	
Diagnosis	X																	
Medical History[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Toxicity / AE assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Con Med assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood tests[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Troponin, BNP, CK-MB	X													X				
EPO level	X					X				X				X				
Pregnancy test	X																	
Electrocardiogram (EKG)[e]	X	e	e	e	e	e	e	e	e	e	e	e	e	e	e	e	e	

Echocardiography with Doppler[f]	X													X				
Bone Marrow Aspirate and Biopsy	X																X	
Ultrasound (left upper quadrant)	X																X	
Research blood	X	X				X				X				X			X	
Research Bone Marrow	X																X	
Treatment Administration Form and Compliance assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MPN-SAF form		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record HgB level and HgB change[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record RBC transfusion history	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Composite response and toxicity endpoint assessment																	X	

a. Visits are weekly if there is a dose change (escalated or reduced or held for toxicity). Visits are biweekly if dose is maintained. Visits are extended to every 4 weeks (once per cycle) as long as dose is maintained for 4 weeks.
b. Must record baseline comorbidities, pre-existing symptoms
c. Spleen size should be recorded
d. Blood tests are: CBC, CMP, UA, Phosphorous, LDH
e. Electrocardiogram required at screening. Only required at subsequent visits in the event of a dose increase.
f. Echocardiogram or Cardiac MRI will be done once every 2 cycles (8 weeks or 56 days)
g. Baseline HgB is defined as median HgB within 28 days of Cycle 1, Day 1
h. Include erythrocyte transfusion history 8 weeks prior to screening

Tier 2 Schedule of Assessments	**Screening**	**Treatment Tier 2**																							
		Cycle 1				**Cycle 2**				**Cycle 3**				**Cycle 4**				**Cycle 5**				**Cycle 6**			
	Pre-study D-28 to -1	**Wk1[a]**	**Wk2[a]**	**Wk3[a]**	**Wk4[a]**	**Wk5[a]**	**Wk6[a]**	**Wk7[a]**	**Wk8[a]**	**Wk9[a]**	**Wk10[a]**	**Wk11[a]**	**Wk12[a]**	**Wk13[a]**	**Wk14[a]**	**Wk15[a]**	**Wk16[a]**	**Wk17[a]**	**Wk18[a]**	**Wk19[a]**	**Wk20[a]**	**Wk21[a]**	**Wk22[a]**	**Wk23[a]**	**Wk24**
Informed Consent Form	X																								
Inclusion/Exclusion Criteria	X																								
Enrollment	X																								
Demographics	X																								
Diagnosis	X																								
Medical History[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Toxicity / AE assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Con Med assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood tests[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Troponin, BNP, CK-MB	X													X											X
EPO level	X					X				X				X				X				X			
Pregnancy test	X																								
Electrocardiogram (EKG)[e]	X	e	e	e	e	e	e	e	e	e	e	e	e	e	e	e	e	e	e	e	e	e	e	e	e
Echocardiography with Doppler[f]	X													X											X
Bone Marrow Aspirate and Biopsy	X																								X
Ultrasound (left upper quadrant)	X																								X
Research blood	X	X				X				X				X				X				X			X
Research Bone Marrow	X																								X
Treatment Administration Form and Compliance assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MPN-SAF form		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

End of Tier2 p patients meeting composite response and toxicity endpoints may continue vactosertib

Record HgB level and HgB change[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record RBC transfusion history	X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Composite response and toxicity endpoint assessment																									X

*Patients who have completed Tier 1 would not require repeat assessments if done within 28 days of Tier 2 enrollment

a. Visits are weekly if there is a dose change (escalated or reduced or held for toxicity). Visits are biweekly if dose is maintained. Visits are extended to every 4 weeks (once per cycle) as long as dose is maintained for 4 weeks.

b. Must record baseline comorbidities, pre-existing symptoms

c. Spleen size should be recorded

d. Blood tests are: CBC, CMP, UA, Phosphorous, LDH

e. Electrocardiogram required at screening. Only required at subsequent visits in the event of a dose increase.

f. Echocardiogram or Cardiac MRI will be done once every 2 cycles (8 weeks or 56 days)

g. Baseline HgB is defined as median HgB within 28 days of Cycle 1, Day 1

h. Include erythrocyte transfusion history 8 weeks prior to screening

6.2. Screening Visit (*-21 days before start of treatment*)

Potentially eligible patients will be identified by chart review and treating physicians and offered an opportunity to provide informed consent. Screening laboratory, history and physical examination will be performed after subjects have provided written informed consent. Eligible subjects will be enrolled on study within 21 days of screening and subjects will begin vactosertib (DL1) within 28 days of screening. The following procedures will be performed within 28 days of starting the first dose of vactosertib (DL1):

6.2.1. Informed consent
Potentially eligible subjects will be identified by treating physician and written Informed Consent Obtained before any study-specific procedures are performed.

6.2.2. Once Informed Consent is provided, subjects will complete screening tests:

6.2.2.1. Screening Blood Studies
- CBC
- CMP, Uric Acid, Phosphorus and LDH
- Serum erythropoietin (EPO) level
- Cardiac troponin, BNP, and CK-MB
- Myeloid molecular panel by NGS

6.2.2.2. EKG

6.2.2.3. Transthoracic Echocardiogram

6.2.2.4. Abdominal Sonogram of upper left quadrant to record Spleen size

6.2.2.5. History and Physical Exam

6.2.2.6. Record palpated spleen size

6.2.2.7. Record ECOG performance status

6.2.2.8. Bone marrow aspirate (BMA) and biopsy

6.2.2.9. Collection of Research blood (20mL) and bone marrow specimens (for pSMAD and VAF quantification).

6.2.2.10. Recording of Transfusion History for the two months (8 weeks) prior to screening.

6.3. Treatment Phase

6.3.1. Cycle 1, Day 1 (D0) Testing and Procedures:

6.3.1.1.1. 6.3.1.1. Pre-dose evaluation:History and Physical Exam

6.3.1.1.2. Record palpated Spleen size

6.3.1.1.3. Laboratory Testing

- CBC
- CMP
- Uric Acid
- Phosphorus
- LDH

6.3.1.1.4. Establish and Record Baseline Hemoglobin: Baseline Hemoglobin is defined as the median hemoglobin within 28 days of Cycle 1, Day 1 (D0).

6.3.1.1.5. EKG (QTc) in the event of a dose increase

6.3.1.1.6. Complete MPN-SAF-TSS Myeloproliferative symptom assessment form total symptom score)[33] (Appendix A)

6.3.1.1.7. Record baseline co-morbidities and pre-existing symptoms.

6.3.1.2. Dispense study drug (vactosertib 50 mg tabs, #130) for cycle from research pharmacy and deliver to eligible subject during clinic visit.

6.3.1.3. Starting dose for Tier 1 is DL1. Subject will receive the one dose of vactosertib (DL1) under supervision of treating physician or research study nurse.

6.3.1.4. Research blood sample (20mL) will be collected either with SOC labs (if they are on a stable dose of vactosertib) or one hour after vactosertib dose (if dose of vactosertib is modified).

6.3.1.5. Subject will return for *Follow-up Testing and Procedures* (section 6.3.2) in 7 (± 2) days after first dose of vactosertib.

6.3.2. Follow-up Testing and Procedures

The following testing and procedures will be performed at all scheduled follow-up time points. This includes all of the following settings:

- *7 days (±2) days after Cycle 1, Day 1 (D0);*
- *On Day 1 of any subsequent Cycle (N>1);*
- *7 days (±2) days after a decision to Escalate dose;*
- *7 days (±2) days after a decision to Hold vactosertib,*
- *7 days (±2) days after decision to Restart vactosertib following a Hold,*
- 14 days (±4) days after an initial decision to *Maintain* vactosertib dose, and
- Day 1 of the next cycle of vactosertib after at least two, consecutive 'Maintain' dose-adjustment decisions at the same dose level.

6.3.2.1. Pre-dose evaluation:

6.3.2.1.1. History and Physical Exam
6.3.2.1.2. Record palpated spleen size
6.3.2.1.3. Laboratory testing
- CBC, CMP, Uric Acid, Phosphorus, LDH

6.3.2.1.4. EKG (QTc) in the event of a dose increase
6.3.2.1.5. Complete MPN-SAF-TSS (Myeloproliferative symptom assessment form total symptom score)(Appendix A)
6.3.2.1.6. Pill Counts to assess compliance (subjects return all vials at visit for pill counts).
6.3.2.1.7. Toxicity assessment (CTCAE v5 criteria)
6.3.2.1.8. Erythropoietic Response assessment (*see Table 3 andsection 10.1)*
6.3.2.1.8.1. Record Interval PRBC Transfused Volume
6.3.2.1.8.2. Record Current Hemoglobin
6.3.2.1.8.3. Record Hemoglobin change = Current Hemoglobin – Baseline Hemoglobin (g/dL)
6.3.2.1.8.4. If Day 1 of Cycle, serum EPO is measured.

6.3.2.2. Record Dose Adjustment Decision (*see Table 3 section 7),* the dose adjustment decision options are outlined in section 6.3.3
6.3.2.3. Dose Adjustment Testing and Procedures (*section 6.3.2.2)*
6.3.2.4. If Day 1 of Cycle,
- Pill Counts to assess compliance (subjects return all vials at visit for pill counts).
- Dispense study drug (vactosertib 50 mg tabs) for one cycle from research pharmacy and deliver to subject during clinic visit.
- Research blood sample (20mL) will be collected one hour after vactosertib dose (also collected on C1D8).

6.3.3. **Dose Adjustment Decision** (*see Table 3 section 7)*

6.3.3.1. **Escalate** to next dose level
- Subject will receive one dose of vactosertib at escalated dose level under supervision of treating physician or research study nurse.
- Research blood sample (20mL) will be collected approximately 1hr after escalated dose taken.
- If dose is at maximum level (DL4), and patient has at least stable disease, then patient can remain on study at maximum level (DL4).
- If dose is at maximum level (DL4), and patient has progressive disease, then patient will be removed from study.
- Subject will return for Follow-up Testing and Procedures in 7 (± 2) days from start of new dose level.

6.3.3.2. **Maintain** current dose level

6.3.3.2.1. New Maintain Decision:
- Subject will return for Follow-up Testing and Procedures in 14 (± 3) days.

6.3.3.2.2. Ongoing Maintain Decision:

- After at least two, consecutive Maintain dose-adjustment decision at the same dose level, subject will return for Follow-up Testing and Procedures no later than Day 1 of the next cycle of vactosertib.

6.3.3.3. **Hold** vactosertib

- If last dose received is at minimum dose level (DL0), patient will be removed from study. Otherwise:

6.3.3.3.1. New Hold Decision

- Subject will return for Follow-up Testing and Procedures in 7 (± 2) days.

6.3.3.3.2. Ongoing Hold Decision

- If dose is held > 28 days, subject will be removed from study.
- If dose is held < 28 days, subject will return for Follow-up Testing and Procedures in 7 (±2) days

6.3.3.4. **Restart** vactosertib

- Vactosertib dose will be reduced to one dose level lower than the last dose level received.
- If last dose received was at minimum dose level (DL0), patient should have already been removed from study.
- Subject will return for Follow-up Testing and Procedures in 7 (± 2) days from start of new dose level.
- Subject will receive one dose of vactosertib at restarted dose level under supervision of treating physician or research study nurse.
- Research blood sample (20mL) cycle 1 will be collected approximately 1hr after dose taken.

6.3.4. **Additional Scheduled Studies and Procedures**:

Additional studies will be performed at regular intervals for all Subjects independent of the current dose of vactosertib; provided the indicated studies have not already been performed within 7 days.

6.3.4.1. Cardiac Evaluation after every three cycles is completed (every 84 ± 7 days):

- Transthoracic Echocardiogram
- Cardiac troponin, BNP, CK-MB

6.3.4.2. Serum EPO is measured on Day 1 of each cycle (every 28 ± 3 days).

6.3.4.3. Subjects will maintain a diary to record adverse events that occur between clinic visits (e.g., patient diaries).

6.3.5. **End of Tier Testing and Procedures**:

At the end of Cycle 4 (approximately Week 16 ± 7 days), the following procedures will be performed for all Subjects.

6.3.5.1. History and Physical Exam

- Record palpated spleen size

6.3.5.2. Laboratory testing

- CBC

- CMP, Uric Acid, Phosphorus, LDH
- Serum EPO level
- Cardiac troponin, BNP, CK-MB

6.3.5.3. Abdominal Sonogram of upper left quadrant to record Spleen size

6.3.5.4. EKG (QTc) in the event of a dose increase

6.3.5.5. Complete MPN-SAF-TSS (Myeloproliferative symptom assessment form total symptom score)(Appendix A)

6.3.5.6. Bone marrow aspirate and biopsy to assess response.

6.3.5.7. Collection of Research Blood and Bone Marrow Specimens

6.3.5.8. Pill Counts to assess compliance (subjects return all vials at visit).

6.3.5.9. Toxicity assessment (CTCAE v5 criteria)

6.3.5.10. Erythropoietic Response assessment (Table 3)

- Record Interval PRBC Transfused Volume
- Record Current Hemoglobin
- Record Current Hemoglobin – Baseline Hemoglobin Change (g/dL)
- Record Epo Level

6.3.5.11. Subjects also follow Follow-up Testing and Procedures.

- Patients continue to follow on study until all laboratory and pathology results are available for evaluation of criteria for ongoing treatment (see Section 6.3.7 *Ongoing Treatment for Patients Demonstrating Clinical Benefit*)

6.3.5.12. Full Revised IWG-MRT/ELN Response Criteria for MF/PV/ET will be recorded as appropriate[2,3]

Note: After the planned study treatment, subjects meeting the criteria for ongoing treatment (see Section 6.3.7 *Ongoing Treatment for Patients Demonstrating Clinical Benefit*) will have the option to continue receiving vactosertib until disease progression or unacceptable toxicity.

6.3.6. Tier 2 Treatment Plan

The study will proceed to Tier 2 as long as vactosertib is deemed safe and tolerable according to predefined criteria (see *Criteria for Decision to Proceed to Tier 2* and *Statistical Considerations and Justification of Proposed Sample Size* sections). The Tier 2 arm will enroll additional patients to reach a statistically predetermined cohort size that can preliminarily assess efficacy of vactosertib, or lack thereof, with sufficient power and statistical significance (see *Statistical Considerations and Justification of Proposed Sample Size* section).

6.3.6.1. Screening, enrollment and registration for Tier 2 will be performed as described for Tier 1.

6.3.6.2. Treatment phase of Tier 2 including clinical follow-up visits and rules for dose adjustment and/or removal from study will proceed as for Tier 1 with the possible exception of starting dose level.

6.3.6.3. Starting Dose for Tier 2:

The starting dose on Tier 2 will be identified as follows:

- The lowest dose level of vactosertib for which no DLT was observed in Tier 1 AND The lowest dose level for which at least one of the 12 subjects enrolled on Tier 1 met *Criteria for Clinical Benefit*.
- Or, if a single dose level does not fulfil both Criterion 1 and Criterion 2, the starting dose level for Tier 2 will lowest dose from Tier 1 for which no DLT was identified.

6.3.6.4. Each subject will follow *Intrapatient Dose Adjustment Rules* (Table 3). The same schema for dose escalation and monitoring for toxicity outlined in the description of the Tier 1 patients will be followed.

6.3.6.5. Subjects enrolled on Tier 2 will have bone marrow exam at the end of Cycle 4 (approximately Week 16 ± 7 days).

6.3.6.6. End of Tier 2 testing and procedures will be performed as per Tier 1 End of cycle 4 testing and procedures with the exception that it will be performed after completion of the 6th cycle of vactosertib. An End of Tier bone marrow exam is not required for subjects enrolled on Tier 2 since a scheduled exam is performed at the completion of Cycle 4.

6.3.6.7. After the planned 6 cycles of study treatment, subjects meeting the criteria for ongoing treatment (see Section 6.3.7 *Ongoing Treatment for Patients Demonstrating Clinical Benefit*) will have the option to continue receiving vactosertib until disease progression or unacceptable toxicity.

6.3.7. **Ongoing Treatment for Patients Demonstrating Clinical Benefit**:

After completion of planned study vactosertib treatment on either Tier, subjects meeting one of the following criteria will be provided the option of continuing vactosertib for up to 2 years or until such a time that they manifest disease progression or unacceptable toxicity:

- Subject meets *Criteria for Clinical Benefit* after completion of planned therapy on their study Tier of vactosertib, or
- Subject has not experienced a dose limiting toxicity (DLT) from vactosertib and has maintained at least stable disease after completion of planned therapy on their study Tier as per IWG-MRT/ELN Response Criteria.

7. Study Intervention

7.1 Study Intervention/Device Description

Vactosertib is an off-white solid, and a crystalline, non-hygroscopic material, with a single endothermic event at 143.5ºC. Vactosertib exhibits a high aqueous solubility at low pH range which decreases with increasing pH, a behavior consistent with a weak basic molecule (TED-133). General information regarding the drug substance is provided below:

Appearance	White to off-white, crystalline powder
Thermogravimetric Analysis (TGA)	< 0.12% weight loss up to about ~130°C
Differential Scanning Calorimetry (DSC)	Endothermic transition with onset at ~138°C
Hygroscopicity	No weight gain was observed in the range of 25%-92% relative humidity at 25°C; non-hygroscopic
Powder X-Ray Diffraction	Crystalline
pH (in water at 25 ± 3°C)	Aqueous solubility: < 0.02 mg/mL; pH of a saturated solution: 7.2
pH-Solubility Profile	The solubility is higher at lower pH range (eg, 25.05 mg/mL at pH

7.2 Availability

Vactosertib is an investigational agent supplied to investigators by MedPacto Inc.

7.3 Acquisition and Accountability

Vactosertib Inventory Records– The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents received from MedPacto Inc. on a Drug Accountability Record Form (DARF).

7.4 Formulation, Appearance, Packaging, and Labeling

For clinical studies, film-coated tablets containing 10, 20, 50, 100 and 200 mg of vactosertib are currently available. The vactosertib film-coated tablets are formulations for oral administration. They are plain, white to off-white, round, biconvex tablets containing vactosertib drug substance.
The vactosertib film-coated tablets contain the following inactive ingredients: lactose monohydrate (Fastflo 316), microcrystalline cellulose(Avicel PH 102), crospovidone (Kollidon CL F), povidone Kollidon 30, magnesium stearate, and opadry white. The proposed clinical drug product vactosertib (10, 20, 50,100 and 200 film-coated tablets) is compressed from 5% w/w (10, 20mg), 10% w/w(50mg), 40%w/w(100, 200mg) drug loaded common stock wet granulation, and the same manufacturing process is used for all film-coated tablets.

7.5 Product Storage and Stability

Vactosertib tablets (10, 20, 50 and 100 mg) are packaged in tightly closed, white, opaque, HDPE bottles with a 1-g silica gel desiccant canister. The bottles are heat-induction sealed with a child-resistant cap. Based on the available laboratory stability data, vactosertib tablets (10, 20, 50, 100 and 200mg), should be stored at 15°C to 25°C (59°F to 77°F) and protected from light. Recent data indicate that 10 mg, 20 mg, and 50 mg vactosertib remain stable up to 36 months, 60 months, and 30 months, respectively, under all testing conditions with the exception of high-intensity fluorescent visible light with a minimum of 200-watt h/m2 UV-A irradiation. 100 mg and 200 mg Vactosertib remain stable up to 3 months under the same testing conditions as above. Stability test for a longer

time period is underway: 50 mg, 100 mg, and 200 mg vVactosertib up to 60 months, 24 months, and 24 months, respectively.

The product should be stored in the bottle provided and used according to the instructions on the label.

7.6 Preparation

N/A

7.7 Dosing and Administration

Vactosertib tablets will be administered orally twice a day in a 5-days on, 2 days off regimen. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 13. Appropriate dose modifications for vactosertib are described in Section 6.

7.7.1 Dose adjustment rules for Tier 1, C1D1 (D0) and interval study visits

Tier 1 - C1D1 (D0)

Overview of study visit interval:

All subjects begin treatment on C1D1 (D0) at DL1 of vactosertib (50mg BID). All subjects return one week (7 days ± 2) after C1D1 (D0) and the vactosertib dose is adjusted according to the dose adjustment rules defined in Section 7.7.1 Table 3. The study visit interval is weekly (7 days ± 2) any time the dose adjustment rule dictates dose escalation or a dose hold. If the dose adjustment rule dictates maintaining the current dose, then the visit interval is extended to approximately every 2 weeks. After at least two, consecutive 'Maintain' dose-adjustment decisions at the same dose level, then the next visit is extended to no later than Day 1 of the next cycle of vactosertib (approximately every 4 weeks).

Once Tier 1 has enrolled 3 patients, enrollment will be held until each patient has completed at least the first cycle of therapy before enrollment is re-opened.

Study Visit Interval Based Upon Dose Adjustment Decision:

All subjects begin treatment on C1D1 (D0) at DL1 of vactosertib (50mg BID for Tier 1). All subjects return one week (7 days ± 2) after C1D1 (D0) and the vactosertib dose is adjusted according to the dose adjustment rules defined in Section 7.7.1 Table 3. The study visit interval is weekly (7 days ± 2) any time the dose adjustment rule dictates dose escalation or a dose hold. If the dose adjustment rule dictates maintaining the current dose, then the visit interval is extended to approximately2 weeks. After at least two, consecutive Maintain dose-adjustment decisions at the same dose level, then the next visit is extended to no later than Day 1 of the next cycle of vactosertib (approximately every 4 weeks).

7.7.2 Dosing Delays/Dose Modifications for vactosertib

Clinical Parameter	Escalate to Next Dose Level	Maintain Current Dose Level	Hold Dose	Restart After Dose Hold
Erythropoietic Response	Inadequate	Adequate		
Hemoglobin (HGB) absolute value, change in HGB from baseline*, and Erythrocyte transfusion	HGB ≤10 g/dL AND ≤2 g/dL increase from baseline HGB OR any Erythrocyte transfusion	HGB >10 g/dL OR > 2g/dL increase from baseline HGB AND No Erythrocyte transfusion	HGB >12 g/dL	HGB<12 g/dL
Current Toxicity (CTCAE v5)	≤Grade 2	≤Grade 2 OR >Grade 2 not requiring change in treatment	>Grade 2 Requiring Change in Treatment	<Grade 2 and Requiring No New Change in Treatment
Dose hold Toxicity during Cycle	Dose Hold Not Required During Cycle	Dose Hold Not Required During Cycle		
Current Dose Dose Levels: (DL0) 50 mg daily; (DL1) 50 mg bid; (DL2) 100 mg bid; (DL3) 150 mg bid; (DL4) 200 mg bid. Dosing schedule, 5 days on, 2 days off	< Highest Dose Level	≤ Highest Dose Level		Most Recent Dose >(DL0)
Rule	All True	All True	Any True	All True
Next Study Visit†	7±2 days	1st Maintain§ 14±3 days 2nd or greater Maintain D1 of next cycle	7±2 days	7±2 days

Table 3: Intrapatient Dose Adjustment Rules.
The parameters shown are used to adjust the vactosertib dose on a continuing basis. The dose is escalated to the next level if ALL criteria for escalation are met. The decision to Hold vactosertib is made if ANY hold criteria is met at any point during the cycle. Otherwise the dose level is maintained. The criteria to Escalate, Maintain or Hold a dose are non-overlapping. Dose decrements by one level will follow any HOLD. * Baseline HGB is defined as the median HGB in the 4 weeks prior to D1 of protocol treatment. † Subject will maintain a diary of adverse events between study visits. § Visits are weekly if there is a dose change (Escalate, Hold or Restart). Visits are bi-weekly if the decision is to Maintain the current dose. Visits are extended to every 4 weeks (D1 of each new cycle) after the second or greater, consecutive Maintain decision.

7.8 General Concomitant Medication and Supportive Care Guidelines

1) Transfusions:
   a) Packed red blood cell (PRBC) transfusions for HGB <7g/dL, or symptomatic anemia, are permitted.
   b) Platelet transfusions are permitted for bleeding or platelet counts < 10,000/µL.

2) Growth Factors and Antimicrobials:
   a) Administration of ESAs is not be permitted on the trial1.
   b) Administration of GCSF and use of prophylactic antimicrobials for severe neutropenia is permitted at the discretion of the investigator.

7.9 Duration of Therapy and Criteria for Removal from Study

7.9.1. Tier 1 duration is 16 weeks (4 treatment cycles) and Tier 2 duration is 24 weeks (6 treatment cycles).

7.9.2. In the absence of treatment delays due to adverse event(s), treatment may continue for 6-10 cycles or until one of the following criteria applies:

7.9.2.1. Disease progression at the MTD,

7.9.2.2. Intercurrent illness that prevents further administration of treatment,

7.9.2.3. Unacceptable adverse events, specifically:

- Adverse event(s) that necessitate a dose hold for >28 days,
- Adverse events that occur at DL0

7.9.2.4. Patient decides to withdraw from the study, or

7.9.2.5. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

7.10 Duration of Follow Up

Patients will be followed for 6 months after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.10 Measures to Minimize Bias: Randomization and Blinding

N/A. This study is an open label single arm (non-randomized) study

7.12 Study Intervention/Follow-up Compliance

Subject compliance with the dosing schedule will be entered on a drug diary that the subject will complete and return to the site for review. A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff (see section 8.3)

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

See section 7.9

8.1.1 Discontinuation of Study Intervention

8.1.1. Tier 1 Stopping Rule:

The primary objective of Tier 1 is to assess the feasibility of protocol therapy in subjects with advanced MPNs as measured by the incidence of dose limiting toxicity (DLT, see *Definition of Dose Limiting Toxicity* section). Toxicities are assessed by CTCAEv5 criteria. Up to a total of 12 patients will be accrued to Tier 1. Tier 1 will be stopped for safety considerations under the following conditions:

- Any patient has grade 5 (lethal) DLT occurring within the first 12 weeks of starting vactosertib; or
- More than two patients experience a dose-limiting toxicity (DLT) at any dose, within the first 12 weeks on study.

Trial accrual will be suspended and a DSMB convened if either of these *Tier 1 Stopping Rule* criterion is triggered. If more than two patients have a DLT at the same dose level, then further accrual to that dose level and higher dose levels will be suspended. Pending review with DSMB, the study may be re-opened with amendment reflecting changes to the permitted dose levels. A planned stop to Tier 1 accrual will occur after 12 subjects have received at least one dose of vactosertib. At this time, the DSMB will be convened if fewer than 1 of the first 12 patients experience clinical benefit.

Protocol therapy will be considered safe if the *Tier 1 Stopping Rule* is not triggered. The following table provides the marginal probability of declaring the intervention unsafe for different rates of severe toxicity (as defined by *Tier 2 Stopping Rule*). This *Tier 1 Stopping Rule* protects against an unexpectedly high rate of severe toxicity.

Tier 1	True Rate of Severe Toxicity				
	5%	10%	15%	20%	30%
Probability of Declaring Unsafe	12%	35%	56%	73%	91%

If the Tier 1 safety boundaries are not crossed, this treatment strategy will be considered safe for expansion to Tier 2. Feasibility and toxicity will continue to be monitored in the Tier 2 portion of the study. A total of 37 patients will be accrued (Tier 1 + Tier 2) and the Tier 2 rule stopping rule applies to all subjects (up to 37) enrolled.

8.1.2. Tier 2 Stopping Rule:

- Any patient has grade 5 (lethal) DLT occurring within the first 12 weeks of starting vactosertib; or

- More than five patients experience a dose-limiting toxicity (DLT) at any dose, within the first 12 weeks on study.

Protocol therapy will be considered safe if the *Tier 2 Stopping Rule* is not triggered. The following table provides the marginal probability of declaring the intervention unsafe for different rates of severe toxicity (as defined by *Tier 2 Stopping Rule*). The *Tier 2 Stopping Rule* protects against an unexpectedly high rate of severe toxicity.

Tier 2	True Rate of Severe Toxicity				
	5%	10%	15%	20%	30%
Probability of Declaring Unsafe	3.1%	31%	67%	89%	99%

8.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- Participant lost to follow-up after several attempts to contact subject to schedule study visit.

8.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls. These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Correlative/Special Studies

9.1. On-target Pharmacodynamic Response Reported by SMAD2/3 Phosphorylation

9.1.1. Collection of Specimen(s):

9.1.1.1. Blood specimens are collected at the following times:

9.1.1.1.1. Screening and at End of Tier Testing.

9.1.1.1.2. One hour after observed dose any time a new dose level is used (e.g., following a dose escalation, dose restart, dose reduction).

9.1.1.2. Bone marrow Specimens

9.1.1.2.1. Bone marrow aspirate specimens are collected at Screening and at end of Cycle 4 (16 weeks ± 7 days). In the event of a dry tap, the requirement for the bone marrow aspirate is waived (a biopsy is still required).

9.1.1.2.2. Bone marrow biopsy sections will be obtained at Screening and at end of Cycle 4. Sections will be obtained from hematopathology after clinical evaluation is complete. Unstained, sections will be cut from the residual tissue block. No separate research specimen is required.

9.1.2. Handling of Specimens(s):

9.1.2.1. Blood specimens are collected in standard EDTA (purple top) vacutainer tubes.

9.1.2.2. Bone marrow aspirate specimens will be collected into heparinized syringes and transferred to standard heparin (green top) vacutainer tubes.

9.1.2.3. Bone marrow biopsy sections will be obtained from Weill Cornell Medicine hematopathology director Giorgio Inghirami, MD, PhD.

9.1.3. Shipping of Specimen(s): Specimens will be hand-delivered to the Scandura Lab.

9.2. Molecular Response Reported by JAK2V617F, CALR type 1 or type 2, MPLW515L/K Driver Mutation Variant Allele Frequency

9.2.1. Collection of Specimen(s):

9.2.1.1. Blood specimens are collected at Screening, at end of Cycle 4 (16 weeks ± 7 days) and at End of Tier Test.

9.2.1.2. Bone marrow aspirate specimens are collected at Screening and at end of Cycle 4.

9.2.1.3. Bone marrow biopsy sections will be obtained from hematopathology after clinical evaluation is complete. Unstained, sections will be cut from the residual tissue block. No separate research specimen is required.

9.2.2. Handling of Specimens(s):

9.2.2.1. Blood specimens are collected in standard EDTA (purple top) vacutainer tubes.

9.2.2.2. Bone marrow aspirate specimens will be collected into heparinized syringes and transferred to standard heparin (green top) vacutainer tubes.

9.2.3. Shipping of Specimen(s): Specimens will be hand-delivered to Scandura Lab.

10. Measurement of Effect

10.1. Response Criteria (Criteria for Clinical Benefit)

The following criteria are used to decide if subject can be offered the opportunity to receive more than 4 cycles of vactosertib AND for decision to proceed to the Tier 2 expansion phase after Tier 1. These are adapted from the IWG-MRT and ELN consensus reports on response determination in patients with MPNs.

10.1.1 Symptomatic Response

- Defined by a reduction in MPN-SAS total score by ≥ 50% compared to pretreatment score.

10.1.2 Splenic Response

Defined by:

- Non-palpable spleen when baseline spleen size was 5-10 cm below left costal margin;
- At least 50% reduction in spleen size when baseline spleen is > 10 cm below left costal margin
- At least 35% reduction in spleen size as assessed by US, CT or MRI.

Note: A baseline spleen size < 5 cm below left costal margin is not eligible for spleen response;

10.1.3 Erythropoietic Response

Defined by any of the following:

- HGB increase of 1.5g/dL compared to baseline HGB;
- Reduction in PRBC transfusion rate to ≤ 50% of pre-treatment transfusion rate; or
- Reduction in PRBC transfusions by ≥ 4 Units over an 8-week period.

10.2 Duration of Response

10.2.1. Duration of overall response:

The duration of overall response is measured from the time measurement criteria are met for symptomatic, splenic or erythropoietic response (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started)

10.2.2. Duration of stable disease:

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

10.3 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression.

10.4. Other Response Parameters

10.4.1. Molecular response: measured by change in blood (and/or marrow) allelic ratio of MPN driver mutations (JAK2, CALR or MPL).

10.4.2 Histologic response: measured by change in bone marrow biopsy cellularity and fibrosis grade.

10.4.3 SMAD2/3 phosphorylation: Measured in peripheral blood and/or bone marrow hematopoietic cells.

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

Neither the Investigator nor MedPacto will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol

amendments will be submitted to the relevant institutional IEC/IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB/IEC requirements, applicable laws and regulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects' medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

12.1 Study Design/Endpoints

12.1.1. Optimal Two-Stage Design, and Criteria to Proceed to Tier 2:

A Simon Two-stage Optimum Design was used to minimize the number of subjects exposed to vactosertib if it is found to be an unsuitable agent for the treatment of anemic patients with Ph-neg MPNs. Further development of vactosertib would be warranted if ≥20% of subjects met *Criteria for Clinical Benefit* (section 10.1) without dose-limiting toxicity (see *Definition of Dose Limiting Toxicity* section). The study will be terminated early if fewer than 1 subject treated in the first tier (up to 12 subjects) meet these criteria. Using these criteria, there is less than a 10% chance of inappropriately accepting (α, type 1 error) vactosertib if it is not truly useful. Conversely, there is less than a 10% chance of inappropriately rejecting (β, type 2 error) vactosertib if it is actually a useful drug for anemic patients with Ph-neg MPNs.

Table 4: Optimal Two Stage Design	
Response Probability Indicating Unacceptably Low vactosertib Activity	0.05
Response Probability Indicating Substantial vactosertib Activity	0.20
Probability of Accepting Poor Drug	0.1
Probability of Rejecting Good Drug	0.1
Number of Tier 1 Subjects	12
Number of Tier 1 Responders to Advance to Tier 2	**≥1**
Maximal Number of Subjects	37
Number of Tier 2 Responders to Advance Development	**≥4**

The Simon Two-stage Optimum Design is expected to minimize the number of subjects exposed to vactosertib if it is found to be an unsuitable agent for the treatment of anemic patients with Ph-neg MPNs (see *Criteria for Decision to Proceed to Tier 2* section). If 1 or more subjects meets the *Composite Response & Toxicity Endpoint* (**Table 5**) then the study will proceed to Tier 2 and another 25 subjects will be enrolled. After completion of Tier 2, if four or more subjects meet the *Composite Response & Toxicity Endpoint* then vactosertib

will have shown preliminary efficacy and feasibility to justify further evaluation as an agent to treat anemic patients with Ph-Neg MPNs.

12.2.2 Composite response/ Toxicity measure

Responding subjects will have met *Criteria for Clinical Benefit* **(**section 9.1**)** for at least 8 weeks. This will ensure that a stable vactosertib dosing schedule can be achieved. Responding subjects will not experience dose limiting toxicity (see *Definition of Dose Limiting Toxicity*). Only subjects meeting all criteria will be considered responders.

Table 5: Composite Response & Toxicity Endpoint	
Adequate Response	Meets Criteria for Clinical Benefit
Stable Response	Meets Criteria for Clinical Benefit to vactosertib for ≥ 8 weeks
Tolerable	No Dose Limiting Toxicity Experienced

12.2 Sample Size/Accrual Rate

Total sample size of the study is 37 patients, 12 for Tier 1 and 25 for Tier 2. The number of potentially eligible subjects seen at our institution is on average 10 per month based on an i2b2 database query. The projected accrual rate to the study is estimated to be 2 patients per month.

12.3 Stratification Factors

The study is not powered for statistical analysis of subgroups. Relevant factors that will be collected include MPN diagnosis, MPN duration and driver mutation, demographic variables such as subject age and gender. Monitoring and efficacy determination will be done for the entire population without stratification.

12.4 Analysis of Endpoints

12.4.1 Analysis of Primary Endpoints

Please see Table 4 and Section 12.1 for the detailed analysis of the Primary Endpoints.

12.4.2 Analysis of Secondary Endpoints

Clinical response to vactosertib will be assessed using the *Criteria for Clinical Benefit* outlined above as a composite endpoint. Patients achieving any of these criterial will be considered to have achieved clinical benefit. This endpoint will be used to define a preliminary estimate of the potential efficacy of vactosertib in the study population. Complete enrollment to both tiers (37 total) will allow us to confidently identify a *Clinical Benefit* response rate of more than 30%. This estimate has a significance of ≤0.1 and a power of 0.8 and is based upon a reported clinical improvement rate of ≤10% (almost

entirely due to symptomatic response) in similar patient populations with best available therapy[34,35]. Reported rates of splenic and/or erythropoietic responses to best available therapy are ≤ 3%. The 37 subjects enrolled on this study will allow Splenic Response and Erythropoietic Response rates of at least 20% to be individually tested with a power of 80% and a significance of < 0.1%. If after complete accrual of 37 subjects, more than 11 patients meet criteria for Composite Response, or more than 7 patients meet criteria for Splenic or Erythropoietic Response, vactosertib will be considered to have sufficient efficacy for definitive testing in a randomized study.

The secondary endpoints of erythropoietic (HGB and RBC transfusion), symptomatic, and splenic responses will be directly tested as described in the preceding section. While limited by the small sample size, additional endpoints will be assessed including molecular (MPN driver variant allele frequency), pharmacodynamic (SMAD2/3 phosphorylation in bone marrow and/or blood CD34+ hematopoietic stem and progenitor cells), and histologic (bone marrow cellularity and fibrosis score) responses. The incidence of hematologic toxicities, infections, disease progression, thrombosis events, and the probability of overall and progression free survival, will be monitored. Secondary endpoints will be reported using descriptive statistics but no formal hypothesis testing will be performed.

Other secondary endpoints will be reported using descriptive statistics but no formal hypothesis testing will be performed. The following endpoints will be analyzed:

12.4.2.1 Histologic response defined by any reduction in grade of bone marrow fibrosis by histopathologic assessment at 16 weeks.

12.4.2.2 Molecular response defined by a decrease in allelic ratio of MPN-driver mutations (eg. JAK2, CALR, and MPL allelic ratio) in blood and/or bone marrow cells.

12.4.2.3 Pharmacodynamic Response defined as any of the following:

- Reduced immunohistochemical staining for SMAD2/3 phosphorylation in bone marrow biopsy sections (See Figure 1).
- Reduced mean fluorescence intensity of SMAD2/3 phosphorylation staining in peripheral blood hematopoietic stem and progenitor cells (HSPCs) or mature progeny as assessed by flow cytometry (See Figure 2).
- Reduced mean fluorescence intensity of SMAD2/3 phosphorylation staining in bone marrow hematopoietic stem and progenitor cells (HSPCs) or mature progeny as assessed by flow cytometry.

12.4.2.4 ToxicityThe incidence of hematologic toxicities, infections, disease progression, thrombosis events, and the probability of overall and progression free survival, will be monitored.

12.5 Interim Analysis

Reports of toxicity and efficacy will be submitted for DSMB review at the following time points:

- completion of Tier1;
- completion of Tier2;
- any time one of the stopping rules is met.

Unscheduled Interim Analysis will be performed if more than three patients have a DLT at the same dose level or if more than five patients in both tiers, at any dose level, have a DLT. In the former situation, further accrual to that dose level and higher dose levels will be suspended. In the latter situation, further accrual to the study with be halted. Reports of toxicity and efficacy will be submitted for DSMB review in that instance for review and guidance as to whether the dose level can be re-opened or accrual to the study can proceed and if the study should be amended to permanently close the problematic dose levels or closed altogether.

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with vactosertib. Consultation with the Biostatistics Office will allow for completion of this section.

12.6.2 Evaluation of Response

All patients included in the study will be assessed for response to treatment if they have received at least 4 cycles of treatment. Consultation with the Biostatistics Office will allow for completion of this section.

12.6.3 Definition of Safe Minimum Dose

- The lowest dose level of vactosertib for which no DLT was observed in Tier 1 AND
- The lowest dose level for which at least one of the 12 subjects enrolled on Tier 1 met *Criteria for Clinical Benefit*.

Or, if a single dose level does not fulfil both Criterion 1 and Criterion 2, the Safe Minimum Dose will be the lowest dose from Tier 1 for which no DLT was identified.

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed

by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

13.1.1 Investigational Agent (Expected Adverse Events)

Advanced MPNs are associated with significant and potentially life-threatening toxicities. In the patient population eligible for study treatment, we expect rare grade 3 or grade 4 drug-related toxicities. However, a subset of patients are likely to have pre-existing grade 3 or grade 4 hematologic and non-hematologic toxicities. Pre-existing toxicities will be carefully recorded prior to start of vactosertib. There are no data regarding the vactosertib in patients with advanced MPNs.

Table 6: Treatment emergent AEs (≥5%) from vactosertib monotherapy trials

AE terms	MP-001 (n=35), n (%)	MP-VAC-105 (n=16), n (%)	MP-MDS-01 (n=9), n (%)	Total (n=60), n %
All	35 (100)	6 (38)	7 (78)	48 (80)
Headache	9 (26)	5 (32)	1 (12)	15 (25)
Nausea	13 (38)	1 (7)	0 (0)	14 (24)
Fatigue	12 (35)	0 (0)	1 (12)	13 (22)
Decreased appetite	11 (32)	0 (0)	1 (12)	12 (20)
Diarrhea	8 (23)	1 (7)	2 (23)	11 (19)
Abdominal pain	7 (20)	0 (0)	1 (12)	8 (14)
Constipation	7 (20)	0 (0)	1 (12)	8 (14)
Anaemia	5 (15)	0 (0)	2 (23)	7 (12)
Dyspnoea	7 (20)	0 (0)	0 (0)	7 (12)
Vomiting	6 (18)	0 (0)	1 (12)	7 (12)
Back pain	6 (18)	0 (0)	0 (0)	6 (10)
Muscular weakness	6 (18)	0 (0)	0 (0)	6 (10)
Pruritus	4 (12)	0 (0)	1 (12)	5 (9)
Pyrexia	5 (15)	0 (0)	0 (0)	5 (9)
Arthralgia	4 (12)	0 (0)	0 (0)	4 (7)
Aspartate aminotransferase increased	4 (12)	0 (0)	0 (0)	4 (7)

Cough	3 (9)	0 (0)	1 (12)	4 (7)
Hyponatraemia	3 (9)	0 (0)	1 (12)	4 (7)
Hypophosphataemia	3 (9)	0 (0)	1 (12)	4 (7)
Pain	4 (12)	0 (0)	0 (0)	4 (7)
Pleural effusion	4 (12)	0 (0)	0 (0)	4 (7)
Asthenia	3 (9)	0 (0)	0 (0)	3 (5)
Blood alkaline phosphatase increased	3 (9)	0 (0)	0 (0)	3 (5)
Dehydration	3 (9)	0 (0)	0 (0)	3 (5)
Dermatitis acneiform	2 (6)	0 (0)	1 (12)	3 (5)
Dizziness	2 (6)	0 (0)	1 (12)	3 (5)
Dyspepsia	3 (9)	0 (0)	0 (0)	3 (5)
Hypokalaemia	2 (6)	0 (0)	1 (12)	3 (5)
Muscle spasms	3 (9)	0 (0)	0 (0)	3 (5)
Non-cardiac chest pain	2 (6)	0 (0)	1 (12)	3 (5)
Oedema peripheral	3 (9)	0 (0)	0 (0)	3 (5)
Rash maculo-papular	3 (9)	0 (0)	0 (0)	3 (5)
Respiratory failure	3 (9)	0 (0)	0 (0)	3 (5)
Rhinitis allergic	3 (9)	0 (0)	0 (0)	3 (5)
Urinary tract infection	3 (9)	0 (0)	0 (0)	3 (5)
Weight decreased	3 (9)	0 (0)	0 (0)	3 (5)

Table 7: Grade 3 or 4 treatment emergent AEs from vactosertib monotherapy trials

AE Terms	MP-001 (n=35), n (%)	MP-MDS-01 (n=9), n (%)	Total (n=60), n %
All	16 (46)	6 (67)	22 (37)
Respiratory failure	3 (9)	0 (0)	3 (5)
Abdominal pain	2 (6)	0 (0)	2 (4)
Anaemia	0 (0)	2 (23)	2 (4)
Back pain	2 (6)	0 (0)	2 (4)
Hyponatraemia	2 (6)	0 (0)	2 (4)
Acidosis	1 (3)	0 (0)	1 (2)
Alanine aminotransferase increased	1 (3)	0 (0)	1 (2)
Arthritis	0 (0)	1 (12)	1 (2)
Aspartate aminotransferase increased	1 (3)	0 (0)	1 (2)
Asthma	0 (0)	1 (12)	1 (2)

Blood bilirubin increased	1 (3)	0 (0)	1 (2)
Cerebrovascular accident	1 (3)	0 (0)	1 (2)
Convulsion	1 (3)	0 (0)	1 (2)
Dehydration	1 (3)	0 (0)	1 (2)
Dyspnoea	1 (3)	0 (0)	1 (2)
Gastrointestinal haemorrhage	1 (3)	0 (0)	1 (2)
Headache	1 (3)	0 (0)	1 (2)
Hemiparesis	1 (3)	0 (0)	1 (2)
Hypokalaemia	1 (3)	0 (0)	1 (2)
Hypophosphataemia	0 (0)	1 (12)	1 (2)
Nausea	1 (3)	0 (0)	1 (2)
Pleural effusion	1 (3)	0 (0)	1 (2)
Pulmonary oedema	1 (3)	0 (0)	1 (2)
Pyelonephritis	1 (3)	0 (0)	1 (2)
Sepsis	1 (3)	0 (0)	1 (2)
Sinus tachycardia	1 (3)	0 (0)	1 (2)
Small intestinal obstruction	1 (3)	0 (0)	1 (2)
Stridor	1 (3)	0 (0)	1 (2)
Tumour pain	1 (3)	0 (0)	1 (2)
Upper gastrointestinal haemorrhage	0 (0)	1 (12)	1 (2)
Vomiting	1 (3)	0 (0)	1 (2)
Weight decreased	1 (3)	0 (0)	1 (2)

No subjects experienced Grade 3 or 4 AEs in MP-VAC-105 study. And three grade 5 events were reported from vactosertib monotherapy trials; disease progression (MP-001), gastric ulcer perforation (MP-001), and metastatic ovarian cancer (MP-001), none of which were causally related with vactosertib.

Listed below are the adverse events that were deemed related to, or from which one could not exclude the possibility of its relationship with vactosertib, as determined by MedPacto. For the purpose of determining regulatory authority reportability, when assessing expectedness, listed below are the adverse events that are considered to be expected (Table X).

Table 8 List of adverse events of Vactosertib that can be considered expected

System Organ Class (MedDRA SOC)	Adverse Event (MedDRA PT)
Gastrointestinal disorders	Constipation
	Diarrhoea
	Dyspepsia
	Nausea
	Vomiting

Immune system disorders [1)]	Asthma
	Interstitial lung disease
Renal and urinary disorder	Tubulointerstitial nephritis
Respiratory, thoracic and mediastinal disorders	Lung infiltration [2)] – not related, as a descriptive term rather than diagnostic. However, it can be considered as related when there is underlying immune mechanism involved.
General disorders and administration site conditions	Fatigue
Investigations	Alanine aminotransferase increased
	Aspartate aminotransferase increased
Nervous system disorders	Headache
Skin and subcutaneous tissue disorders	Rash [3)]
	Pruritus

1) Considered related, in line of worsening of immune-related AE when combined with immune checkpoint inhibitor
2) Considered not related, as a descriptive term rather than diagnostic. However, it can be considered as related when there is underly ing immune mechanism involved.
3) Even though the preferred term of reported AE is not exactly 'rash', if the event is not significantly different from 'rash' in clinical perspective, it could be assessed as 'expected'

But among the adverse events listed in this table, those with the severity of 4 or 5 are considered unexpected.

Table 9: Serious AEs from vactosertib monotherapy trials

AE Terms	MP-001 (n=35), n (%)	MP-VAC-105 (n=16), n (%)	MP-MDS-01 (n=9), n (%)	Total (n=60), n %
All	16 (46)	1 (7)	2 (23)	19 (32)
Respiratory failure	2 (6)	0 (0)	0 (0)	2 (4)
Abdominal pain	1 (3)	0 (0)	0 (0)	1 (2)
Asthma	0 (0)	0 (0)	1 (12)	1 (2)
Back pain	1 (3)	0 (0)	0 (0)	1 (2)
Cerebrovascular accident	1 (3)	0 (0)	0 (0)	1 (2)
Convulsion	1 (3)	0 (0)	0 (0)	1 (2)
Dehydration	1 (3)	0 (0)	0 (0)	1 (2)
Disease progression	1 (3)	0 (0)	0 (0)	1 (2)
Dyspnoea	1 (3)	0 (0)	0 (0)	1 (2)
Gastric ulcer perforation	1 (3)	0 (0)	0 (0)	1 (2)
Gastrointestinal haemorrhage	1 (3)	0 (0)	0 (0)	1 (2)
Hemiparesis	1 (3)	0 (0)	0 (0)	1 (2)
Nausea	1 (3)	0 (0)	0 (0)	1 (2)
Ovarian cancer metastatic	1 (3)	0 (0)	0 (0)	1 (2)

Pericarditis	1 (3)	0 (0)	0 (0)	1 (2)
Pleural effusion	1 (3)	0 (0)	0 (0)	1 (2)
Pneumonia	1 (3)	0 (0)	0 (0)	1 (2)
Presyncope	0 (0)	1 (7)	0 (0)	1 (2)
Pyelonephritis	1 (3)	0 (0)	0 (0)	1 (2)
Sepsis	1 (3)	0 (0)	0 (0)	1 (2)
Small intestinal obstruction	1 (3)	0 (0)	0 (0)	1 (2)
Stridor	1 (3)	0 (0)	0 (0)	1 (2)
Tumour pain	1 (3)	0 (0)	0 (0)	1 (2)
Upper gastrointestinal haemorrhage	0 (0)	0 (0)	1 (12)	1 (2)
Vomiting	1 (3)	0 (0)	0 (0)	1 (2)

Three SAEs from vactosertib monotherapy were reported as vactosertib related AEs: cerebrovascular accident (MP-001), respiratory failure (MP-001), presyncope (MP-VAC-105).

Table 10: Treatment emergent AEs leading to vactosertib discontinuation from vactosertib monotherapy trials

AE terms	MP-001 (n=35), n (%)	Total (n=60), n %
All	8 (23)	8 (14)
Cerebrovascular accident	1 (3)	1 (2)
Convulsion	1 (3)	1 (2)
Dyspnoea	1 (3)	1 (2)
Gastric ulcer perforation	1 (3)	1 (2)
Ovarian cancer metastatic	1 (3)	1 (2)
Respiratory failure	1 (3)	1 (2)
Small intestinal obstruction	1 (3)	1 (2)
Stridor	1 (3)	1 (2)

No patients from MDS-01 and MP-VAC-105 studies experience AE leading to treatment discontinuation.

Table 11: Adverse drug reaction (≥3%) from vactosertib monotherapy

AE Term s	MP-001 (n=35), n (%)	MP-VAC-105 (n=16), n (%)	MP-MDS-01 (n=9), n (%)	Total (n=60), n (%)
Headache	5 (15)	5 (32)	1 (12)	11 (19)
Fatigue	10 (29)	0 (0)	1 (12)	11 (19)
Nausea	9 (26)	1 (7)	0 (0)	10 (17)
Diarrhoea	5 (15)	1 (7)	1 (12)	7 (12)
Decreased appetite	6 (18)	0 (0)	0 (0)	6 (10)

Vomiting	5 (15)	0 (0)	0 (0)	5 (9)
Hypophosphataemia	3 (9)	0 (0)	1 (12)	4 (7)
Constipation	4 (12)	0 (0)	0 (0)	4 (7)
Dermatitis acneiform	2 (6)	0 (0)	1 (12)	3 (5)
Aspartate aminotransferase increased	3 (9)	0 (0)	0 (0)	3 (5)
Pruritus	3 (9)	0 (0)	0 (0)	3 (5)
Abdominal pain	2 (6)	0 (0)	0 (0)	2 (4)
Alanine aminotransferase increased	2 (6)	0 (0)	0 (0)	2 (4)
Amylase increased	2 (6)	0 (0)	0 (0)	2 (4)
Anaemia	2 (6)	0 (0)	0 (0)	2 (4)
Blood alkaline phosphatase increased	2 (6)	0 (0)	0 (0)	2 (4)
Dysgeusia	2 (6)	0 (0)	0 (0)	2 (4)
Dyspepsia	2 (6)	0 (0)	0 (0)	2 (4)
Lipase increased	2 (6)	0 (0)	0 (0)	2 (4)
Muscular weakness	2 (6)	0 (0)	0 (0)	2 (4)
Pyrexia	2 (6)	0 (0)	0 (0)	2 (4)
Rash maculo-papular	2 (6)	0 (0)	0 (0)	2 (4)

- Vactosertib may increase immunologic toxicities of when administered in combination with anti-cancer PD1/PD-L1 pathway inhibitors.

Dose Limiting Toxicity.

- Dose limiting toxicity is defined as any of the following: Any occurrence of death as result of adverse event regardless of attribution;
- Any non-hematologic grade ≥3 toxicity (CTCAEv5 criteria), except for nausea, vomiting or diarrhea lasting 3 days or less;
- Any grade 4 neutropenia (CTCAEv5 criteria) of any duration;
- Any grade ≥ 3 neutropenia that has not recovered to grade ≤ 2 within 7 days of onset;
- Any grade ≥ 3 febrile neutropenia (temperature ≥);
- Any grade ≥ 3 thrombocytopenia associated with clinically significant bleeding; or requiring platelet transfusion.

13.1.2 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE

reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  -All adverse events will be considered possibly related to the study drug unless there is clear evidence that the event is not related to the study drug.

13.1.3 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
https://research.weill.cornell.edu/compliance-integrity/wcm-institutional-review-board/immediate-reporting-policy

13.1.5 Reporting Events to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.1.6 Events of Special Interest

Not applicable.

13.1.7 Reporting of Pregnancy

If a female subject becomes pregnant during study, they will be withdrawn from study and all study procedures. Permission will be requested from subject to follow pregnant woman to pregnancy outcome. Pregnancy will be reported as an SAE as outlined in sections 13.2.

13.2 Definition of SAE

In accordance with US Food and Drug Administration (FDA) regulations, an AE will be classified as a Serious Adverse Event (SAE), whether or not it is considered to be associated with the study drug, when it meets any of the following criteria:

- Results in death;
- Is life-threatening (that is, places patient at immediate risk of death);

- Requires inpatient hospitalization or prolongation of existing hospitalization (note: planned hospitalization or outpatient surgery due to a pre-existing condition will not be regarded as an SAE in this study);
- Results in persistent or significant disability/incapacity; or
- Other important medical events that, based upon appropriate medical judgment, are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the other outcomes defining an SAE.

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.2.2 Reporting of SAE to FDA

IND application sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is serious. Fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information.

i. death,
ii. a life-threatening adverse event,
iii. in-patient hospitalization or prolongation of existing hospitalization,
iv. a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
v. a congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or research subject and may require medical or surgical intervention to prevent one of the outcomes listed as serious

CDER INDs:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

13.2.3 Reporting of SAE to MedPacto Inc.

Institution will send MedPacto copies of any and all serious adverse event reports filed with the FDA or other applicable regulatory authorities, as well as copies of any correspondence with the FDA or other applicable regulatory authorities, regarding any and all serious adverse events, irrespective of association with the Study Drug(s) in the course of the Clinical Trial, within five (5)

business days of such report or correspondence being sent to the FDA or other applicable regulatory authorities. Copies should be faxed directly to MedPacto Safety Department at 82-31-888-9949.

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the patient discontinues participation from the study.

13.4 Time Period and Frequency for Event Assessment and Follow Up

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Reportable events will be monitored with start dates occurring any time after informed consent is obtained until 30 days after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

Note: Per FDA IND guidance, no attribution of relatedness or expectedness to study agent is to be considered separately from other adverse events.

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

14.1.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPIRTSOs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UPIRTSO report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UPIRTSO;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UPIRTSO.

To satisfy the requirement for prompt reporting, UPIRTSOs will be reported using the following timeline:

- UPIRTSOs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UPIRTSO will be reported to the IRB and to the DCC/study sponsor within 24 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP) within the IRB's receipt of the report of the problem from the investigator.

15. Data and Safety Monitoring Plan (DSMP)

Subjects will be closely monitored by the treating physician and investigators. Laboratory and clinical evaluations will be performed regularly to assess efficacy and potential toxicities. All subjects will undergo a thorough physical examination at least once per cycle and at more frequent intervals when study agent doses are being adjusted per prospective rules Decision *(*see Table 3). Subjects will be provided with contact information and instructions to contact research staff to report any new or worrisome symptoms. Safety data will be evaluated by the investigator on an ongoing basis. Adverse event reporting is described Section 13 *Adverse Event Reporting Requirements*.

The principal investigator will be primarily responsible for monitoring the safety of the study, adverse events, both serious and non-serous and deaths that occur during study participation by subjects. All adverse events will be monitored until they resolve or are clearly determined to be due to a subject's disease or intercurrent illness(es).

At the completion of Tier 1, all data necessary to evaluate Criteria for Decision to Proceed to Tier 2 section) will be reported to WCM Statistician, WCM DSMB and Medpacto. The Simon Two-stage

Optimum Design is expected to minimize the number of subjects exposed to vactosertib if it is found to be an unsuitable agent for the treatment of anemic patients with Ph-neg MPNs. If 1 or more subjects meets theendpoint then the study will proceed to Tier 2 and another 25 subjects will be enrolled). This decision will be submitted to WCM IRB at the time of continuing review.

After completion of Tier 2, all data necessary to evaluate will be reported to WCM Statistician, WCM DSMB and Medpacto. If four or more subjects meet the Composite Response & Toxicity Endpoint then vactosertib will have shown preliminary efficacy and feasibility to justify further evaluation as an agent to treat anemic patients with Ph-Neg MPNs. This interpretation will be submitted to WCM IRB at the time of continuing review.

Should the Stopping Rules for Tier 1 or for Tier 2 be met, accrual of new subjects will be immediately suspended and the WCM IRB and Medpacto will be notified. The study DSMB will meet to review study data. The DSMB may either recommend permanent closure of the study or may allow protocol revision/amendment and submission to WCM IRB for review. DSMB recommendations will be submitted to Medpacto and WCM IRB.

All protocol amendments and consent form modifications will be made by the Principal Investigator. Medpacto will have the opportunity to review and approve the changes prior to submission of these changes to the local IRB.

Section 7.9, *Criteria for Removal from Study*, details treatment stopping rules for individual patients.

Appendix A

Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)

Instructions: Please circle the number corresponding with how each symptom as affected you.

Symptom	1 to 10 (0 if absent) ranking* 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your	
• General activity	(Does not interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely interferes)
• Mood	(Does not interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely interferes)
• Walking ability	(Does not interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely interferes)
• Normal work (includes work both outside the home and daily chores)	(Does not interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely interferes)
• Relations with other people	(Does not interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely interferes)
• Enjoyment of life	(Does not interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely interferes)

Circle the one number that describes how, during the past Week how much difficulty you have had with each of the following symptoms

2

Filling up quickly when you eat (Early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal pain	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with headaches	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Dizziness/ Vertigo/ Lightheadedness	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/ Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Difficulty sleeping	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Depression or sad mood	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with sexual desire or Function	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Cough	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
What is your overall quality of life?	(As good as it can be) 0 1 2 3 4 5 6 7 8 9 10 (As bad as it can be)

3

Appendix B

The Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score(MPN-SAF TSS): Prospective International Assessment of an Abbreviated SymptomBurden Scoring System among 1408 MPN Patients

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Myeloproliferative Neoplasm Symptom Assessment FormTotal Symptom Score (MPN-SAF TSS)

Symptom	1 to 10 (0 if absent) ranking 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours*	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes how, during the past week how muchdifficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/ Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

* Question used with permission from the MD Anderson Cancer Center BriefFatigue Inventory ©

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