Official Protocol Title:	A Phase 2 Multi-Center, Open Label Study to Assess the Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of Bomedemstat in Patients with Polycythemia Vera (PV)
NCT Number:	NCT05558696
Document Date:	29-Jul-2024

Protocol Title	A Phase 2 Multi-Center, Open Label Study to Assess the Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of Bomedemstat in Patients with Polycythemia Vera (PV)
Protocol No.	IMG-7289-CTP-203 / MK-3543-004
Investigational Product	Bomedemstat (IMG-7289 / MK-3543)
Indication	Polycythemia Vera
Study Phase	Phase 2
EudraCT Number	2022-002262-32
IND Number	130,789
Sponsor	**Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc.** **126 East Lincoln Avenue** **P.O. Box 2000** **Rahway, NJ 07065 USA**
Version and Date	
Amendment 04	29 July 2024

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 4	29-JUL-2024	The statistical methods section has been updated to state that all endpoints will be descriptive, and no formal hypothesis testing will be conducted.
Amendment 3	20-FEB-2024	The change was made to allow eligible participants to enroll in the bomedemstat extension study.
Amendment 2	07-JUL-2023	This change was made to update the Sponsor name and address due to the acquisition of Imago BioSciences, Inc. by Merck & Co., Inc.
Amendment 1	03-NOV-2022	Updated Screening Bone Marrow Aspirate and Biopsy, Dosing and Administration of Bomedemstat, Eligibility Criteria, Prohibited Medications, Guidelines, List of Inhibitors/Inducers, Requirements on the Length of Contraception, Bone Marrow Sampling Requirements, Section 16.6 – Criteria for Intolerance/Resistance to HU, Subject Contacts and PK Sampling, Summary of Clinical Data.
Original Protocol	07-JUL-2022	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 4

Overall Rationale for the Amendment:

The statistical methods section has been updated to state that all endpoints will be descriptive, and no formal hypothesis testing will be conducted.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 12.2, Power	Section revised to state that all endpoints will be descriptive, and that no formal hypothesis testing will be conducted. References to the null hypothesis and alternative hypothesis were removed.	This change was made to address non-Merck protocol template. This is a single arm study. As a result, no formal hypothesis testing will be done, and all statistical analysis will be descriptive.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 2, PROTOCOL SYNOPSIS	Study Objectives, Hypothesis: Removed section.	Section no longer applicable as no formal hypothesis testing will be conducted.
	Study Objectives, Primary Objectives: Revised first primary objective regarding timing of safety and tolerability evaluation.	To provide period during which safety and tolerability will be evaluated.
	Study Objectives, Primary Objectives: Revised second primary objective regarding reduction of Hct.	To clarify that reduction of Hct needs to be sustained for 12 weeks without concomitant phlebotomy.
	[redacted]	[redacted]
	Patient Reported Outcomes (PRO): Updated PRO objectives.	Updated based on new data.
	Bomedemstat Dosing: Updated daily dosing from 36 weeks to 52 weeks.	To clarify that the intent is for participants to be treated for 52 weeks.
	Bomedemstat Dosing (titrations): Updated Hct titration target to <42%.	Due to the natural fluctuation in hematocrit, setting a titration target just below the treatment target is designed to ensure that patients continuously maintain an Hct level below 45%.

Section Number and Name	Description of Change	Brief Rationale
	Bomedemstat Titration and Re-challenge Rules: Updated Hct level for titration and rechallenge rules.	To ensure patients maintain an Hct less than 45% once they achieve a stable dose.
	Exclusion Criterion 8: Removed strong inhibitors of CYP2D6.	Strong inhibitors and inducers of CYP2D6 were removed from the list of prohibited medications based on preclinical studies on file which show that bomedemstat is not a significant substrate.
	Guideline 2: Removed medication with potential to induce or inhibit CYP2D6 from list of medications to be monitored closely for potential effects of co-administration.	Refer to Section 2 rationale regarding exclusion criterion 8.
	Guideline 2: Removed strong inhibitors of CYP2D6 from list of medications prohibited while on study treatment.	Refer to Section 2 rationale regarding exclusion criterion 8.
	Prohibited Medications/Treatments: Removed strong inhibitors and inducers of CYP2D6 from list of prohibited medications during the study.	Refer to Section 2 rationale regarding exclusion criterion 8.
Section 3.5.4, Summary of Clinical Experience	Added clarification that IB should be referred to for further updates regarding bomedemstat data.	To clarify that any updates about clinical experience of bomedemstat are provided in the current IB.
Section 4, OBJECTIVES	Removed Hypothesis from section heading.	Refer to Section 2 rationale on removal of hypothesis language.
Section 4.1, Hypothesis	Removed section, renumbered subsequent sections.	Refer to Section 2 rationale on removal of hypothesis language.
Section 4.2, Objectives	Removed subsection numbering and heading, renumbered subsequent sections.	Section heading no longer required now that Hypothesis subsection is removed.
Section 4.1, Primary	Revised first primary objective regarding timing of safety and tolerability evaluation.	Refer to Section 2 rationale on revision of first primary objective.
	Revised second primary objective regarding reduction of Hct.	Refer to Section 2 rationale on revision of second primary objective.
Section 4.3, Exploratory	Re-ordered Exploratory heading from Section 4.2.5 to Section 4.3.	[redacted]
[redacted]	Moved [redacted] section as a subsection of the Exploratory Objectives.	Refer to Section 2 rationale on moving [redacted] under Exploratory Objectives.
Section 4.3.2, Patient [redacted]	Moved [redacted] section as a subsection of the Exploratory Objectives.	Refer to Section 2 rationale on moving [redacted] under Exploratory Objectives.
	Updated PRO objectives.	Refer to Section 2 rationale on update of PRO objectives.
Section 5.1, Overview	Updated daily dosing from 36 weeks to 52 weeks.	Refer to Section 2 rationale on language update in Bomedemstat Dosing (daily dosing).
Section 6.1.2, Exclusion Criteria	Exclusion Criterion 8: Removed strong inhibitors of CYP2D6.	Refer to Section 2 rationale regarding exclusion criterion 8.

Section Number and Name	Description of Change	Brief Rationale
Section 6.4, Guidelines	Guideline 2: Removed medication with potential to induce or inhibit CYP2D6 from list of medications to be monitored closely for potential effects of co-administration.	Refer to Section 2 rationale regarding exclusion criterion 8.
	Guideline 2: Removed strong inhibitors of CYP2D6 from list of medications prohibited while on study treatment.	Refer to Section 2 rationale regarding exclusion criterion 8.
Section 6.5, Prohibited Medications/ Treatments	List Number 6: Removed strong inhibitors and inducers of CYP2D6 from list of prohibited medications during the study.	Refer to Section 2 rationale regarding exclusion criterion 8.
	List Number 8: Removed strong inhibitors of CYP2D6 from list of prohibited medications during the study.	Refer to Section 2 rationale regarding exclusion criterion 8.
Section 7.2.2, Administration and Dosage	Updated daily dosing from 36 weeks to 52 weeks.	Refer to Section 2 rationale on language update in Bomedemstat Dosing (daily dosing).
	Updated Hct titration target to <42%.	Refer to Section 2 rationale on updated Hct titration target.
	Table 1: Updated Hct level for titration and rechallenge rules.	Refer to Section 2 rationale on updated Hct level in Bomedemstat Titration and Re-challenge Rules.
Section 11.2, Adverse Events	Updated overdose definition and procedures.	To align definition of overdose with the definition being implemented for MK-3543.
Section 12.1, General Considerations	Added clarification that detailed methodology for statistical analyses will be documented in a separate SAP.	To clarify that SAP will be provided as a separate document from the protocol.
Section 12.2, Power	Updated definition of the primary endpoint (response rate) to align with updates made to the primary objective elsewhere in the protocol.	Refer to Section 2 rationale on revision of second primary objective.
	Added text and table regarding observed response rates.	To provide an estimated clinically meaningful response rate for this estimation only study, which is based on the response rates for existing agents.
Section 12.5, Primary Analysis	Revised language on primary objective regarding reduction of Hct.	Refer to Section 2 rationale on revision of second primary objective.
	Added clarification that primary analysis will be summarized using a point estimate and its 95% CI using exact binomial method with reference to Clopper and Pearson.	To clarify the analysis for the primary endpoint.

Section Number and Name	Description of Change	Brief Rationale
Section 12.6, Secondary Analysis	Added week 52 timepoints for secondary analysis.	Refer to Section 2 rationale on language update in Bomedemstat Dosing (daily doing).
	Added clarification that spleen volume will be analyzed centrally.	To clarify that central review is being utilized for this study.
Section 12.7, Exploratory Endpoints	Re-ordered Exploratory Endpoints heading from previous Section 12.9 to Section 12.7.	Refer to Section 2 rationale on moving [redacted] under Exploratory Objectives.
[redacted]	Moved [redacted] as a subsection of the Exploratory Endpoints.	Refer to Section 2 rationale on moving [redacted] under Exploratory Objectives.
[redacted]	Moved [redacted] section as a subsection of the Exploratory Endpoints.	Refer to Section 2 rationale on moving [redacted] under Exploratory Objectives.
	Updated PRO analysis to align with updates made to PRO objectives elsewhere in the protocol.	Refer to Section 2 rationale on update in PRO objectives.
	Added clarification on how PRO analysis will be analyzed and summarized with reference to Liang and Zeger.	To clarify the analysis for the PRO endpoints.
Section 12.8, Interim Analysis	Added new section for Interim Analysis.	To add a planned interim analysis for efficacy evaluation.
Section 16.7, Strong CYP3A4 Inhibitors and Strong CYP3A4 Inducers	Revised section heading and table to remove strong CYP2D6 inhibitors.	Refer to Section 2 rationale regarding exclusion criterion 8.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
<, ≤, >, ≥	less than, less than or equal to, greater than, greater than or equal to
±	plus or minus
µL	microliter
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
ATRA	all-*trans* retinoic acid or tretinoin
BCR-ABL	breakpoint cluster region-Abelson
BM	bone marrow
Bomedemstat (IMG-7289 / MK-3543)	*N*-[(2*S*)-5-{[(1*R*,2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1*H*-1,2,3-triazol-1-yl)benzamide, **bis-tosylate salt**
BUN	blood urea nitrogen
°C	degrees Centigrade
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CI	confidence interval
cLDA	constrained longitudinal data analysis
Clinical Benefit	not meeting “progressive disease” criteria as *per* Appendix 16.5 and safely tolerating bomedemstat
CoREST	Co-repressor for RE1-silencing transcription factor
CR	complete remission or response
CRO	contract research organization
CRP	C-reactive protein
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
Cxcl	chemokine (C-X-C Motif) ligand

Abbreviation	Definition
CV	coefficient of variation
CYP	cytochrome P450
D	day
dL	deciliter
DIC	disseminated intravascular coagulation
DILI	drug-induced liver injury
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DNMT1	DNA-methyltransferase 1
D_s	starting dose
DSMC	Data Safety Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture
ELN	European Leukemia Network
EMH	extramedullary hematopoiesis
EMR	electronic medical records
EoS	end of study
EoT	end of treatment
EPO	erythropoietin
ESC	embryonic stem cell
ET	essential thrombocythemia
FAD	flavin adenine dinucleotide
Free base of bomedemstat	*N*-[(2*S*)-5-{[(1*R*,2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, **free base**
FSH	follicle stimulating hormone
G	gram
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GFI1	growth factor independent 1 transcription factor
GFP^+	green fluorescent protein cell-positive
GFR	glomerular filtration rate

Abbreviation	Definition
GGT	gamma glutamyltransferase
GM-CSF	granulocyte-macrophage colony stimulating factor
GMP	Good Manufacturing Practices
H	histone
Hb	hemoglobin
HBV	hepatitis B virus
Hct	hematocrit
HCV	hepatitis C virus
HDAC	histone deacetylase
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HREC	Human Research Ethics Committee
HSC	hematopoietic stem cell
HU	hydroxyurea; Hydrea®, hydroxycarbamide
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	interferon
IFN-α	interferon alpha
IL	interleukin
INR	International normalized ratio
IP	investigational product
IRB	Institutional Review Board
ISF	Investigator Site File
IUD	intrauterine device
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
JAK	Janus Kinases
K	lysine
KD	knockdown
KDM1A	lysine-specific demethylase 1
Kg	kilogram
L	liter
LAM	lactational amenorrhea method

Abbreviation	Definition
LDH	lactate dehydrogenase
LIC	leukemia initiating cell
LPE	Limited Physical Examination
LSD1	lysine-specific demethylase 1
LSDi	LSD1 inhibition or inhibitors
MAO	monoamine oxidase(s)
MAOI	monoamine oxidase inhibitor(s)
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
Mg	milligram
mITT	modified intent-to-treat
mL	milliliter
MPL	myeloproliferative leukemia virus oncogene, thrombopoietin receptor
MPN	myeloproliferative neoplasias or neoplasms, myeloproliferative diseases
MRI	magnetic resonance imaging
mRNA	messenger RNA
MTD	maximum tolerated dose
MYB	V-Myb Avian Myeloblastosis Viral Oncogene Homolog
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
nM	nanomolar
NSAID	nonsteroidal anti-inflammatory drug
NuRD	nucleosome remodeling and histone deacetylase
OCT4	octamer-binding transcription factor 4
ONC	Office of the National Coordinator for Health Information Technology
PD	pharmacodynamic(s)
PE	physical examination
PEG-IFN	pegylated interferon alfa-2a; peginterferon alfa-2a; Pegasys®, Besremi®
PGIC	Patient Global Impression of Change
PI	Principal Investigator (at each site responsible for patient care)

Abbreviation	Definition
PISCF	Participant Information Sheet/Consent Form
PK	pharmacokinetic(s)
PKAP	Pharmacokinetic Analysis Plan
PMF	primary myelofibrosis
POCBP	participant of childbearing potential
PPV-MF	post-polycythemia vera myelofibrosis
PR	partial remission or response
PRO	Patient Reported Outcome
PT	prothrombin time
PV	polycythemia vera
QD	once daily
RBC	red blood cell
RDW	red cell distribution width
REST	RE-1 silencing transcription factor
RNA	ribonucleic acid
SAB	Safety Advisory Board
SABP	Safety Advisory Board Plan
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOX2	sex determining region Y-box 2
SRM	Study Reference Manual
SRY	sex determining region Y
TCP	tranylcypromine
TEAE	treatment emergent adverse event
TF	transcription factor
ULN	upper limit of normal
US	United States
VPN	virtual private network
WBC	white blood cell
WHO	World Health Organization

2 PROTOCOL SYNOPSIS

Protocol Title: A Phase 2 Multi-Center, Open Label Study to Assess the Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of Bomedemstat in Patients with Polycythemia Vera (PV)

Protocol No: IMG-7289-CTP-203 / MK-3543-004

Sites: Approximately 15 sites in the United States, United Kingdom, and Australia with additional sites and countries as needed.

Study Objectives:

Primary Objectives: To evaluate in patients with PV treated with bomedemstat the:

- Safety and tolerability of bomedemstat up to Week 52
- Incidence of patients who achieve a sustained reduction of hematocrit (Hct) to <45% for 12 weeks without concomitant phlebotomy by Week 36

Secondary Objectives: To evaluate in patients with PV treated with bomedemstat the:

- Durability of reduction of hematocrit to <45% without phlebotomy
- Incidence and durability of reduction of platelet count to ≤450 × 10^9/L
- Incidence and durability of reduction of white blood cell (WBC) count to <10 × 10^9/L
- Incidence of new thrombotic or major hemorrhagic events
- Incidence of achieving a reduction in spleen volume by Week 36 in patients with enlarged spleen at baseline
- Incidence of progression to post-polycythemia vera myelofibrosis (PPV-MF), myelodysplastic syndrome (MDS) or transformation to acute myeloid leukemia (AML)

[redacted]

Investigational Drug: The active drug substance is identified as bomedemstat (IMG-7289 / MK-3543). Bomedemstat is an irreversible inhibitor of LSD1. The chemical name is: N-[(2S)-5-{[(1R, 2S)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4- methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt.

Bomedemstat will be supplied as capsules in multiple strengths. These strengths, based on bomedemstat free base, *i.e.*, the active substance, may include: 5, 10, 25 and 50 mg. Capsule strengths provided may change throughout the duration of the study. Such details will be included *via* updates to the Pharmacy Manual.

Study Population: Approximately twenty patients eighteen years of age or older in a population of PV patients requiring cytoreduction that have failed at least one standard cytoreductive therapy (failure is the equivalent of resistance or intolerance).

Methodology: This is a Phase 2 multi-center, open-label study evaluating the safety, efficacy, pharmacokinetics and pharmacodynamics of bomedemstat administered orally once daily in patients with PV.

Preclinical testing of LSD1 inhibition in mouse models of myeloproliferative neoplasm induced apoptosis in mutant stem/progenitor cells, reduced inflammatory cytokines, reduced spleen length and weight, decreased bone marrow fibrosis if present, and reduced extramedullary hematopoiesis. Additionally, LSD1 inhibition with bomedemstat was shown in a *Jak2*^{V617F} mouse model of essential thrombocythemia (ET)/PV to selectively decrease the number of malignant megakaryocytes as well as reduce elevated platelets, red cells and granulocytes (Jutzi *et al.,* 2018).

Bomedemstat has been investigated in patients with AML, myelodysplastic syndrome (MDS), myelofibrosis (MF) and ET, with notable improvements in the MF and ET populations including dose-dependent decreases in IL-8, platelets, and neutrophils. In the clinical setting of PV, bomedemstat is expected to reduce red cell production. As a consequence of hematopoietic stem cells acquiring a *JAK2* (somatic) mutation, hematopoiesis in PV, especially the megakaryocyte-erythroid progenitor, is biased toward the erythrocytic lineage, a maturation process dependent on LSD1 activity. Consistent with preclinical models, LSD1 inhibition in PV is expected to reduce elevated red cell mass, platelets and neutrophils.

The therapeutic goal for the treatment of PV is to inhibit the activity of LSD1 in hematopoietic cells for only a *fraction* of the 24-hour dosing cycle, sufficient to reduce the production of red cells whose over-production characterizes this condition. In association with this therapeutic goal, considerations leading to the choice of a safe starting dose include chronic toxicology studies in conjunction with the clinical experience to date, the starting dose of bomedemstat of 40 mg/d has been selected (see Section 3.7 for additional details pertaining to starting dose and regimen).

To ensure patient safety, a Safety Advisory Board (SAB) will perform reviews at least quarterly of safety parameters and pharmacodynamic markers to draw conclusions around the safety and pharmacodynamic effect of bomedemstat.

Study Conduct: Patients will be treated daily for 36 weeks, returning every other week (bi-weekly) for the first 12 weeks (Weeks 2, 4, 6, 8, 10 and 12) and then monthly for the remaining 24 weeks (Weeks 16, 20, 24, 28, 32 and 36) for study assessments and dose titration as needed (see Section 7.2.2). It is anticipated that by Week 12, the majority of patients will have achieved a stable dose. For safety purposes, bi-weekly visits may continue at the PI's discretion post-Week 12 if necessary.

Patients deriving clinical benefit (defined as not meeting progressive disease criteria as *per* Appendix 16.5) and safely tolerating bomedemstat may continue to receive bomedemstat beyond Week 36, with no interruption in dosing. Such patients will return for study assessments monthly. Patients discontinuing treatment with bomedemstat should undergo End of Treatment (EoT) and End of Study (EoS) visits. After 52 weeks of treatment, eligible patients may transition to a bomedemstat extension study. If available, patients who qualify can undergo an EoT visit and transition to the bomedemstat extension study without the need for a Follow up Period/EoS visit.

Patients will be followed closely throughout the study for Adverse Events (AEs) by frequent monitoring of clinical signs and symptoms as well as safety labs. Efficacy and pharmacodynamic effects will be closely monitored by frequent hematology assessments of peripheral blood. Throughout dosing, transfusions or phlebotomy may be administered if needed in accordance with standard institutional guidelines.

Bomedemstat Dosing: All patients will begin dosing on Day 1 at the starting dose of 40 mg/d and be treated daily for 52 weeks. Through the use of dose titration (see Section 7.2.2), the dose of bomedemstat will be adjusted for each patient to that dose that provides sufficient exposure to safely inhibit the activity of LSD1 in hematopoietic cells for a fraction of the dosing cycle without resulting in Grade ≥1 thrombocytopenia. Given the short lifespan of a human platelet compared to a red cell, approximately 7 days *versus* approximately 120 days, patients will be dosed using the platelet count as a biomarker of the activity of bomedemstat on the inhibition of LSD1. Details on the selection and rationale for the starting dose and titration schedule can be found in Section 3.7. Dose-titration, both upward and downward, is contingent on a hematology assessment. The first up-titration is not permitted before Week 6, and the second up-titration may occur no sooner than 6 weeks after the first up-titration (*e.g.*, if an up-titration occurs at Week 6, the next up-titration may not occur until Week 12). Beginning at Week 16, up-titrations are permitted no more frequently than every 4 weeks from the previous up- or down-titration.

Down-titrations can be made (or the current dose maintained) at any time in the best interest of the patient. Up-titrations will be made in increments of 5 or 10 mg, and down-titrations in decrements of 10 mg/d.

[redacted]

[redacted] The hematocrit titration target expected to be associated with a clinically significant therapeutic effect is:

- A hematocrit <42%

Titration and re-challenge rules to be used for titration assessment purposes, based on evaluation of platelet, absolute neutrophil (ANC) and Hct counts are noted below.

Bomedemstat Titration and Re-challenge Rules

Important: ANC ≥0.5 × 10^9/L (500 neutrophils/μL) is needed for up-titration. For ANC below this threshold, maintain or adjust the current dose in accordance with the rules below.

Hematology Assessment		Titration and Re-challenge Rules		
Plt Count (× 10^9/L)	**Hct %**	**Titration?**	**Titration Rule**	**Re-challenge Rule¥**
≥450	N/A	Up-titrate▫	Increase by 10 mg/d▫	N/A
150 – <450	42% – 45%	Up-titrate▫	Increase by 5 mg/d▫	N/A
150 – <450	<42%	Maintain dose	N/A	N/A
50 – <150	N/A	Down-titrate	Decrease by 10 mg/d	N/A
<50	**N/A**	**HOLD DOSE**	**N/A**	**At 50% of prior dose** when platelets return to ≥100**

ANC, absolute neutrophil count; CBC, complete blood count; Hct, hematocrit; N/A, not applicable; Plt, platelet.
▫ The first up-titration is not permitted before Week 6, and the second up-titration may occur no sooner than 6 weeks after the first up-titration (*e.g.*, if an up-titration occurs at Week 6, the next up-titration may not occur until Week 12). Beginning at Week 16, up-titrations are permitted no more frequently than every 4 weeks from the previous up- or down-titration. Down-titrations can be made (or the current dose maintained) at any time in the best interest of the patient.
**Patients requiring a dose hold should have CBC with differential monitored at least weekly for safety and to enable re-challenge as soon as platelet count returns to ≥100 × 10^9/L, if safe to do so. Re-challenge at 50% of the previous mg/d dose.
¥Upon re-challenge, all of the above rules reapply.

Study Duration: Screening may commence up to 28 days prior to first dose. Patients will receive approximately 52 weeks of dosing in this study. Participants may be eligible to enroll in the bomedemstat extension study if the participant is safely tolerating bomedemstat and receiving clinical benefit in the opinion of the investigator. Patients will be followed for 30 days post last dose. The anticipated duration of participation in the study is expected to be approximately 60 weeks from first patient visit to last patient visit.

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Study Procedures and Assessments: The procedures and assessments outlined below are also summarized in Study Visit Procedures Section 9 and the Schedule of Assessments Appendix 16.1.

Informed Consent must be provided by the patient before any study-related procedures initiate.

AEs will be assessed at every visit from time of consent through 30 days post last dose (to the EoS/ED visit).

Complete Medical History including demographics, confirmation of PV diagnosis per WHO; PV disease history; PV treatment history; and phlebotomy history.

Washout of prior cytoreductive therapy for condition under study for 2 weeks (4 weeks for interferon) prior to study drug initiation. Phlebotomy may continue as clinically indicated.

The Myelofibrosis Symptom Assessment Form (MFSAF) v4.0 7-day recall will be completed during Screening as close to Day -7 as possible and within the 2 days leading up to or on the day of every visit throughout the study except for any additional bi-weekly visits implemented after Week 12 for patients whose dose has not stabilized (see Study Reference Manual for details).

ECOG Performance Status (Appendix 16.4) will be assessed at every visit throughout the study except for any additional bi-weekly visits implemented after Week 12 for patients whose dose has not stabilized.

Patient Global Impression of Change (PGIC) will be completed at Weeks 12, 24 and 36, and every 12 weeks thereafter as long as the patient qualifies for treatment, at EoT, ED, and upon suspicion of disease progression (see Study Reference Manual for details).

Physical Examinations (PE): a **Full PE** will be performed at Screening and includes height, weight, vital signs, and spleen measurement. **Limited PEs** will be performed pre-dose Day 1 and at every visit throughout the study except for any additional bi-weekly visits implemented after Week 12 for patients whose dose has not stabilized. Limited PEs include:

- Weight;
- A review of body systems to assess change from the previous PE;
- Vital signs: heart rate, respiratory rate, temperature and systolic/diastolic blood pressure; and,
- Spleen measurement: the spleen edge is determined by palpation, measured in centimeters, using a soft ruler/tape, from the costal margin to the point of greatest splenic protrusion in the mid-clavicular line. The spleen should be measured in the same manner at all visits, ideally by the same examiner.

Serum pregnancy testing will be performed for participants of childbearing potential (POCBP) at Screening, pre-dose Day 1, every 4 weeks throughout the study (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, etc.) as long as the patient qualifies for treatment, upon suspicion of disease

progression, at the EoT and EoS/ED visits, and if pregnancy is suspected while the patient remains on study.

Bone marrow aspirate* and biopsy will be performed for morphology review, including fibrosis grade and correlative studies:

- During Screening UNLESS performed within the 3 months prior to the first dose of bomedemstat **AND** bone marrow biopsy slides or the formalin fixed paraffin embedded block are available from that sampling and can be provided to the central laboratory for review. **Importantly**, fibrosis score will be performed locally on Screening samples to enable assessment of patient eligibility.
- At Week 36 (±7 days).
- Approximately every 12 months (±28 days) thereafter as long as the patient qualifies for treatment.
- At EoT, ED, and upon suspicion of disease progression (unless performed within the prior 5 weeks).

*Aspirate from the first pull whenever possible, but none beyond the second, is required (except in case of a dry tap).

MRI (CT) of spleen: Spleen volume should be measured by MRI (or CT if the patient is not a candidate for MRI) of the abdomen according to standard procedures.

- Pre-dose Day 1 (±2 days).
- At Week 12, Week 24, and Week 36 visits (±7 days).
- Approximately every 6 months (±14 days) thereafter, as long as the patient qualifies for treatment.
- At EoT, ED, and upon suspicion of disease progression (unless performed within the prior 5 weeks).

Clinical laboratory measures: The following laboratory measures will be performed during Screening, including erythropoietin (if test is available at institution), pre-dose Day 1, upon suspicion of disease progression, at the EoT and EoS/ED visits, and in accordance with the below:

- Serum chemistry: every 4 weeks throughout the study (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, etc.) as long as the patient qualifies for treatment
- Hematology with automated or manual differential (as needed to ensure all analytes are resulted): every clinic visit throughout the study
- Coagulation (PT/aPTT/INR): every 4 weeks throughout the study (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, etc.) as long as the patient qualifies for treatment
- Urinalysis: at Weeks 12, 24, and 36, and every 12 weeks thereafter as long as the patient qualifies for treatment (Weeks 48, 60, etc.)

Subject contacts (*i.e.*, phone or email) for PK purposes:

- On Day -1, the subject will be contacted and reminded to fast overnight (at least 8 hours)

- On *the day prior* to the Week 2 visit, and on *the day prior* to either the Week 4, Week 6 or Week 8 visit, as applicable, the subject will be contacted and study staff will:
  - Collect and record the exact time the subject took their bomedemstat that day
  - Remind the subject to fast overnight (at least 8 hours) and that bomedemstat will be administered in the clinic

Pharmacokinetics: The PK analysis consists of three sessions of sparse sampling:

- *Session 1*: Day 1 of dosing
- *Session 2*: Week 2 (Day 15)
- *Session 3*: Any regularly scheduled study visit from Week 4 (Day 29) to Week 8 (Day 57)

Each PK sample time-point requires approximately 4 mL of blood, and at each session, 5 samples will be drawn for a total of 20 mL of blood. The required sampling times at each session are:

- Pre-dose (-60 minutes)
- 1h (±15 minutes) post-dose
- 2h (±30 minutes) post-dose
- 4h (±30 minutes) post-dose
- 6h (±60 minutes) post-dose

Genomic analysis:

- Germline samples (cheek swab and hair roots) may be collected at any time during Screening, up to and including pre-dose Day 1. Repeat sampling may be necessary, pending sample viability and yield.
- Blood samples will be collected pre-dose Day 1, Weeks 12, 24, and 36, every 12 weeks thereafter as long as the patient qualifies for treatment, upon suspicion of disease progression, at EoT and EoS/ED visits.

Future Correlative Studies: Blood samples will be collected for potential future studies pre-dose Day 1, Weeks 12, 24, and 36, every 12 weeks thereafter as long as the patient qualifies for treatment, upon suspicion of disease progression, at EoT and EoS/ED visits.

Cytokines: Blood samples will be collected pre-dose Day 1, Weeks 12, 24, and 36, every 12 weeks thereafter for as long as the patient qualifies for treatment, upon suspicion of disease progression, and at the EoT and EoS/ED visits.

Titration Assessment: At every visit following Day 1, patients will be assessed for dose titrations using the titration and re-challenge rules in Table 1.

- The first up-titration is not permitted before Week 6, and the second up-titration may occur no sooner than 6 weeks after the first up-titration (*e.g.*, if an up-titration occurs at Week 6, the next up-titration may not occur until Week 12). Beginning at Week 16, up-titrations are permitted no more frequently than every 4 weeks from the previous

up- or down-titration. Down-titrations can be made (or the current dose maintained) at any time in the best interest of the patient.

Qualification Assessments: At Week 36, patients will be assessed for eligibility to receive additional treatment. Patients deriving clinical benefit and safely tolerating bomedemstat *per* the Principal Investigator (PI) qualify for continued treatment.

Eligibility Criteria: All applicable Inclusion and none of the Exclusion Criteria must be met.

Inclusion Criteria:

1. Age ≥18 years.
2. History of confirmed diagnosis of Polycythemia Vera *per* World Health Organization (WHO) diagnostic criteria for myeloproliferative neoplasms (Appendix 16.2, Arber *et al.*, 2016).
3. Bone marrow fibrosis score of Grade 0 or Grade 1, as *per* a slightly modified version (Appendix 16.3, Arber *et al.*, 2016) of the European Consensus Criteria for Grading Myelofibrosis (Thiele *et al.*, 2005).
4. Patients that have failed at least one standard cytoreductive therapy to lower hematocrit (failure is the equivalent of resistance or intolerance). A modified version of the European Leukemia Net (ELN) criteria for intolerance or resistance to hydroxyurea is located in Appendix 16.6, (Barosi *et al.*, 2010). Ruxolitinib and interferon refractoriness or intolerance will be left to the discretion of the Investigator.
5. Platelet count ≥250 × 10^9/L.
6. ANC ≥1.5 × 10^9/L.
7. Life expectancy >36 weeks.
8. Able to swallow capsules.
9. Must have discontinued prior cytoreductive therapy for condition under study for 2 weeks (4 weeks for interferon) prior to study drug initiation. Phlebotomy may continue as clinically indicated.
10. Amenable to blood draws, spleen size determination, bone marrow evaluations, and peripheral blood sampling during the study.
11. Participants of childbearing potential (POCBP) and fertile men (see Section 6.1) must agree to use an approved method of contraception from Screening until 30 days* after last bomedemstat dose. Methods of contraception include: estrogen and progestogen combined hormonal contraception which inhibits ovulation; progestogen-only hormonal contraception associated with inhibition of ovulation; intrauterine device (IUD); bilateral tubal occlusion; vasectomized partner in a monogamous sexual relationship (vasectomy or tubal ligation at least six months prior to dosing); and, complete sexual abstinence (defined in Section 6.1). Males with a pregnant partner must agree to use a condom to avoid exposure to the developing child. Patients practicing

abstinence must agree to use an approved method of contraception should they become sexually active during the study.

See Appendix 16.10 for contraceptive guidance.

Exclusion Criteria

1. Eastern Cooperative Oncology Group (ECOG) performance status (Appendix 16.4) of 3 or greater.
2. Pregnant or breastfeeding or planning on being pregnant while on study treatment and 30 days after the last dose of study treatment.
3. Unresolved treatment-related toxicities from prior therapies (unless resolved to baseline or ≤Grade 1).
4. Uncontrolled active infection.
5. Known positive for HIV if not well-controlled (*i.e.*, undetectable viral load), or active hepatitis, type A, B, or C. Patients with occult or prior HBV may be included if HBV DNA is undetectable. Patients who are positive for HCV antibody are eligible only if HCV RNA PCR is negative.
6. Evidence of increased risk of bleeding, including any of the following:
   - aPTT or PTT >1.5 × the upper limit of normal
   - International normalized ratio (INR) >1.5 × the local upper limit of normal in the absence of therapeutic anticoagulation
   - History of severe thrombocytopenia or platelet dysfunction unrelated to a myeloproliferative disorder or its treatment
   - Known bleeding disorder (*e.g.*, dysfibrinogenemia, factor IX deficiency, hemophilia, Von Willebrand's disorder, Disseminated Intravascular Coagulation [DIC], fibrinogen deficiency, or other clotting factor deficiency)
7. Evidence of significant renal or hepatic insufficiency as defined by any of the following:
   - Calculated glomerular filtration rate (GFR; using the Cockcroft-Gault equation) <40 mL/min or serum creatinine >1.5 × the local upper limit of normal
   - Aspartate transaminase (AST) or alanine aminotransferase (ALT) ≥3 × the local upper limit of normal
8. Current use of a prohibited medication (*e.g.*, strong inhibitors and inducers of CYP3A4 including antiarrhythmics such as propafenone, monoamine oxidase A and B inhibitors (MAOIs), romiplostim, etc.) or expected to require any of these medications during treatment with the investigational drug.
9. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to bomedemstat or LSD1 inhibitors (*i.e.*, monoamine oxidase inhibitors; MAOIs) that contraindicates participation.
10. Patients with impaired decision-making capacity.

GUIDELINES: These guidelines are not intended to supersede best clinical judgment by the Investigator. Please contact the Medical Monitor with questions or with planned/known divergences from these guidelines.

1. In general, supportive care (transfusions, administration of anti-microbials, etc.) should be maintained in accordance with institutional policy. Additionally, it is advised that:
    a. Patients with a platelet count ≤10 × 10^9/L (10,000/µL) be transfused.
    b. Patients with a hemoglobin <8 g/dL be transfused.
    c. Phlebotomy be performed to maintain a hematocrit <45%.
2. Patients taking medications with the potential to induce or inhibit CYP3A4 should be monitored closely for potential effects of co-administration. The Investigator may consider more frequent monitoring of CBC if clinically indicated. Strong inhibitors and inducers of CYP3A4 are prohibited while on study treatment (Appendix 16.7).
3. Cessation of bomedemstat is invariably associated with a rebound in thrombopoiesis and platelet counts may easily exceed the baseline value. When bomedemstat is discontinued, the platelet count and hematocrit should be monitored closely and an alternative cytoreductive therapy to lower platelets and hematocrit may commence within 24-48 hours, if appropriate.

PROHIBITED MEDICATIONS/TREATMENTS: The following medications and vaccinations are prohibited during the study. Please consult the Medical Monitor with any questions.

- Investigational vaccines (*i.e.*, those not licensed or approved for Emergency Use) are not allowed.

  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.
- All cytotoxic agents, including hydroxyurea
- All hematopoietic growth factors: romiplostim, eltrombopag, erythropoietin (EPO), granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF)
- Monoamine oxidase A and B inhibitors (MAOIs)
- Anticoagulant, anti-platelet, and nonsteroidal anti-inflammatory drug (NSAID) including aspirin use is prohibited only when a patient's platelet count is <100 × 10^9 /L (100 k/µL)
- Strong inhibitors and inducers of CYP3A4
- Class 1c antiarrhythmics such as propafenone
- Chloroquine and others whose metabolites are strong inhibitors of CYP3A4 (Appendix 16.7)

Management of Study Toxicities: Adverse event severity will be reported using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5, published 27-NOV-2017. Please refer to Section 8.2 for additional detail on management of study toxicities, including reduction of the starting dose should it be necessary.

Hematologic Toxicity: Hematologic values outside of the normal reference range are inherent features of MPNs and are expected effects of many therapeutic attempts to manage these diseases. The effects of bomedemstat on normal myeloid hematopoiesis observed in non-clinical and clinical studies are expected; these are pharmacodynamic effects of LSD1 inhibition by bomedemstat, thus are considered on-target effects.

Non-hematologic Toxicity: Patients who experience a Grade 3 or 4 non-hematologic AEs deemed related to bomedemstat (possibly, probably or definitely) may have their dose adjusted downward by 50% if the PI deems it safe for the patient to continue on bomedemstat. Any patient that experiences an AE that results in discontinuation of bomedemstat therapy may begin alternative cytoreductive therapy to lower platelets and hematocrit within 24-48 hours.

Stopping Rules:

Bomedemstat will be discontinued in the event of any one of the following:

- Post Grade 3 or 4 non-hematologic AEs deemed related to bomedemstat (possibly, probably, or definitely), the patient's clinical condition either worsens at any time or fails to demonstrate significant improvement within 14 days, or the PI deems it unsafe for the patient to continue on bomedemstat.
- Post temporary interruption of bomedemstat due to platelet counts $<50 \times 10^9$/L (50k/µL), the patient's platelet counts do not return to $>150 \times 10^9$/L (150k/µL) within 21 days.

Patients who discontinue bomedemstat will enter follow-up beginning with the EoT visit.

3 INTRODUCTION

3.1 Background on the Disease to be Treated

The breakpoint cluster region-Abelson (*BCR-ABL)1*-negative myeloproliferative neoplasms (MPNs) are a family of related neoplastic disorders of bone marrow. The three main chronic *BCR-ABL1*-negative MPNs are polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) (Spivak 2017). The cardinal clinical features of these disorders are increased red cell mass in PV, increased platelet count in ET, and bone marrow fibrosis in PMF. The MPNs are clonal disorders arising most frequently from acquired (somatic) mutations in a multipotent hematopoietic stem/progenitor cell, resulting in abnormalities in red cell, granulocyte and platelet production often in association with marrow fibrosis and extramedullary hematopoiesis and, in some cases evolution to acute myeloid leukemia (AML).

PV is an indolent hematologic cancer characterized by erythrocytosis, thrombocytosis, elevated cytokines, and the potential to develop myelofibrosis and AML (Vannucchi *et al.*, 2017). Transformation to post-PV myelofibrosis and post-PV acute leukemia occurs at estimated rates of 20% (at 15 years) and <10% (at 20 years), respectively. Risk factors for poor survival include age over 60, leukocytosis, and a prior history of thrombosis (Barbui *et al.*, 2012).

Virtually all patients with PV have a mutation in Janus kinase 2 (*JAK2*), the majority resulting in the amino acid substitution, JAK2^{V617F}. In the setting of MPNs, *JAK2* mutations lead to constitutive signaling of the JAK–STAT pathway resulting in unregulated trilineage myeloid cell proliferation and excess cytokine production. Although *JAK2*^{V617F} homozygous subclones are found both in ET and PV patients, the expansion of a dominant homozygous subclone occurs almost exclusively in patients with PV (Passamonti *et al.*, 2017).

The main goals in the management of PV are to control symptoms and prolong survival by preventing thrombosis and leukemic transformation (Benevolo *et al.*, 2021). The safety and efficacy of low-dose aspirin and phlebotomy for the prevention of thrombotic complications in PV is well established in patients with no contraindication to aspirin therapy (Landolfi *et al.*, 2004). For patients at high-risk (age >60 years and/or prior history of thrombosis), cytoreductive therapy is needed in addition to low-dose aspirin and phlebotomy to reduce their thrombotic risk (Benevolo *et al.*, 2021). Hydroxyurea (HU), interferon alpha and peginterferon alfa (PEG-IFN) have been shown to be effective in the prevention of thrombotic events in patients with PV (Padrnos *et al.*, 2020). In addition, ropeginterferon was recently approved by the EMA in 2019 in adult PV patients without splenomegaly and by the FDA in 2021 (Gotlib, 2022).

HU is typically used as a first-line treatment, although PEG-IFN or ropeginterferon can be considered as well (NCCN Guidelines, 2022). HU is well tolerated in most patients, however, about 15–24% of patients become resistant or intolerant, with HU resistance affecting survival and increasing the risk of progression to myelofibrosis or acute leukemia (Alvarez-Larrán *et al.*, 2012; Alvarez-Larrán *et al.*, 2016). If patients become intolerant or resistant to their first-line treatment, the recommended treatment options are ruxolitinib, PEG-IFN (if not previously used), HU (if not previously used), or ropeginterferon or a clinical trial (NCCN Guidelines, 2022).

For high-risk PV patients that are resistant or intolerant to HU, PEG-IFN has demonstrated the ability to produce hematologic responses and suppress the malignant clone (Yacoub *et al., 2019*). However, long-term data regarding its potential effect on rates of transformation to AML and myelofibrosis are awaited (Padrnos *et al.*, 2020). Furthermore, while the pegylated forms of IFN seem to be better tolerated with fewer side effects than the earlier, non-pegylated forms, there still remains a concern of toxicity (Gotlib, 2022). Ruxolitinib is another second-line treatment that has been shown to effectively control the hematocrit, decrease spleen size, and reduce the symptom burden in patients with PV who are resistant or intolerant to HU (Vannucchi *et al.*, 2015). However, in a 5-year follow-up of these patients who initially had a response with ruxolitinib, roughly one-third did not maintain their clinicohematologic response. Additionally, patients treated with ruxolitinib were more likely to develop a herpes zoster infection and non-melanoma skin cancer compared to patients in the control arm receiving best available therapy (Kiladjian *et al.*, 2020). Based on the data available, there is still an unmet need for a therapy that will reduce red cell mass and thrombotic risk while improving the symptom burden among those with PV who are refractory to or intolerant of standard available therapy.

3.2 Background on the Drug Target

Lysine-specific demethylase 1 (LSD1), also known as KDM1A, is an enzyme that removes mono- and dimethyl groups from histone (H) H3 at critical lysines (K), K4 (Shi *et al.*, 2004). Methylation of histone H3K4 is a post-translational modification associated with changes in the confirmation of chromatin and rates of gene expression (Bannister and Kouzarides, 2011; Beisel and Paro, 2011).

LSD1 is localized to specific sites in the genome through the agencies of proteins that bind DNA directly, generally transcription factors (TFs) (Whyte *et al.*, 2012; Whyte *et al.*, 2013). Many TFs, both activators such as V-Myb Avian Myeloblastosis Viral Oncogene Homolog (MYB) and steroid hormone receptors, as well as repressors such as growth factor independence 1 transcription repressor (GFI1) and RE-1 silencing transcription factor (REST), recruit LSD1 to specific genomic locations (Metzger *et al.*, 2005; Saleque *et al.*, 2007; Lin *et al.*, 2010). LSD1 is part of a larger protein complex, containing, *e.g.*, Co-RE-1 silencing transcription factor (CoREST) or nucleosome remodeling and histone deacetylase (NuRD), which dictates the cell- and site-specific chromatin remodeling (Lee *et al.*, 2005; Foster *et al.*, 2010). These complexes may also include deoxyribonucleic acid (DNA) methyltransferase 1 (DNMT1) and histone deacetylases 1, 2 or 3 (HDAC1, 2, and 3) activities all of which contribute to maintaining or modifying the epigenetic state at that specific genomic site (Shi *et al.*, 2005; Orkin and Hochedlinger, 2011). Thus, an important property of LSD1 beyond its own enzymatic activity, is its function as a scaffold for other proteins and epigenetic enzymes that are co-recruited to genomic sites. Likewise, the LSD1 complex bound to specific sites may preclude the binding of other factors that in turn could influence transcription rates.

LSD1 is unique among the many histone demethylases in that it coordinates flavin adenine dinucleotide (FAD) to oxidatively remove one or two methyl groups, in the process producing H_2O_2 and formaldehyde. As such, FAD is an essential co-factor for LSD1 activity (Shi *et al.*, 2004).

The other 34 histone lysine demethylases, collectively termed the Jumonji demethylases, employ an iron-dependent mechanism to remove methyl groups from histone lysines (Klose *et al.*, 2006).

LSD1 plays a key role in regulating the progression from pluripotency to terminal differentiation and balancing quiescence and proliferation in hematopoietic stem cells (Adamo *et al.*, 2011; Wang *et al.*, 2007; Whyte *et al.*, 2012). LSD1 is recruited to "high confidence" promoters and super-enhancers of genes essential for normal development by the "master" TFs octamer-binding transcription factor 4 (OCT4), SRY (sex determining region Y)-box 2 (SOX2), Nanog and the co-activator Mediator. Though not essential for maintenance of the embryonic stem cell (ESC) state, as part of the NuRD complex, LSD1 "decommissions" enhancers of genes maintaining the pluripotency program allowing ESC to differentiate. LSD1 is essential for the complete shutdown of the ESC gene expression program as cells transition to more differentiated cell states (Whyte *et al.*, 2012). The role LSD1 plays in ESCs is phenomenologically similar to the essential role LSD1 plays during myeloid hematopoiesis, in which enhancers active in hematopoietic stem cells (HSCs) generating a stem cell gene expression signature are also "decommissioned", allowing commitment of progenitors to specific myeloid lineages (Lara-Astiaso *et al.*, 2014). Enhancers essential for terminal myeloid differentiation in lineage-specific progenitor cells, the so-called *de novo* enhancers, must be poised for activation by the placement of H3K4me1 marks. As progenitors commit to differentiation, LSD1 is down-regulated dramatically allowing *de novo* enhancers and promoters to be stably activated with progressive methyl or acetyl additions on H3K4 and H3K27, respectively (Lara-Astiaso *et al.*, 2014).

3.3 Background on LSD1 in Myeloid Neoplasia

Over-expression of *LSD1* messenger RNA (mRNA) and excess LSD1 protein have been observed in many tumor types, including poorly differentiated neuroblastoma, squamous cell carcinoma, Ewing's sarcoma, AML, neuroendocrine carcinomas and epithelial tumors such as breast, prostate, bladder, small cell lung and colon cancers (Metzger et al., 2005; Kahl et al., 2006; Schulte et al., 2009; Lim et al., 2010). In MPNs, LSD1 was over-expressed mainly in megakaryocytes and erythroid precursors and to a lesser degree in early myeloid cells (Niebel *et al.*, 2014). Treatment of various tumor types in culture with LSD1 inhibition or inhibitors (LSDi) has been reported to inhibit tumor growth, reduce their potential for migration and invasion, reduce clonogenic potential and eliminate cancer stem cells, induce markers of differentiation appropriate to the cell lineage, and induce apoptosis (Somervaille and Cleary, 2006; Somervaille *et al.*, 2009; Harris *et al.*, 2012; Zhang *et al.*, 2013). In various models of mouse leukemia, treatment with LSDi induced monocytic markers of differentiation, reduced clonogenic potential of leukemia initiating cells (LICs), and induced cell death (Harris *et al.*, 2012).

LSD1 activity is present in a high proportion of malignant myeloid blasts cells (Lin *et al.*, 2011; Rhodes *et al.*, 2007; Wouters *et al.*, 2009). LSD1 gene expression is among the highest in immunophenotypically stem/progenitor populations of myeloid neoplastic cells (Goardon *et al.*, 2011; Somervaille *et al.*, 2009; Harris *et al.*, 2012).

Proof-of-concept studies of the therapeutic activity of LSDi were performed in well established, preclinical mouse models of MPNs (*Jak2*^{V617F}, *Mpl*^{W515L}). Compared to mice treated with vehicle, LSDi in *Mpl*^{W515L} mice markedly suppressed myeloproliferation reducing granulocyte and platelet

counts, thus establishing therapeutic efficacy. Spleen weights in treated animals showed a dose-proportional decrease. Histopathological analysis of bone marrow and spleen confirmed a marked reduction in myeloproliferation, as well as a reversal of extramedullary hematopoiesis (EMH). Most notably, there was near-complete resolution of reticulin fibrosis in the bone marrow in the LSDi treatment arm. LSDi had a significant impact on serum inflammatory cytokine concentrations as exemplified by a very marked reduction in the plasma concentration of the Chemokine (C-X-C Motif) Ligand 5 (Cxcl5 or interleukin [IL]-8 in humans), a key participant in the pathologic inflammatory state of MPN.

LSDi also reduced the mutant cell burden. In mice treated with vehicle, 74.6% of circulating cells were green fluorescent protein cell-positive (GFP^+), while only 43.2% of circulating cells were GFP^+ in LSDi-treated mice. Flow cytometry analysis of spleen and bone marrow revealed reduced numbers of cluster of differentiation (CD)$11b^+/Gr1^+$ myeloid cells and $CD41^+$ megakaryocytes. The numbers of mutant GFP^+ myeloid cells and megakaryocytes in these tissues were also significantly reduced by LSDi treatment. The decrease in platelet counts and mutant clone burden, and the improvement in the inflammatory environment after 28 days of LSDi supported targeting LSD1 in patients with an MPN.

3.4 Background on Bomedemstat

Bomedemstat is an orally available, irreversible inhibitor of LSD1, active against LSD1 and human AML cells at concentrations of <5 nM. Irreversible inhibitors of LSD1 include the monoamine oxidase (MAO) inhibitor tranylcypromine (TCP), used for the treatment of depression for decades. The targets of TCP therapy, however, include all FAD-dependent monoamine oxidases in addition to LSD1. TCP inactivates LSD1 in a manner identical to its action on MAO-A and MAO-B because these three enzymes share a similar oxidative chemistry. Bomedemstat has >4000-fold selectivity for LSD over monoamine oxidase A and B, the mostly closely related human enzymes. Pharmacokinetic (PK) studies in mouse, rat and dog and PK modeling in human systems suggest that once-daily dosing in humans would be sufficient to achieve therapeutic exposures. Twenty-six- and thirty-nine-week toxicologic studies in rat and dog, respectively, showed that normal myeloid hematopoiesis is impacted in the anticipated fashion: platelet, red cell, and granulocyte production is reduced following administration but is fully reversible when drug has cleared. There were no observable extramedullary effects that could *not* be attributed to the pharmacodynamic (PD) effects on myeloid differentiation. The anticipated dosing for the treatment of MPN is expected to be continuous daily dosing.

3.5 Summary of Clinical Data

The following Phase 1 and 2 clinical trials investigating bomedemstat are underway or completed. Refer to the bomedemstat IB for additional information.

- **IMG-7289-CTP-101:** Open label, multi-center Phase 1/2a study assessing the safety, steady-state pharmacokinetics and pharmacodynamics of bomedemstat administered with and without ATRA (all-*trans* retinoic acid or tretinoin) to patients with advanced myeloid malignancies (n=45)

- **IMG-7289-CTP-102:** Open label, multi-center Phase 2b study to assess the safety, steady-state pharmacokinetics and pharmacodynamics of bomedemstat in patients with myelofibrosis (n=90)
- **IMG-7289-CTP-201:** Open label, multi-center Phase 2b study to assess the safety, efficacy and pharmacodynamics of bomedemstat in patients with essential thrombocythemia (n=73)

3.5.1 Summary of IMG-7289-CTP-101

Bomedemstat was administered safely as a single agent to 19 patients and in combination with ATRA to 26 patients with AML or myelodysplastic syndrome (MDS) for up to 500 days at doses ranging from 0.75-6.0 mg/kg. Of the 45 patients treated, 44 (98%) reported at least one serious adverse event (SAE). Eight (18%) patients had an SAE leading to death, only one of which (in a combination therapy patient) was assessed as related (classified as possibly, probably, or definitely related) to bomedemstat by the Investigator. SAEs deemed related to bomedemstat by the Investigator were reported for 13 (29%) of patients. Eleven (24%) patients discontinued treatment with bomedemstat due to an adverse event (AE). Only one event leading to discontinuation, in a bomedemstat alone patient, was deemed related to bomedemstat by the Investigator. No dose limiting toxicities (DLTs) were reported. There were also no safety signals observed by the Data Safety Monitoring Committee (DSMC) and no obvious relationship between dose and incidence or severity of AEs.

Overall, including both AML and MDS patients, 12/45 patients (26.7%; 95% CI 14.6, 41.9) in the study had an objective response defined as stable disease or better with study drug treatment. Of the 39 patients with AML who received study drug, an objective response was achieved in 11/39 (28.2%, 95% CI 15.0, 44.9) with the best overall response reported as: not evaluable for 12 patients (30.8%), resistant disease for 11 patients (28.2%), stable disease for 10 patients (25.6%), and partial response (PR) for 1 patient (2.6%). Of the 6 patients with MDS who received study drug, an objective response was achieved in 1/6 (16.7%, 95% CI 0.4, 64.1) with the best overall response reported as: disease progression for 2 patients (33.3%), not evaluable for 2 patients (33.3%), and stable disease for 1 patient (16.7%).

3.5.2 Summary of IMG-7289-CTP-102

Ninety (90) myelofibrosis patients were enrolled (note: only 89 unique patients were treated; 020-102 was taken off-study after a prolonged period off of study drug due to logistical challenges posed by the COVID-19 pandemic in the UK, and subsequently re-enrolled as patient 020-103); eighteen dosed with bomedemstat at a starting dose of 0.25 mg/kg/day in the Phase 1/2a, and twenty-five at a starting dose of 0.5 mg/kg/day and forty-seven at a starting dose of 0.6 mg/kg/d in the Phase 2b portion of the study.

In a preliminary analysis of the clinical data, platelet counts were reduced in all patients. Of the ninety patients included in this safety analysis (89 unique patients), 44 reported a total of 86 SAEs; three of these SAEs led to death (septic shock, respiratory failure and cerebrovascular accident, all deemed unrelated to bomedemstat per the Principal Investigator [PI]). Fourteen (16%) of the 86 SAEs reported, splenomegaly, cardiac failure, headache, rectal hemorrhage,

abdominal discomfort, abdominal wall hematoma, anemia, gastrointestinal hemorrhage, nausea (n=2), pyoderma gangrenosum, sepsis, thrombocytopenia and vertigo were assessed by the Investigator as related to bomedemstat. No safety signals were noted by the Safety Advisory Board (SAB).

3.5.3 Summary of IMG-7289-CTP-201

Seventy-three (73) ET patients were enrolled and administered bomedemstat at a starting dose of 0.6 mg/kg/day. In a preliminary analysis of the clinical data, platelet count was reduced to ≤400 × 10^9/L in 97% (35/36) of patients treated for more than 36 weeks with 83% (30/36) achieving a durable (≥12 weeks) platelet count of ≤400 × 10^9/L. Of the 73 patients included in this analysis, 17 reported a total of 28 SAEs. Five (18%) of the 28 SAEs reported (mouth hemorrhage, lower gastrointestinal hemorrhage, ileal ulcer, chronic gastritis and thrombocytopenia) were assessed as related to bomedemstat per the Investigator. No safety signals have been noted by the SAB.

3.5.4 Summary of Clinical Experience

Bomedemstat has demonstrable clinical activity in AML, MDS, myelofibrosis (MF) and ET patients. In accordance with each of the above referenced clinical protocols, a DSMC/SAB has regularly performed reviews of available safety data and, to date, there have been no apparent dose-related trends in AEs or changes in laboratory safety data, vital sign measurements, PE, or 12-lead electrocardiograms (ECGs) (collected in a subset of patients only) noted. There appears to be no obvious relationship between dose and incidence or severity of AEs.

For further details, please refer to the IB for updates and additional information regarding bomedemstat clinical studies, safety and efficacy data, preclinical toxicology, metabolism, and pharmacology.

3.6 Potential Clinical Risks and Benefits when Treating with an LSD1 Inhibitor

The treatment effects with an LSDi are distinct from treatment with standard cytotoxic agents or with JAK inhibitors. LSDi has specific effects on each myeloid lineage and appears to have different effects on each lineage for a given MPN. In wild-type healthy animals, LSD1 activity is required for the differentiation of progenitors to red cells, platelets and granulocytes. (LSD1 activity is not needed for monopoiesis.) Hence, LSDi changes the cellular composition in the marrow and the morphology of these cells. Likewise, distribution of blood cells based on lineage is also affected with an increase in the production of monocytes and a decrease in the other myeloid cell types; the production of platelets appears to be more sensitive to LSDi than granulocyte or red cell production. The treatment paradigm is to titrate drug exposure to that which lowers platelets into the normal range. The sensitivity to a given exposure of bomedemstat in PV patients, however, may be variable and understanding that dose-response is one of the objectives of this study.

The morphologic and clinical pathology changes may not be familiar to clinicians and hematopathologists. As such, there is potential for confusion in the interpretation of peripheral

hematologic parameters and the morphology of bone marrow cells. Outlined below are some of the anticipated clinical scenarios that might be observed in PV patients treated with bomedemstat based on non-clinical and clinical studies conducted by Sponsor and published reports of the effects of inhibiting LSD1:

1. With *complete* pharmacologic inhibition of LSD1, the red cell, platelet and neutrophil counts can be expected to decrease with zero order kinetics as a function of the lifespan of each cell type; hence, a linear decrease over time. Human platelets circulate for an average of seven to ten days; if LSD1 were to be inhibited completely, the platelet count would be predicted to fall below 10×10^9/L (10 k/μL) within a week. In this study, the goal is to safely reduce the red cell mass, as reflected by hematocrit as well as bring the platelet and WBC counts near or into the normal range. Notwithstanding, as thrombopoiesis appears most sensitive to LSDi, severe thrombocytopenia represents the greatest clinical risk.
2. The effects of LSDi on normal hematopoiesis are fully reversible. Bomedemstat is an irreversible inhibitor of LSD1, but as the bulk of drug is cleared in less than eight hours and production of newly synthesized LSD1 restores activity, megakaryocyte and red cell maturation will rebound within several days to weeks and can even exceed baseline values. If bomedemstat is discontinued, the platelet count and hematocrit should be monitored closely and an alternative cytoreductive therapy to lower platelets may commence within 24-48 hours after the cessation of bomedemstat, if appropriate.
3. As a consequence of inhibition of LSD1 in both rat and dog, megakaryocytes appear dysplastic and form syncytia in proportion to the degree of LSDi. Platelet volumes also increase dramatically as LSDi reaches a maximum and platelet counts fall. These effects are fully reversible after cessation of drug exposure.

Please refer to the IB for Safety Information.

3.7 Bomedemstat Dose Justification

A summary of the starting dose and titration schedule are provided below. Further information, including additional relevant data, can be found in the IB.

3.7.1 Rationale for and Safety of the Proposed Bomedemstat Starting Dose

The phenotypic effects of LSDi are mediated through changes in the gene expression patterns that are a consequence of transcriptional reprogramming that occurs in the absence of LSD1 activity (Harris *et al.*, 2012). The phenotypic consequences are cell-specific, and include proliferation, differentiation or cell death. In the primary pharmacology studies with bomedemstat, as well as in the assay for self-renewal potential (clonogenicity) these changes take place over a period of days to weeks. Complete and sustained inhibition of LSD1 may be the best strategy to rapidly reduce the leukemic stem cell burden in the case of AML; however, in a less aggressive myeloid neoplasm such as PV, chronic treatment at doses that do not completely inhibit LSD1 is anticipated to be well tolerated while having a significant impact on disease. At well tolerated doses in mouse MPN models, the gradual loss of cells bearing the MPN mutation (in *Jak2* or *Mpl*) is observed over the course of LSDi. What emerges from these mouse studies is

a strategy that balances safety with clinical efficacy: inhibit the enzyme for only a *fraction* of the 24-hour dosing cycle to allow some normal hematopoiesis to occur, thus preventing profound thrombocytopenia. This optimal therapeutic dose must be identified through dose-titration in each patient because variations in the severity of disease and likely other factors such as variable baseline normal thrombopoiesis, and variable PK will dictate the response to bomedemstat.

The therapeutic goal for the treatment of PV is to inhibit the activity of LSD1 in hematopoietic cells for only a *fraction* of the 24-hour dosing cycle, sufficient to reduce the production of red cells whose over-production characterizes this condition. Considerations leading to the choice of a safe starting dose include chronic toxicology studies in conjunction with the clinical experience of the patients who have received bomedemstat to date in IMG-7289-CTP-101 (AML), -102 (MF) and -201 (ET). In the CTP-101 protocol, bomedemstat was administered to patients with high-risk AML and MDS; the therapeutic thesis in that study was to *completely* inhibit LSD1 in all hematopoietic cells, targeting both leukemic stem cells and blasts, recognizing patients would need clinical support for cytopenias. The starting dose was 0.75 mg/kg/d and the effective dose, at which no safety signals were observed, was deemed to be 6.0 mg/kg/d. Though the great majority of the patients entered the study with Grade 3/4 thrombocytopenia, patients at all dose levels of bomedemstat required platelet transfusions. This sensitivity of thrombopoiesis to LSDi in high-risk AML/MDS patients may reflect the generally compromised nature of the bone marrow, including the reduction of megakaryocytes, in that disease.

Taking this observation into account in association with the therapeutic goal for the treatment of myeloproliferative neoplasms - inhibiting LSD1 activity in hematopoietic cells for only a fraction of the 24- hour dosing cycle - and PK modeling, the original starting dose in the CTP-102 protocol for myelofibrosis patients was 0.25 mg/kg/d. Platelet counts in the first twenty patients ranged from 102 to 1309 × 10^9/L and all required a dose increase to lower platelet counts. In a recent analysis of the ongoing IMG-7289-CTP-102 study in myelofibrosis patients, the daily dose of bomedemstat needed by a majority of patients to achieve a platelet count in the target range (50-75 × 10^9/L) ranged between 0.6 to 0.8 mg/kg/d with the full dosing spectrum of 0.4-1.5 mg/kg. The dose needed to reduce the platelet count to the target range in patients with MF or ET is not correlated with the starting platelet count or antecedent hematologic history. Platelet counts in patients with PV will, on average, be significantly higher than those in patients with myelofibrosis who have failed treatment with the standard of care. Notwithstanding, the kinetics of changes in platelet counts in patients with PV treated with bomedemstat are expected to be similar to those patients with myelofibrosis and ET.

Because the function of the megakaryocytic lineage is the most sensitive to LSDi, the platelet count is used as a biomarker for both safety and efficacy. Patients have been titrated through dose adjustments to a disease-specific target platelet count range to identify each individual patient's optimal dose of bomedemstat. The optimal dose is defined as that constant dose that maintains the platelet count in the prescribed target range over a period of at least 8 weeks. In CTP-102, the target platelet count range is 50-75 × 10^9/L (50-75 k/μL); in CTP-201, the target platelet count range is 200-400 × 10^9/L (200-400 k/μL). Titration rules are necessary because of the wide variation in exposure among patients (coefficient of variation [CV] is ~100%) for a given dose. Titration, however, has the benefit of enhancing safety and treatment responses; the ability

to titrate the dose in each patient to a specific objective clinical endpoint, *e.g.*, a platelet count in the normal range in the case of ET, maximizes the number of patients who receive a maximally effective dose and minimizes instances of over-dosing, *viz.*, thrombocytopenia.

The dosing regimens of bomedemstat in CTP-102 and CTP-201 include a weight-proportional starting dose of 0.6 mg/kg/d and weight-proportional incremental dose changes. The 0.6 mg/kg/d starting dose in patients with MF (CTP-102) was determined to be the optimal dose for approximately 25% of the patients with another 50% requiring one or two up-titrations. The remaining 25% of patients either required a third up-titration or a down-titration from the starting dose. In the CTP-201 (ET) study, patients received the same 0.6 mg/kg/d starting dose, ranging from 35 to 70 mg QD. For those patients dosed long enough to identify an optimal dose, the mean total daily starting dose was 46 mg QD and mean optimal dose was 54 mg QD. Of evaluable patients (N=36), this starting dose matched the optimal dose for 14% of patients; 31% required a down-titration whereas 56% required an up-titration. No patient in the CTP-201 study experienced a platelet count below 75 × 10^9/L (75 k/µL) by Day 28 indicating that the bi-weekly monitoring of the platelet count was sufficient to identify patients who required dose-adjustments and to prevent the occurrence of CTCAE v5 Grade ≥2 thrombocytopenia. Dose reductions have consistently resulted in an increase of platelet counts of >20% over a two-week period without an interruption in dosing.

PK studies in patients with AML (IMG-7289-CTP-101), MF, and ET receiving bomedemstat indicate that clearance is not influenced by body mass or body mass index, hence, the replacement of weight-proportional dosing with a fixed starting dose and fixed-dose increments. In the CTP-201 (ET) study patients for whom the optimal dose has been established (N=36), a fixed starting dose of 50 mg would be optimal for an estimated 8%, 53% would require an up-titration, and 36% would require a down-titration. Importantly, an estimated 70% would require an up- or down-titration of 20 mg or less.

PV is a trilineage disease in which the production of red cells, granulocytes and megakaryocytes are typically increased above normal levels. Platelet counts at the time of diagnosis are often elevated (mean 720 × 10^9/L [720 k/µL]) significantly above the normal range (>450 × 10^9/L [450 k/µL]), though lower than mean platelet counts in patients with ET (Kiladjian *et al.*, 2008). Accordingly, to enable PV patients to reach the optimum dose sufficient to reduce platelets below 450 × 10^9/L (450 k/µL) and the hematocrit below 45% while still maintaining an adequate safety margin, a bomedemstat starting dose of 40 mg QD has been selected. Up- or down-titrations will be 5 or 10 mg (as *per* Table 1 in Section 7.2.2).

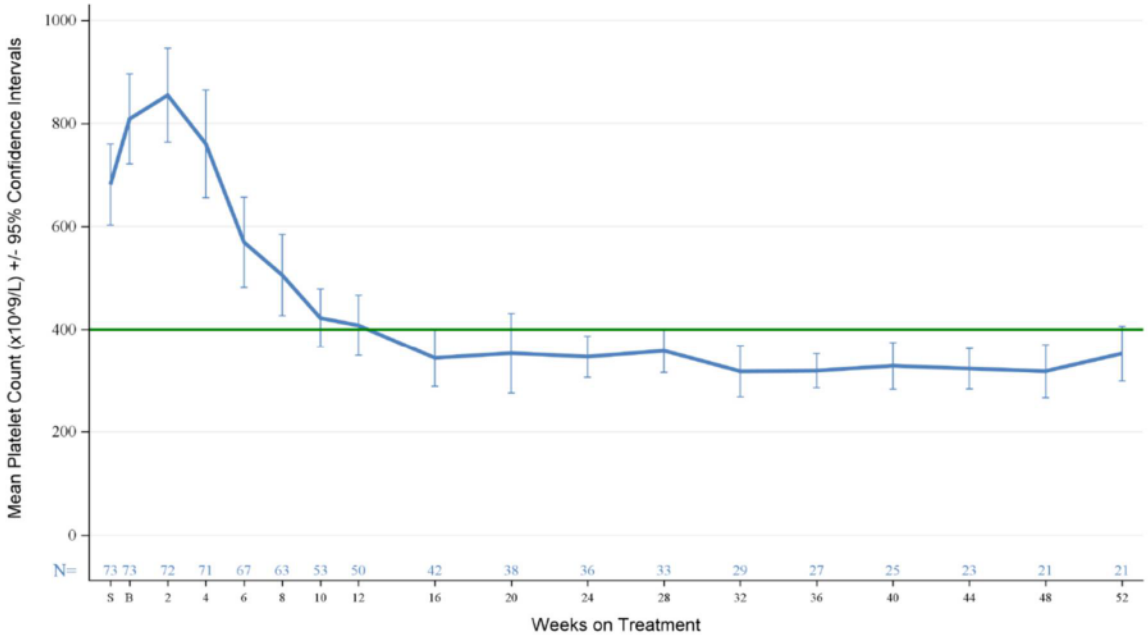
3.7.2 Rationale for the Bomedemstat Titration Schedule

Data from CTP-102 (MF) showed that dose-adjustment intervals of one week did not allow sufficient time for both drug exposure and platelet counts to reach steady-state. Though two-week intervals resulted in fewer subsequent dose titrations, 14 days between up-titrations was still not sufficient to reach a stable steady-state platelet count. The CTP-102 protocol was amended to permit up-titrations every three weeks and deemed adequate. In CTP-201 (ET), because the visit schedules are initially based on bi-weekly assessments, up-titrations are

allowed every four weeks. (In both studies, down-titrations may be made at any time in the interests of the patient at the treating physician's discretion.)

In examining the dose-response data in the CTP-102 and CTP-201 studies, platelet and WBC counts rose in the first 14 days of treatment with bomedemstat despite a washout period prior to the first dose (see Figure 1 below for CTP-201 platelet data). We ascribe this phenomenon to the recovery of the bone marrow following myelosuppression by the previous cytoreductive treatment regimen, with the patient's bone marrow rebounding to their "baseline disease state". Allowing for this phenomenon and to minimize subsequent dose adjustments, the first up-titration is not permitted before Week 6, and the second up-titration may occur no sooner than 6 weeks after the first up-titration (*e.g.*, if an up-titration occurs at Week 6, the next up-titration may not occur until Week 12). Beginning at Week 16, up-titrations are permitted no more frequently than every 4 weeks from the previous up- or down-titration. Down-titrations can be made (or the current dose maintained) at any time in the best interest of the patient.

Figure 1: Mean Platelet Count (±95% Confidence Interval) in 67 Patients with ET Treated with Bomedemstat in IMG-7289-CTP-201



Abbreviations: S=Screening, B=Last non-missing value closest to Day 1.
Following subjects have no day 1 so imputed last screen to day 1: 003-206,024-201,024-205,050-204,051-203

The safety of longer durations of treatment is supported by the 26- and 39-week toxicology studies in rat and dog, respectively. Treated animals in which thrombopoiesis is not completely inhibited show no observable adverse effects. The primary effects of LSDi appear confined to the bone marrow with secondary effects a consequence of cytopenias at higher doses.

At the doses proposed in this study, the concentration of bomedemstat is sufficient to inhibit the activity of LSD1 in hematopoietic cells for a fraction of the 24-hour dosing period allowing LSD1 activity to return and resume its function in normal hematopoiesis. Chronic daily administration of bomedemstat in rat, dog and humans has been well tolerated. No safety signals have been

observed in the AML/MDS, myelofibrosis or ET studies with bomedemstat at doses up to 6 mg/kg/d (360 mg/d for a 60 kg person).

In summary, the starting dose of 40 mg with titration adjustments of ± 5-10 mg has been chosen for this trial based on the safety, efficacy, and PK observed in clinical trials of bomedemstat in patients with ET and other MPNs. Given that platelet count is a marker of both safety and efficacy in the treatment of MPNs, and that PK data has demonstrated that body mass does not affect the clearance of bomedemstat, data suggests that the majority of patients enrolled will receive optimum clinical benefit at a steady-state dose of 40 mg ± 10 mg with manageable toxicity.

4 OBJECTIVES

PV is an indolent hematologic neoplasm characterized by erythrocytosis and often thrombocytosis, leukocytosis, elevated cytokines and a host of symptoms that include itching and fatigue. Splenomegaly is a consequence of extramedullary hematopoiesis. The clinical objectives of treatment are to reduce the rate of thrombosis. PV, like other MPNs, can evolve to myelofibrosis and/or AML.

This trial will study the effects of bomedemstat, an irreversible inhibitor of the enzyme LSD1, as a treatment of PV. LSD1 is an enzyme that regulates the maturation of megakaryocytes and erythrocytes from progenitors. Like other MPNs, PV results from an acquired mutation in HSCs that causes JAK/STAT pathway activation; in the case of PV, the mutation is almost always in the *JAK2* gene. Unlike ET, the bias of progenitor cell differentiation is toward the erythrocytic lineage (though PV is a trilineage disease). Given this skewed differentiation, the therapeutic hypothesis for treating PV with an LSD1 inhibitor such as bomedemstat is the greater sensitivity of erythropoiesis to LSDi than in ET or MF.

The following primary, secondary, and exploratory objectives will be evaluated in patients with PV treated with bomedemstat.

4.1 Primary

- Safety and tolerability of bomedemstat up to Week 52
- Incidence of patients who achieve a sustained reduction of hematocrit (Hct) to <45% for 12 weeks without concomitant phlebotomy by Week 36

4.2 Secondary

- Durability of reduction of hematocrit to <45% without phlebotomy
- Incidence and durability of reduction of platelet count to ≤450 × 10^9/L
- Incidence and durability of reduction of white blood cell (WBC) count to <10 × 10^9/L
- Incidence of new thrombotic or major hemorrhagic events
- Incidence of achieving a reduction in spleen volume by Week 36 in patients with enlarged spleen at baseline
- Incidence of progression to post-polycythemia vera myelofibrosis (PPV-MF), MDS, or transformation to AML

[redacted]

5 INVESTIGATIONAL PLAN

5.1 Overview

This is a Phase 2 multi-center, open-label study evaluating the safety, efficacy, PK and PD of bomedemstat administered orally QD in patients with PV.

The therapeutic goal for the treatment of PV is to inhibit the activity of LSD1 in hematopoietic cells for only a *fraction* of the 24-hour dosing cycle, sufficient to reduce the production of red cells whose over-production characterizes this condition. In association with this therapeutic goal, considerations leading to the choice of a safe starting dose include chronic toxicology studies in conjunction with the clinical experience of the patients who have received bomedemstat to date, the starting dose of bomedemstat of 40 mg/d has been selected.

To ensure patient safety, a SAB will perform reviews at least quarterly of safety parameters and PD markers to draw conclusions around the safety and PD effects of bomedemstat in this patient population.

Treatment will begin on Day 1 at the starting dose of 40 mg/d and continue daily for 52 weeks. Through the use of dose titration (see titration rules in Section 7.2.2), the dose of bomedemstat will be adjusted for each patient to that dose that provides sufficient exposure to safely inhibit the activity of LSD1 in hematopoietic cells for a fraction of the dosing cycle without resulting in Grade ≥1 thrombocytopenia. Given the short lifespan of a human platelet compared to a red cell, approximately 7 days *versus* approximately 120 days, patients will be dosed using the platelet count as a biomarker of the activity of bomedemstat on the inhibition of LSD1. Details on the selection and rationale for the starting dose and titration schedule can be found in Section 3.7.

Patients will return every other week (bi-weekly) for the first 12 weeks (Weeks 2, 4, 6, 8, 10, and 12) and then monthly for the remaining 24 weeks (Weeks 16, 20, 24, 28, 32, and 36) for study assessments and dose titrations as needed (see Section 7.2.2). It is anticipated that by Week 12 the majority of patients will have achieved a stable dose. For safety purposes, bi-weekly visits may continue at the PI's discretion post-Week 12 if necessary. At Week 36 a 'qualification' assessment will be performed to determine whether the patient is deriving clinical benefit (defined as not meeting progressive disease criteria as *per* Appendix 16.5) and safely tolerating bomedemstat. Patients qualifying for continued treatment beyond Week 36 should continue bomedemstat without interruption in dosing and return for study assessments monthly. Patients discontinuing treatment with bomedemstat should undergo an End of Treatment (EoT) visit on the day of last dose or as soon as possible thereafter, and an End of Study (EoS) visit approximately 30 days post last dose.

After all ongoing patients have reached 52 weeks of treatment, eligible patients may transition to a bomedemstat extension study. If available, patients who qualify can undergo an EoT visit and transition to the bomedemstat extension study without the need for a Follow up Period/EoS visit.

Patients will be followed closely throughout the study for both AEs by frequent monitoring of clinical signs and symptoms as well as safety labs. Efficacy and PD effects will be closely monitored by frequent hematology assessments of peripheral blood. Throughout dosing,

transfusions and phlebotomy may be administered if needed in accordance with standard institutional guidelines.

6 STUDY POPULATION

6.1 Study Entry Criteria

For purposes of eligibility, the following definitions apply:

- A participant is considered of childbearing potential (POCBP), *i.e.*, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.
- Abstinence is defined as refraining from heterosexual intercourse. True abstinence, when this is in line with the preferred and usual lifestyle of the subject is permitted. Periodic abstinence (*e.g.*, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to investigational product (IP), and withdrawal are not acceptable methods of contraception.

6.1.1 Inclusion Criteria

Patients must meet <u>all</u> of the applicable Inclusion Criteria and none of the Exclusion Criteria to be eligible for enrollment in this study:

1. Age ≥18 years.
2. History of confirmed diagnosis of Polycythemia Vera *per* World Health Organization (WHO) diagnostic criteria for myeloproliferative neoplasms (Appendix 16.2, Arber *et al.*, 2016).
3. Bone marrow fibrosis score of Grade 0 or Grade 1, as *per* a slightly modified version (Appendix 16.3, Arber *et al.*, 2016) of the European Consensus Criteria for Grading Myelofibrosis (Thiele *et al.*, 2005).
4. Patients that have failed at least one standard cytoreductive therapy to lower hematocrit (failure is the equivalent of resistance or intolerance). A modified version of the European Leukemia Net (ELN) criteria for intolerance or resistance to hydroxyurea is located in Appendix 16.6, Barosi *et al.*, 2010). Ruxolitinib and interferon refractoriness or intolerance will be left to the discretion of the Investigator.
5. Platelet count ≥250 × 10^9/L.
6. ANC ≥1.5 × 10^9/L.
7. Life expectancy >36 weeks.
8. Able to swallow capsules.

9. Must have discontinued prior cytoreductive therapy for condition under study for 2 weeks (4 weeks for interferon) prior to study drug initiation. Phlebotomy may continue as clinically indicated.
10. Amenable to blood draws, spleen size determination, bone marrow evaluations, and peripheral blood sampling during the study.
11. Participants must agree to use an approved method of contraception from Screening until 30 days after last bomedemstat dose.

Participants Assigned Male Sex at Birth If a participant is capable of producing sperm, the participant agrees to the following during the intervention period and for at least the time needed to eliminate the study intervention after the last dose of study intervention. The length of time required to continue contraception for the study intervention is 30 days:

- Abstains from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent

  OR

- Uses contraception as detailed below unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:

  - Uses a penile/external condom when having penile-vaginal intercourse with a nonparticipant of childbearing potential who is not currently pregnant and should also be advised of the benefit for that partner to use an additional method of contraception, as a condom may break or leak.

    Note: Participants capable of producing ejaculate whose partner is pregnant or breastfeeding must agree to use penile/external condom during each episode of sexual activity in which the partner is at risk of drug exposure via ejaculate.

  - Contraceptive use by participants capable of producing sperm should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

Participants assigned Female Sex at Birth A participant assigned female sex at birth is eligible to participate if not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a POCBP

  OR

- Is a POCBP and:

  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or is abstinent from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis),

during the intervention period and for at least the time needed to eliminate the study intervention after the last dose of study intervention. The length of time required to continue contraception for the study intervention is 30 days.

- The investigator should evaluate the potential for contraceptive method failure (*i.e.*, non-compliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.
- Abstains from breastfeeding during the study intervention period and for at least 30 days after study intervention with bomedemstat.
- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

See Appendix 16.10 for contraceptive guidance.

6.1.2 Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

1. Eastern Cooperative Oncology Group (ECOG) performance status (Appendix 16.4) of 3 or greater.
2. Pregnant or breastfeeding or planning on being pregnant while on study treatment and 30 days after the last dose of study treatment.
3. Unresolved treatment-related toxicities from prior therapies (unless resolved to baseline or ≤Grade 1).
4. Uncontrolled active infection.
5. Known positive for human immunodeficiency virus (HIV) if not well-controlled (*i.e.*, undetectable viral load), or active hepatitis, type A, B, or C. Patients with occult or prior HBV may be included if HBV DNA is undetectable. Patients who are positive for HCV antibody are eligible only if HCV ribonucleic acid (RNA) PCR is negative.
6. Evidence of increased risk of bleeding, including any of the following:
   - aPTT or PTT >1.5 × the upper limit of normal (ULN)
   - International normalized ratio (INR) >1.5 × the local ULN in the absence of therapeutic anticoagulation
   - History of severe thrombocytopenia or platelet dysfunction unrelated to a myeloproliferative disorder or its treatment
   - Known bleeding disorder (*e.g.*, dysfibrinogenemia, factor IX deficiency, hemophilia, Von Willebrand's disorder, Disseminated Intravascular Coagulation [DIC], fibrinogen deficiency, or other clotting factor deficiency)

7. Evidence of significant renal or hepatic insufficiency as defined by any of the following:
   - Calculated glomerular filtration rate (GFR; using the Cockcroft-Gault equation) <40 mL/min or serum creatinine >1.5 × the local ULN
   - Aspartate transaminase (AST) or alanine aminotransferase (ALT) ≥3 × the local ULN
8. Current use of a prohibited medication (*e.g.*, strong inhibitors and inducers of CYP3A4 including antiarrhythmics such as propafenone, monoamine oxidase A and B inhibitors [MAOIs], romiplostim, etc.) or expected to require any of these medications during treatment with the investigational drug.
9. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to bomedemstat or LSDi (*i.e.*, monoamine oxidase inhibitors; MAOIs) that contraindicates participation.
10. Patients with impaired decision-making capacity.

6.2 Patient Enrollment

A sufficient number of patients who fulfill the inclusion/exclusion criteria documented in Section 6.1 will be screened to ensure approximately 20 patients are enrolled and treated in this study.

6.3 Patient Withdrawal

In accordance with the Declaration of Helsinki, Good Clinical Practice (GCP), and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines and applicable regulations governing human subject protection, a subject has the right to withdraw from the study at any time for any reason. Subjects may also be removed from the study by the Sponsor or Investigator. The reason for withdrawal, if given, will be provided to the Sponsor and documented in the electronic case report form (eCRF). Patients will be requested to return for follow-up beginning with an EoT visit as *per* Section 9.5.1.

The Sponsor or Investigator may remove patients from the study for various reasons, including:

- Taking another investigational medicinal agent during their involvement in the study
- Use of a prohibited medication
- Major violation of, or deviation from, study protocol procedures which, in the judgment of the Medical Monitor, could adversely affect the patient or the integrity of the study including missing an extended duration of bomedemstat doses or other evidence of major non-compliance
- Withdrawal from the study is, in the Investigator's judgment, in the patient's best interest
- Experiencing an event that meets any of the Stopping Rules as *per* Section 8.2.3.

6.4 Guidelines

Patient safety is paramount. The guidelines provided below are intended to provide some consistency across sites by providing guidance to be used by the Investigator, the study staff and the patient to safeguard patient safety while maintaining data integrity. The guidelines are not

intended to supersede best clinical judgment by the Investigator. Please contact the Medical Monitor with questions or with planned/known divergences from these guidelines.

1. In general, supportive care (transfusions, administration of anti-microbials, etc.) should be maintained in accordance with institutional policy. Additionally, it is advised that:
    a. Patients with a platelet count ≤10 × 10^9/L (10,000/μL) be transfused.
    b. Patients with a hemoglobin (Hb) <8 g/dL be transfused.
    c. Phlebotomy be performed to maintain a hematocrit <45%.
2. Patients taking medications with the potential to induce or inhibit CYP3A4 should be monitored closely for potential effects of co-administration. The Investigator may consider more frequent monitoring of complete blood count (CBC) if clinically indicated. Strong inhibitors and inducers of CYP3A4 are prohibited while on study treatment (Appendix 16.7).
3. Cessation of bomedemstat is invariably associated with a rebound in thrombopoiesis and platelet counts may easily exceed the baseline value. When bomedemstat is discontinued, the platelet count and hematocrit should be monitored closely and an alternative cytoreductive therapy to lower platelets and hematocrit may commence within 24-48 hours, if appropriate.

6.5 Prohibited Medications/Treatments

The following medications and vaccinations are prohibited during the study. Please consult the Medical Monitor with any questions.

1. Investigational vaccines (*i.e.*, those not licensed or approved for Emergency Use) are not allowed.

    Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.
2. All cytotoxic agents, including hydroxyurea
3. All hematopoietic growth factors: romiplostim, eltrombopag, erythropoietin (EPO), granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF)
4. Monoamine oxidase A and B inhibitors (MAOIs)
5. Anticoagulant, anti-platelet, and nonsteroidal anti-inflammatory drug (NSAID) including aspirin use is prohibited only when a patient's platelet count is <100 × 10^9 /L (100 k/μL)
6. Strong inhibitors and inducers of CYP3A4
7. Class 1c antiarrhythmics such as propafenone
8. Chloroquine and others whose metabolites are strong inhibitors of CYP3A4 (Appendix 16.7)

6.6 Patients Who Terminate Early or Discontinue Study Medication

All patients who terminate the study early or discontinue bomedemstat, including those who discontinue bomedemstat due to an event meeting any of the Stopping Rules as *per* Section 8.2.3, will be requested to return for follow-up visits, beginning with an EoT visit as detailed in

Section 9.5.1. If a patient refuses to enter follow-up, then an Early Discontinuation (ED) visit should be performed as detailed in Section 9.5.2.

6.7 Treatment Failure

Patients not deriving clinical benefit (*i.e.*, those meeting "progressive disease" criteria as *per* Appendix 16.5) will discontinue bomedemstat and undergo EoT and EoS visits.

7 STUDY TREATMENT

7.1 Formulation, Labeling, Packaging and Storage

7.1.1 Formulation

The drug product is bomedemstat, a bis-tosylate salt. The free base of bomedemstat is the active moiety. Bomedemstat will be supplied in capsules of multiple strengths. These strengths, based on bomedemstat free base, *i.e.*, the active substance, may include: 5 mg, 10 mg, 25 mg, and 50 mg. Additional strengths may be added over the duration of the study. Details on capsules, including strengths, colors and sizes, can be found in the Pharmacy Manual.

The capsules will be manufactured in accordance with Annex 13 and principles of current Good Manufacturing Practices (cGMP) at:

Xcelience LLC
4910 Savarese Circle
Tampa, FL 33634 USA

Changes to this section will be included *via* updates to the Pharmacy Manual and/or notifications to sites, as appropriate.

7.1.2 Packaging and Labeling

Bomedemstat will be supplied to the site by Sponsor (or designee) in bottles containing capsules in accordance with all applicable regulatory requirements. Labels will also be in accordance with all applicable regulatory requirements for the labeling of active pharmaceutical ingredients and with Annex 13 of GMP. Labels will contain the drug name, protocol number, lot number, expiry date, storage conditions, name of the (local) Sponsor and a caution that drug is for clinical trials use only.

7.1.3 Storage

The recommended long-term storage conditions for bomedemstat are for the storage temperature not to exceed 25°C. Bomedemstat supplies must be stored in a secure area with access limited to the Investigator and authorized staff, under physical conditions consistent with bomedemstat-specific requirements and under the appropriate conditions according to the country, state and regional laws. Procedures for bomedemstat storage and accountability will be detailed in a Pharmacy Manual.

7.2 Dispensing, Administration, Dosage and Missed Doses

7.2.1 Dispensing

All material supplied is for use only in this clinical study and should not be used for any other purpose. Only patients enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only authorized site staff may dispense study drug.

The Investigator is responsible for bomedemstat accountability, reconciliation and record maintenance (Section 14.5). The Investigator must provide a prescription form every time drug is dispensed, including (but not limited to) the: identification of the patient to whom drug is to be dispensed, patient's weight, requested dose in mg/d and Investigator (or designee's) signature.

Bomedemstat will be dispensed in accordance with the dose chart provided.

7.2.2 Administration and Dosage

Appropriately trained personnel will provide instruction pertaining to and supervise the administration of bomedemstat on any day it is taken in the clinic. With the exception of PK sampling collection days (Day 1, Week 2 [Day 15] and another selected regularly scheduled study visit between Week 4 [Day 29] to Week 8 [Day 57]), it is not required that bomedemstat be taken in the clinic; this will be determined based on the patient's regular daily dosing time. On PK sampling collection days, bomedemstat is to be administered in the clinic following an overnight fast (at least 8 hours). Fasting should continue until 1 hour post-dose; water *ad libitum* is permitted during this time. When applicable, the date and time of each administration in the clinic will be recorded in the source notes.

Patients should be instructed:

- That bomedemstat may be taken with or without food.
- To take their bomedemstat QD, at approximately the same time. Though it is suggested that patients dose at night before bed, patients may dose at any time of day that is convenient and mindful of the fasting requirements.
- To swallow their bomedemstat capsules whole, with a glass of water.

All patients will begin dosing on Day 1 at the starting dose of 40 mg/d and be treated daily for 52 weeks. Through the use of dose titration, the dose of bomedemstat will be adjusted for each patient to that dose that provides sufficient exposure to safely inhibit the activity of LSD1 in hematopoietic cells for a fraction of the dosing cycle without resulting in Grade ≥1 thrombocytopenia. Given the short lifespan of a human platelet compared to a red cell, approximately 7 days *versus* approximately 120 days, patients will be dosed using the platelet count as a biomarker of the activity of bomedemstat on the inhibition of LSD1. Details on the selection and rationale for the starting dose and titration schedule can be found in Section 3.7. Dose-titration, both upward and downward, is contingent on a hematology assessment. The first up-titration is not permitted before Week 6, and the second up-titration may occur no sooner than 6 weeks after the first up-titration (*e.g.*, if an up-titration occurs at Week 6, the next up-titration may not occur until Week 12). Beginning at Week 16, up-titrations are permitted no more frequently than every 4 weeks from the previous up- or down-titration. Down-titrations can be made (or the current dose maintained) at any time in the best interest of the patient. Up-titrations will be made in increments of 5 or 10 mg/d, and down-titrations in decrements of 10 mg/day.

[redacted]

[redacted] The hematocrit titration target expected to be associated with a clinically significant therapeutic effect is:

- A hematocrit <42%

Titration and re-challenge rules to be used for titration assessment purposes, based on evaluation of platelet, ANC and hematocrit (Hct) counts are noted below.

Table 1: Titration and Re-challenge Rules

Bomedemstat Titration and Re-challenge Rules				
Important: ANC ≥0.5 × 10^9/L (500 neutrophils/µL) is needed for up-titration. For ANC below this threshold, maintain or adjust the current dose in accordance with the rules below.				
Hematology Assessment		**Titration and Re-challenge Rules**		
Plt Count (× 10^9/L)	**Hct %**	**Titration?**	**Titration Rule**	**Re-challenge Rule¥**
≥450	N/A	Up-titrate¤	Increase by 10 mg/d¤	N/A
150 – <450	42% – 45%	Up-titrate¤	Increase by 5 mg/d¤	N/A
150 – <450	<42%	Maintain dose	N/A	N/A
50 – <150	N/A	Down-titrate	Decrease by 10 mg/d	N/A
<50	**N/A**	**HOLD DOSE**	**N/A**	**At 50% of prior dose** when platelets return to ≥100**

ANC, absolute neutrophil count; CBC, complete blood count; Hct, hematocrit; N/A, not applicable; Plt, platelet.
¤ The first up-titration is not permitted before Week 6, and the second up-titration may occur no sooner than 6 weeks after the first up-titration (*e.g.*, if an up-titration occurs at Week 6, the next up-titration may not occur until Week 12). Beginning at Week 16, up-titrations are permitted no more frequently than every 4 weeks from the previous up- or down-titration. Down-titrations can be made (or the current dose maintained) at any time in the best interest of the patient.
** Patients requiring a dose hold should have CBC with differential monitored at least weekly for safety and to enable re-challenge as soon as platelet counts return to ≥100 × 10^9/L, if safe to do so. Re-challenge at 50% of the previous mg/d dose.
¥ Upon re-challenge, all of the above rules reapply.

If needed, please consult the Medical Monitor regarding dose modifications of bomedemstat should an AE requiring a dose reduction occur and for the management of clinically significant changes in platelets, neutrophil counts, or other hematologic parameters.

7.2.2.1 Provisional Dose(s); Unacceptable Toxicity at the Starting Dose (D_s)

Although unlikely, it is possible that unacceptable toxicity may be seen at the D_s, (40 mg/d); the D_s could also be the maximum tolerated dose (MTD). To address this possibility, contingencies are needed. If the SAB determines the D_s is too high, then the enrollment of additional patients at lower doses will be necessary. If required, the D_s will be reduced first to 35, and subsequently to 30 mg/d.

7.2.2.2 Missed Doses

Patients who do not take their bomedemstat dose at the usual time should take it immediately upon noting it was not taken; the patient should not take the dose more than 12 hours after the usual dosing time. If a patient misses a dose, they should not take two doses the following day, but should notify study personnel and continue with their normal daily dose the following day. If vomiting occurs within 30 minutes after taking bomedemstat and all expelled capsules remain intact, another dose may be taken. For a dosing hiatus due to an SAE, the Medical Monitor may be consulted for guidance on re-start of dosing. Patients who miss an extended duration of bomedemstat doses or exhibit serial non-compliance may be removed from the study at the discretion of the Sponsor.

7.2.2.3 Interruption of Dosing

Patients requiring a dose hold according to the Titration and Rechallenge Rules, or due to an (S)AE, should be monitored at least weekly for safety purposes and to enable re-challenge as soon as platelet counts return to the required level, if it is safe to do so. During these visits, patients are required to undergo CBCs with differential only.

8 SAFETY ADVISORY BOARD (SAB) REVIEWS AND MANAGEMENT OF STUDY TOXICITIES

8.1 Safety Advisory Board (SAB) Reviews

Safety will be monitored throughout the study in accordance with a Safety Advisory Board Plan (SABP) by a SAB made up of MPN clinical trials specialists with extensive clinical experience. The SAB will provide recommendations regarding study conduct and guidance to Investigators to ensure the safety and well-being of study patients. To do so, the SAB will review safety parameters and PD markers at least quarterly. Expedited, *ad hoc* reviews may also occur when:

- Fatal or life-threatening reaction assessed as related to bomedemstat (possibly, probably or definitely), regardless of expectedness, is reported
    - A CIOMS/MedWatch form for all expedited (serious, unexpected, related) SAEs will be sent to the SAB for review.
- Occurrence of other safety-related issues such as an event meeting any of the Stopping Rules as *per* Section 8.2.3, or evidence of unexpectedly severe effects on hematopoiesis which pose a medical concern and may necessitate bomedemstat dose adjustment or discontinuation.

In the event an expedited, *ad hoc* safety review is warranted, Sponsor will immediately notify the SAB, provide preliminary information regarding the event(s), and request that a SAB review be scheduled. No later than 2 business days after Sponsor notification of the event(s), Sponsor will provide the SAB with all relevant and available data.

SAB responsibilities will remain in effect until the study has ended.

8.2 Management of Study Toxicities

AE severity will be evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5, published 27-NOV-2017.

Stopping rules are defined in Section 8.2.3 below. Expected bomedemstat toxicities based on non-clinical and clinical studies are reported in the latest available edition of the IB.

8.2.1 Hematologic Toxicity

Hematologic values outside of the normal reference range are inherent features of MPNs and are expected effects of many therapeutic attempts to manage these diseases. The effects of bomedemstat on normal myeloid hematopoiesis observed in non-clinical and clinical studies are expected; these are PD effects of LSDi by bomedemstat, thus are considered on-target effects.

Both genetic knockdown (KD) of LSD1 mRNA and pharmacologic inhibition of LSD1 show that the loss of LSD1 activity arrests the production of mature red cells, platelets, and granulocytes while over-producing monocytes (Sprussel *et al.*, 2012; Kerenyi *et al.*, 2013). Production of cells of lymphoid lineage, B and T cells, is unimpaired indicating that LSD1 has very cell-specific functions and its inhibition also has very specific effects. LSDi in malignant myeloid cells causes the induction of monocytic differentiation markers, as well as a reduction of self-renewal

potential of neoplastic cells, all of which eventually result in apoptosis of treated cells. Thus, the anemia, thrombocytopenia, neutropenia and monocytosis attending LSDi reflect primary PD effects. The kinetics of anemia, thrombocytopenia, and neutropenia following complete LSDi are a function of the lifespan of the individually affected cell types. Over the course of LSDi, platelet and neutrophil counts are the most affected, reflecting their short mean lifespans of approximately seven and twelve days, respectively. Recovery of peripheral counts is reversible, rapid, and temporarily overshoots baseline hematologic values. At lower doses, the effects on hematopoiesis are much less pronounced suggesting that a modicum of residual LSD1 activity is sufficient to support blood cell formation. Thus, both the duration of LSDi as well as the degree of inhibition are critical to the PD effects on myeloid lineages.

The intended dosing plan for PV patients is predicated on the observation that inhibition of LSD1 has a therapeutic effect when LSD1 is inhibited for a fraction of the 24-hour dosing cycle, sufficient to reduce the production of red cells whose over-production characterizes this condition. The concentrations of bomedemstat needed to achieve maximal effects on growth, differentiation and apoptosis *in vitro* with primary patient-derived malignant myeloid cells as well as *JAK2*^{V617F} cell lines are similar to concentrations that *in vivo* inhibit red cell, platelet and granulocyte production. It is therefore expected that PV patients will require treatment at doses sufficient to reduce platelet counts and hematocrit. These reversible cytopenias can be managed clinically as needed with transfusions as well as broad-spectrum antibiotics in the case of febrile neutropenia, as are already standard practices in the routine management of malignant myeloid diseases.

8.2.2 Non-Hematologic Toxicity

Patients who experience a Grade 3 or 4 non-hematologic AE deemed related to bomedemstat (possibly, probably or definitely) may have their dose adjusted downward by 50% if the PI deems it safe for the patient to continue on bomedemstat. Any patient that experiences an AE that results in discontinuation of bomedemstat therapy may begin alternative cytoreductive therapy to lower platelets and hematocrit within 24-48 hours.

8.2.3 Stopping Rules

Bomedemstat will be discontinued in the event of any one of the following:

- Post Grade 3 or 4 non-hematologic AE deemed related to bomedemstat (possibly, probably or definitely), the patient's clinical condition either worsens at any time or fails to demonstrate significant improvement within 14 days, or the PI deems it unsafe for the patient to continue on bomedemstat.
- Post temporary interruption of bomedemstat due to platelet counts <50 × 10^9/L (50 k/µL), the patient's platelet counts do not return to >150 × 10^9/L (150 k/µL) within 21 days.

Patients who discontinue bomedemstat will enter follow-up beginning with the EoT visit.

9 STUDY VISIT PROCEDURES

This section provides comprehensive detail on the visits and assessments required; this section should serve as the main guidance for use during study visits. The Schedule of Assessments (Appendix 16.1) contains these details in schematic form and is provided for use in a supportive/ reference capacity only. In an effort to maintain clarity while facilitating a modicum of brevity, the 'Terms' in Table *2* will be utilized to encompass the broader 'Protocol Meaning' as stated.

Note: If at any time additional clinical evaluation outside of the visit schedule is deemed necessary by the Investigator, then unscheduled visits should occur as appropriate.

Table 2: List of Protocol Terms and Meanings

Term	Protocol Meaning
Adverse Events and Concomitant Medications	Use non-directive questions (*i.e.*, "How are you feeling") to query patient re: any AEs that may have occurred. Also, inquire about medication changes since the last visit.

Limited Physical Examination, including Vital Signs	• Weight
	• Review of body systems for changes from previous visit
	• Vital signs, after patient has sat semi-supine for ~3 minutes, of:
	  ○ Heart rate
	  ○ Respiratory rate
	  ○ Temperature
	  ○ Systolic/diastolic blood pressure
	• Spleen measurement – The spleen edge is determined by palpation, measured in centimeters, using a soft ruler/tape, from the costal margin to the point of greatest splenic protrusion in the mid-clavicular line. The spleen should be measured in the same manner at all visits.

MFSAF	MFSAF is to be completed in the patient's native language during Screening (as close to Day -7 as possible), and within the 2 days leading up to or on the day of every visit throughout the study except for any additional bi-weekly visits implemented after Week 12 for patients whose dose has not stabilized. Ideally, the MFSAF will be completed at the same time and day each week for consistency. Date of completion should be documented each time the MFSAF is completed. Please refer to the Study Reference Manual for additional instructions.

Term	Protocol Meaning
Bone Marrow Sampling	• Aspirate (sample taken from first pull, whenever possible, and no later than the second) and biopsy collected as *per* site standard procedure. • During Screening, UNLESS performed within the 3 months prior to the first dose of bomedemstat **AND** bone marrow biopsy slides or the formalin fixed paraffin embedded block are available from that sampling and can be provided to the central laboratory for review. Local laboratory generated fibrosis scores will be used at Screening to ensure eligibility. See Appendix 16.3 for fibrosis grading. • A central pathology laboratory will perform morphology and fibrosis grading and store samples for correlative studies (Section 10.1.2). • **Note:** Results available from site routine work-up such as morphology, cytogenetics, other genetic interrogations will be collected for study purposes either *via* the eCRF or through collection of local reports.
Dosing Instructions	• Instruct patients to refer to their Dosing Card every day for details on bomedemstat dosing and what to do if a dose is missed • Take their bomedemstat in accordance with Section 7.2.2 • Handle any missed bomedemstat doses as *per* Section 7.2.2.2 • Bring all medication to every clinic visit, including empty bottles
Administer bomedemstat	Administer bomedemstat with a glass of water and record exact time of dosing.
AE, adverse event; eCRF, electronic case report form; MFSAF, Myelofibrosis Symptom Assessment Form.	

9.1 Informed Consent

Patients must provide documented informed consent before undergoing any study-related procedures. The PI, or designee, will explain to the patient the aims of the study, the risks and benefits involved and that their participation is voluntary. Each patient will acknowledge receipt of this information and that they wish to participate in the study by giving written informed consent for their involvement in the study in the presence of the PI, or designee, who will also sign and date the Participant Information Sheet/Consent Form (PISCF). Time, date, name of the person taking consent and any questions raised by the patient must be documented in the source data.

9.2 Screening Period, Including Enrollment

The below assessments may be performed on the same day or multiple days, as needed, throughout the 28-day Screening period. If the patient screen fails at any time during the Screening period, document the reason(s) in the source data and on the Screening & Enrollment log.

9.2.1 Screening (Days -28 to Day -1)

- Review and confirm that patient meets all Inclusion and no Exclusion Criteria
- Complete medical/medication history including:
    - Demographics
    - Confirmation of diagnosis *per* 2016 WHO criteria for PV (Appendix 16.2)
    - PV disease history (*i.e.*, past bleeding episodes and thromboembolic events)
    - Treatment history for: PV, including clinical course with hydroxyurea and/or other PV therapy; and, any previous malignancy, including chemotherapy, surgery and radiation
    - Phlebotomy history
    - All concomitant medication, in addition to any used in the 15 days prior to Screening
- Assess ECOG Performance Status (Appendix 16.4)
- Full physical examination (PE) – review of all body systems including vitals, height (without shoes), weight and spleen palpation
- MFSAF, to be completed as close to Day -7 as possible (See Study Reference Manual [SRM] for details)
- Hematology with auto or manual differential (as needed to ensure all analytes are resulted)
- Serum chemistry, including erythropoietin (if test is available at institution)
- Coagulation (PT/aPTT/INR)
- Serum pregnancy test for POCBP
- Urinalysis
- Germline sample(s) for Central Laboratory genomic analysis
- Bone marrow aspirate and biopsy for morphology review and correlative research UNLESS performed within the 3 months prior to the first dose of bomedemstat **AND** bone marrow biopsy slides or the formalin fixed paraffin embedded block are available from that sampling and can be provided to the central laboratory for review. **Importantly**, fibrosis scores will be performed locally on Screening samples to enable assessment of patient eligibility.
- Instruct patient regarding washout to ensure prior therapy for condition under study is discontinued for 2 weeks (4 weeks for interferon) prior to study drug initiation. Phlebotomy may continue as clinically indicated.
- Schedule next clinic visit

9.2.2 Enrollment

For eligibility purposes, the following should be reviewed and/or confirmed:

- History of recent surgical procedures

- Recent use of investigational drugs
- Laboratory results will be assessed by the PI before enrollment. Any laboratory values confirmed on re-examination to be clinically significant by the PI and that would jeopardize the safety of the patient or impact on the validity of the study results will result in exclusion of that patient.

Once Screening procedures have been performed and it is confirmed that the patient can be enrolled, patients will be enrolled in accordance with procedures detailed in the SRM.

9.2.3 Last Day of Screening Period (Day -1)

- On Day -1, contact the patient and remind them to:
  - Report to the clinic the following day at the agreed time
  - Fast overnight (at least 8 hours) for PK purposes

9.3 Initial Period of Treatment (36-Weeks)

Procedures are presented below for each visit by assessments performed pre-dose, at dosing, and post-dose (as applicable).

9.3.1 Day 1 – Treatment Start

The below assessment has a visit window which permits conduct either pre- or post- Day 1 dose:

- Radiologic/Imaging assessment of spleen volume (±2 day visit window)

9.3.1.1 Pre-Dose Day 1

- AEs and Concomitant Medications
- Assess ECOG Performance Status (Appendix 16.4)
- Limited PE, including vital signs, weight, and spleen palpation
- Ensure MFSAF is completed during visit if not completed earlier in the -2 day window (see SRM for details)
- Hematology (CBC) with auto or manual differential (as needed to ensure all analytes are resulted)
  - Confirm platelet count ≥250 × 10^9/L and ANC ≥1.5 × 10^9/L, with CBC performed up to 2 days ahead of the C1D1 visit to avoid delays in dispensation due to pending lab results.
  - Establish baseline with a pre-dose blood sample collected on C1D1.
- Serum chemistry
- Coagulation (PT/aPTT/INR)
- Serum pregnancy test for POCBP

- Urinalysis
- Germline sample(s) for Central Laboratory genomic analysis, if not collected earlier in Screening
- PK sampling within 60 minutes prior to bomedemstat dosing
- Blood samples for Central Laboratory cytokine analysis
- Blood sample for Central Laboratory genomic analysis
- Blood sample for Central Laboratory correlative research
- Dispense doses sufficient until the next visit and provide Dosing Instructions
- Ensure patient continues to meet eligibility criteria prior to dosing

9.3.1.2 Dosing Day 1

- Administer bomedemstat and record the exact time of dosing in the patient's notes. Fasting should continue until 1 hour post-dose; water *ad libitum* is permitted during this time.

9.3.1.3 Post-Dose Day 1

Patients should remain in clinic for at least 2 hours post first dose and will need to undergo PK sampling through 6 hours post first dose

- PK sampling should occur at the following post-dose time-points with the exact time of sampling recorded in the patient's notes:
    - 1 hour (±15 minutes)
    - 2 hours (±30 minutes)
    - 4 hours (±30 minutes)
    - 6 hours (±60 minutes)
- Query for AEs, using non-directive questions (*i.e.*, "How are you feeling")
- Schedule next clinic visit

9.3.2 Bi-Weekly Visits - Weeks 2, 4, 6, 8, 10, 12 (±2 days*)

*The ±2 day visit window applies to the visit (*e.g.*, 'Week 2/Day 15' visit may be conducted on Day 13, 14, **15**, 16 or 17 as dictated by site and patient schedule), and not to individual assessments, unless otherwise noted. To clarify, the expectation is that all required assessments will be done on a single visit day with the exception of those specifically noted below.

- AEs and Concomitant Medications
- Assess ECOG Performance Status (Appendix 16.4)

- Limited PE, including vital signs, weight and spleen palpation
- Ensure MFSAF is completed during visit if not completed earlier in the -2 day window (see SRM for details)
- Pre-dose: Blood sample for hematology (CBC) with auto or manual differential (as needed to ensure all analytes are resulted) and titration assessment**. If patient requires a dose hold, CBCs should be monitored at least weekly for safety and to enable re-challenge as soon as platelet counts return to the required level, if safe to do so.
- Perform drug accountability and collect study medication
- Dispense doses sufficient until the next visit and provide Dosing Instructions
- Schedule next clinic visit

****Important:*** may be performed up to 2 days ahead of the main visit to avoid delays in dispensation due to either pending lab results or pharmacy procedures and to facilitate all laboratory sampling occurring the same day as the hematology sampling needed for the titration assessment. For example, if a visit is scheduled on a Wednesday, these assessments may be performed Monday or Tuesday, to ensure bomedemstat is dispensed and available for collection at the Wednesday visit.

9.3.2.1 Week 2 (Day 15) and Again at Either Week 4 (Day 29), Week 6 (Day 43) or Week 8 (Day 57) Only

- On the day prior to the applicable study visits, the study coordinator (or site representative) will contact the patient and:
  - Collect and record the exact time the patient took their bomedemstat that day
  - Remind patient that an overnight fast (at least 8 hours) is required for PK purposes and dosing of bomedemstat will occur in the clinic the following day as PK sampling is required

9.3.2.1.1 Pre-Dose

- PK sampling within 60 minutes prior to bomedemstat dosing

9.3.2.1.2 Dosing

- Administer bomedemstat and record the exact time of dosing in the patient's notes. Fasting should continue until 1 hour post-dose; water *ad libitum* is permitted during this time.

9.3.2.1.3 Post-Dose

- PK sampling should occur at the following post-dose time-points with the exact time of sampling recorded in the patient's notes:
  - 1 hour (±15 minutes)
  - 2 hours (±30 minutes)

- 4 hours (±30 minutes)
- 6 hours (±60 minutes)

9.3.2.2 Weeks 4, 8 and 12 only

- Serum chemistry**
- Coagulation (PT/aPTT/INR)**
- Serum pregnancy test for POCBP**

****Important:*** may be performed up to 2 days ahead of the main visit to facilitate all laboratory sampling occurring the same day as the hematology sampling needed for the titration assessment.

9.3.2.3 Week 12 only

- PGIC Questionnaire (see SRM for details)
- Urinalysis**
- Blood sample for Central Laboratory cytokine analysis**
- Blood sample for Central Laboratory genomic analysis**
- Blood sample for Central Laboratory correlative research**
- Radiologic/Imaging assessment of spleen volume (±7-day window)

****Important:*** may be performed up to 2 days ahead of the main visit to facilitate all laboratory sampling occurring the same day as the hematology sampling needed for the titration assessment.

9.3.3 Monthly Visits - Weeks 16, 20, 24, 28, and 32 (±2 days*)

* The ±2-day visit window applies to the visit (*e.g.*, 'Week 16/Day 113' visit may be conducted on Day 111, 112, **113**, 114, or 115 as dictated by site and patient schedule), and not to individual assessments, unless otherwise noted. To clarify, the expectation is that all required assessments will be done on a single visit day with the exception of those specifically noted below.

Note: It is anticipated that by Week 12 all patients will have achieved a stable dose, with bi-weekly visits no longer required. For the exceptional patient whose dose has not stabilized, bi-weekly visits may continue at PI's discretion. For such patients, the following is required at each bi-weekly visit:

- Pre-dose: Blood sample for hematology (CBC) with auto or manual differential (as needed to ensure all analytes are resulted) and titration assessment**. If a patient requires a dose hold, CBCs should be monitored at least weekly for safety and to enable re-challenge as soon as platelet counts return to the required level, if safe to do so.

All other patients will undergo the following at monthly visits:

- AEs and Concomitant Medications
- Assess ECOG Performance Status (Appendix 16.4)
- Limited PE, including vital signs, weight, and spleen palpation
- Ensure MFSAF is completed during visit if not completed earlier in the -2 day window (see SRM for details)
- Pre-dose: Blood sample for hematology (CBC) with auto or manual differential (as needed to ensure all analytes are resulted) and titration assessment**. If a patient requires a dose hold, CBCs should be monitored at least weekly for safety and to enable re-challenge as soon as platelet counts return to the required level, if safe to do so.
- Serum chemistry**
- Coagulation (PT/aPTT/INR)**
- Serum pregnancy test for POCBP**
- Perform drug accountability and collect study medication
- Dispense doses sufficient until the next visit and provide Dosing Instructions
- Schedule next clinic visit

****Important:*** may be performed up to 2 days ahead of the main visit to avoid delays in dispensation due to either pending lab results or pharmacy procedures and to facilitate all laboratory sampling occurring the same day as the hematology sampling needed for the titration assessment. For example, if a visit is scheduled on a Wednesday, these assessments may be performed Monday or Tuesday, to ensure bomedemstat is dispensed and available for collection at the Wednesday visit.

9.3.3.1 Week 24 Only

- PGIC questionnaire (see SRM for details)
- Urinalysis**
- Blood sample for Central Laboratory cytokine analysis**
- Blood sample for Central Laboratory genomic analysis**
- Blood sample for Central Laboratory correlative research**
- Radiologic/Imaging assessment of spleen volume (±7 days)

****Important:*** may be performed up to 2 days ahead of the main visit to facilitate all laboratory sampling occurring the same day as the hematology sampling required for the titration assessment.

9.3.4 Monthly Visit - Week 36 (±2 days*)

* The ±2-day visit window applies to the visit (*e.g.*, 'Week 36/Day 253' visit may be conducted on Day 251, 252, **253**, 254, or 225 as dictated by site and patient schedule), and not to individual assessments, unless otherwise noted. To clarify, the expectation is that all required assessments will be done on a single visit day with the exception of those specifically noted below.

- A Qualification Assessment is required to assess whether the patient is deriving clinical benefit (defined as not meeting progressive disease criteria as *per* Appendix 16.5) and safely tolerating bomedemstat, thereby qualifying for continued treatment.
    - Patients not continuing beyond Week 36 should undergo the procedures associated with the EoT visit (Section 9.5).
    - Patients continuing beyond Week 36 should receive bomedemstat with no interruption in dosing (Section 9.4). Such patients should undergo the procedures detailed below.
- AEs and Concomitant Medications
- Assess ECOG Performance Status (Appendix 16.4)
- Limited PE, including vital signs, weight, and spleen palpation
- Ensure MFSAF is completed during visit if not completed earlier in the -2 day window (see SRM for details)
- PGIC questionnaire (see SRM for details)
- Pre-dose: Blood sample for hematology (CBC) with auto or manual differential (as needed to ensure all analytes are resulted) and titration assessment**. If a patient requires a dose hold, CBCs should be monitored at least weekly for safety and to enable re-challenge as soon as platelet counts return to the required level, if safe to do so.
- Serum chemistry**
- Coagulation (PT/aPTT/INR)**
- Serum pregnancy test for POCBP**
- Urinalysis**
- Blood sample for Central Laboratory cytokine analysis**
- Blood sample for Central Laboratory genomic analysis$^{\Phi}$**
- Blood sample for Central Laboratory correlative research$^{\Phi}$**
- Radiologic/Imaging assessment of spleen volume (±7 days)
- Bone marrow aspirate and biopsy for morphology review and correlative research$^{\Phi}$ (±7 day visit window)
- Perform drug accountability and collect study medication

- Dispense doses sufficient until the next visit and provide Dosing Instructions (necessary only if patient qualifies for continued treatment)

Φ If possible, these bone marrow and blood samples should be collected the same day.

****Important:*** may be performed up to 2 days ahead of the main visit to avoid delays in dispensation due to either pending lab results or pharmacy procedures and to facilitate all laboratory sampling occurring the same day as the hematology sampling needed for the titration assessment. For example, if a visit is scheduled on a Wednesday, these assessments may be performed Monday or Tuesday, to ensure bomedemstat is dispensed and available for collection at the Wednesday visit.

9.4 Additional Treatment Post Week 36

The visits and procedures contained herein may repeat as long as the patient qualifies for additional treatment. Treatment should continue without interruption in dosing. Procedures are presented below for each visit by assessments performed pre-dose, at dosing, and post-dose (as applicable).

9.4.1 Additional Treatment Monthly Visits (±3 days*)

* The ±3-day visit window applies to the visit (*e.g.*, 'Week 40/Day 281' visit may be conducted on Day 278, 279, 280, **281**, 282, 283, or 284 as dictated by site and patient schedule), and not to individual assessments, unless otherwise noted. To clarify, the expectation is that all required assessments will be done on a single visit day with the exception of those specifically noted below.

Note: It is anticipated that patients continuing beyond Week 36 will have already achieved a stable dose, with frequent titrations no longer necessary. For the exceptional patient whose dose has not stabilized, bi-weekly visits may continue at the PI's discretion. For such patients, the following is required at each bi-weekly visit:

- Pre-dose: Blood sample for hematology (CBC) with auto or manual differential (as needed to ensure all analytes are resulted) and titration assessment**. If a patient requires a dose hold, CBCs should be monitored at least weekly for safety and to enable re-challenge as soon as platelet counts return to the required level, if safe to do so.

All other patients will undergo the following at monthly visits.

- AEs and Concomitant Medications
- Assess ECOG Performance Status (Appendix 16.4)
- Limited PE, including vital signs, weight and spleen palpation
- Ensure MFSAF is completed during visit if not completed earlier in the -2 day window (see SRM for details)
- Pre-dose: Blood sample for hematology (CBC) with auto or manual differential (as needed to ensure all analytes are resulted) and titration assessment**. If a patient requires a dose hold,

CBCs should be monitored at least weekly for safety and to enable re-challenge as soon as platelet counts return to the required level, if safe to do so.

- Serum chemistry**
- Coagulation (PT/aPTT/INR) **
- Serum pregnancy test for POCBP **
- Perform drug accountability and collect study medication
- Dispense doses sufficient until the next visit and provide Dosing Instructions

***Important:* may be performed up to 2 days ahead of the main visit to avoid delays in dispensation due to either pending lab results or pharmacy procedures and to facilitate all laboratory sampling occurring the same day as the hematology sampling needed for the titration assessment. For example, if a visit is scheduled on a Wednesday, these assessments may be performed Monday or Tuesday, to ensure bomedemstat is dispensed and available for collection at the Wednesday visit.

9.4.1.1 Every 3 Months Weeks Following Week 36 (±3 days)

The below assessments are required every 12 weeks following Week 36 (Weeks 48, 60, 72, 84, etc.) for as long as the patient continues to qualify for treatment.

- PGIC questionnaire (see SRM for details)
- Urinalysis**
- Blood sample for Central Laboratory cytokine analysis**
- Blood sample for Central Laboratory genomic analysis**
- Blood sample for Central Laboratory correlative research**

***Important:* may be performed up to 2 days ahead of the main visit to facilitate all laboratory sampling occurring the same day as the hematology sampling needed for the titration assessment.

9.4.1.2 Every 6 Months Following Week 36 (±14 days)

The below assessment is required every 6 months following the Week 36 visit for as long as the patient continues to qualify for treatment.

- Radiologic/Imaging assessment of spleen volume

***Important:* may be performed up to 2 days ahead of the main visit to facilitate all laboratory sampling occurring the same day as the hematology sampling needed for the titration assessment.

9.4.1.3 Every 12 Months Following Week 36 (±28 days)

The below assessment is required every 12 months following the Week 36 visit for as long as the patient continues to qualify for treatment.

- Bone marrow aspirate and biopsy for morphology review and correlative research.

9.5 Follow-Up Period Visits

9.5.1 End of Treatment

The EoT visit should be conducted on the day of last dose, or as soon as possible thereafter. For patients completing the study at the end of a 36-week treatment period, the EoT visit will substitute for the Week 36 visit. For patients discontinuing this study to enroll in a bomedemstat extension study, the EoT visit should be conducted on the day of last dose for this study. The Follow Up Period/EoS visit is not required for the patients.

Note: Patients may commence alternative cytoreductive therapy for their PV 24 to 48 hours after stopping treatment with bomedemstat if deemed necessary by their treating physician.

Patients should return to the clinic for the following assessments:

- AEs and Concomitant Medications
- Assess ECOG Performance Status (Appendix 16.4)
- Limited PE, including vital signs, weight, and spleen palpation
- Ensure MFSAF is completed during visit if not completed earlier in the -2 day window (see SRM for details)
- PGIC questionnaire (see SRM for details)
- Hematology with auto or manual differential (as needed to ensure all analytes are resulted)
- Serum chemistry
- Coagulation (PT/aPTT/INR)
- Serum pregnancy test for POCBP
- Urinalysis
- Blood sample for Central Laboratory cytokine analysis
- Blood samples for Central Laboratory genomic analysis[Φ]
- Blood samples for Central Laboratory correlative research[Φ]
- Radiologic/Imaging assessment of spleen volume (±7 days) unless performed within the prior 5 weeks

- Bone marrow aspirate and biopsy for morphology review and correlative research[Φ] (±7 days) unless performed within the prior 5 weeks
- Ensure all study medication has been returned and accounted for (if applicable)
- Schedule the EoS Visit 30 days post last dose

[Φ]If possible, these bone marrow and blood samples should be collected the same day.

9.5.2 End of Study (EoT + 30 [±2 days])/Early Discontinuation Visit

Early Discontinuation (ED): patients should be seen in clinic as soon as possible after stopping study drug if they terminate the study early and refuse to enter the full follow-up period.

End of Study (EoS): patients should be seen in clinic 30 days (±2 days) after the last dose of study drug.

Note: The EoS visit is not required after the EoT visit for patients enrolling and starting treatment in the bomedemstat extension study.

Note: Patients may commence alternative cytoreductive therapy for their PV 24 to 48 hours after stopping treatment with bomedemstat if deemed necessary by their treating physician

The following assessments are required at the EoS/ED visit:

- AEs and Concomitant Medications
- Assess ECOG Performance Status (Appendix 16.4)
- Limited PE, including vital signs, weight, and spleen palpation
- Ensure MFSAF is completed during visit if not completed earlier in the -2 day window (see SRM for details)
- Hematology with auto or manual differential (as needed to ensure all analytes are resulted)
- Serum chemistry
- Coagulation (PT/aPTT/INR)
- Serum pregnancy test for POCBP
- Urinalysis
- Blood sample for Central Laboratory cytokine analysis
- Blood sample for Central Laboratory genomic analysis[Φ]
- Blood sample for Central Laboratory correlative research[Φ]
- Ensure all study medication has been returned and accounted for (if applicable)

Required at Early Discontinuation Only:

- PGIC questionnaire (see SRM for details)
- Radiologic/Imaging assessment of spleen volume (±7 days) unless performed within the prior 5 weeks
- Bone marrow aspirate and biopsy for morphology review and correlative research[Φ] (±7 days) unless performed within the prior 5 weeks

[Φ]If possible, these bone marrow and blood samples should be collected the same day.

9.6 Suspected Disease Progression

If at any time during the study it is suspected that the patient's disease has progressed, the following assessments should be performed:

- AEs and Concomitant Medications
- Assess ECOG Performance Status (Appendix 16.4)
- Limited PE, including vital Signs, weight, and spleen palpation
- Ensure MFSAF is completed during visit if not completed earlier in the -2 day window (see SRM for details)
- PGIC questionnaire (see SRM for details)
- Hematology with auto or manual differential (as needed to ensure all analytes are resulted)
- Serum chemistry
- Coagulation (PT/aPTT/INR)
- Serum pregnancy test for POCBP
- Urinalysis
- Blood sample for Central Laboratory cytokine analysis
- Blood sample for Central Laboratory genomic analysis[Φ]
- Blood sample for Central Laboratory correlative research[Φ]
- Radiologic/Imaging assessment of spleen volume (unless performed within the prior 5 weeks)
- Bone marrow aspirate and biopsy and morphology review and correlative research[Φ] (unless performed within the prior 5 weeks)

[Φ]If possible, these bone marrow and blood samples for genomic analysis should be collected the same day.

10 STUDY ASSESSMENTS FOR SAFETY AND PD ANALYSIS

Blood, bone marrow and/or their contents may be retained for future exploratory studies.

The average of the blood volumes, which varies by institution, is provided below.

Throughout the first ~44 weeks (Screening up to and including the EoS Visit), approximately 480 mL blood, approximately 4-6 mL of bone marrow aspirate fluid and 2-4 cm of trephine bone marrow biopsy will be collected. These estimates do not include any additional procedures required if a patient qualifies for the continued treatment.

See Sections 10.1 and 10.2 for the specifics and volumes required for each test.

10.1 Laboratory Measures

Details on the laboratory assessments performed throughout the study are provided below by category of tests (*i.e.*, serum chemistry, hematology, etc.). Details on the specific laboratory assessments required at each visit are located in Section 9 and in schematic form in Appendix 16.1. When each category of test is required, at a minimum, the following clinical laboratory determinations (or their equivalent) will be performed. Exceptions are noted by asterisk (*) to reflect that the particular analyte will only be analyzed if the test is available at the particular institution.

10.1.1 Local Laboratory Measures

Sponsor will not provide a laboratory manual or study supplies for the collection and handling of samples to be analyzed locally. Local laboratory standard procedures should be followed.

Serum Chemistry: Sodium, potassium, chloride, bicarbonate, glucose, calcium, phosphorus, magnesium, serum creatinine, uric acid, urea* or blood urea nitrogen (BUN)*, albumin, total bilirubin, gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase (LDH), C-reactive protein (CRP), serum ferritin and erythropoietin* (at Screening only).

Hematology: Hb, red blood cell (RBC) count, Hct, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelets, WBC count and automated or manual assessment (as needed to ensure all analytes are resulted) of neutrophils, lymphocytes, monocytes, reticulocytes, nucleated RBC and blasts.

Coagulation: Prothrombin time (PT)*, aPTT and INR.

Serum Pregnancy Test: For POCBP, a serum pregnancy test will be utilized. The result must be confirmed prior to next scheduled dose of bomedemstat.

Urinalysis: Leukocyte esterase, nitrites, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin, and glucose.

Blood sample volume: the volume of blood needed to perform all local laboratory measurements (serum chemistry, hematology and coagulation) *per* time-point varies by institution but is approximately 15 mL; for hematology alone this is approximately 4 mL.

10.1.2 Central Laboratory Measures

Cytokines: Approximately 20 mL blood sample, *per* required time-point. Cytokine profiles may be quantified *via* appropriate methods.

Pharmacokinetics: The PK analysis consists of three sessions of sparse sampling:

- *Session 1*: Day 1 of dosing
- *Session 2*: Week 2 (Day 15)
- *Session 3*: Any regularly scheduled study visit from Week 4 (Day 29) to Week 8 (Day 57)

Each PK sample time-point requires approximately 4 mL of blood, and at each session 5 samples will be drawn for a total of 20 mL of blood. The required samples will be collected following an overnight fast (at least 8 hours); sampling times at each session are:

- Pre-dose (-60 minutes)
- 1h (±15 minutes) post-dose
- 2h (±30 minutes) post-dose
- 4h (±30 minutes) post-dose
- 6h (±60 minutes) post-dose

Fasting should continue until 1 hour post-dose; water *ad libitum* is permitted during this time.

Genomic Testing: At each required sample time-point approximately 20 mL blood will be collected for analysis. At Screening, germline samples consisting of a cheek swab and hair roots will be collected for analysis. If, upon analysis, sample yield is found to be inadequate a repeat sample of either type may be requested. Genomic sample collection, handling, storage and analysis will conform to all applicable national guidelines and regulations.

Future Correlative Studies: Approximately 10 mL additional blood will be collected in conjunction with each genomic blood sampling time-point for the purposes of potential correlative studies. Some sites/countries may require patients provide specific consent for the *analysis* of these samples, which will be collected for all patients. If site process permits, samples collected and stored earlier in the course of their PV (*e.g.,* at time of initial diagnosis), and any available genetic data may be requested.

Bone marrow aspirate and biopsy: will be performed for central evaluation of morphology, including fibrosis grade, and correlative studies. **Importantly**, fibrosis score will be performed locally on Screening samples to enable assessment of patient eligibility. Bone marrow samples used to qualify the patient for the study may have been collected at any time within the 3 months prior to Day 1. In this instance either bone marrow biopsy slides or the formalin fixed, paraffin

embedded block must be available and provided to the central laboratory for review. Additionally, any locally available cytogenetic or genetic interrogations performed on samples obtained at the same time-point as study samples will also be reported in the eCRF or collected *via* local lab reports.

Bone marrow Sampling Requirements: Approximately 2-3 mL bone marrow aspirate sample for central analysis must be collected from the first pull, whenever possible, and no later than the second (except in the case of dry tap). A 1-2 cm section of trephine bone marrow sample must also be collected and sent to the central laboratory in accordance with the instructions in the laboratory manual. To ensure comprehensive analysis of the bone marrow samples, a peripheral blood smear and/or hematology (CBC) report from the day of bone marrow sampling is required for review in conjunction with the bone marrow samples. Refer to the laboratory manual for instructions. Remaining bone marrow aspirate following preparation of the morphology slides may be used for future correlative studies. ***Sample Processing***: Sponsor will provide a laboratory manual documenting the collection and handling of samples to be analyzed centrally. Laboratory supplies will be provided for the collection of all central laboratory samples.

10.2 Radiologic/Imaging Assessment

MRI/CT of abdomen: Spleen volume should be measured by magnetic resonance imaging (MRI) (or computerized tomography [CT] if patient is not a candidate for MRI) of the abdomen according to standard procedures. Please refer to the Imaging Guidelines for additional information.

10.3 Patient Reported Outcomes

Please refer to the SRM for additional instructions on each of the below tools.

Myelofibrosis Symptom Assessment Form (MFSAF): The MFSAF will be completed during Screening as close to Day -7 as possible, and within the 2 days leading up to or on the day of every visit throughout the study except for any additional bi-weekly visits implemented after Week 12 for patients whose dose has not stabilized.

Patient Global Impression of Change (PGIC): The PGIC will be completed at Weeks 12, 24, and 36, and every 12 weeks thereafter for as long as the patient continues to qualify for treatment, at EoT, ED, and upon suspicion of disease progression.

11 SAFETY

The Investigator is responsible for monitoring the safety of patients enrolled in this study.

Once an Investigator determines a patient is a treatment failure (see Section 6.7) or if the patient is withdrawn from treatment early due to an event meeting any of the Stopping Rules as *per* Section 8.2.3, the patient should discontinue study treatment and undergo follow-up period visits beginning with EoT (see Section 9.5.1).

11.1 Pregnancy

It is not known whether bomedemstat can affect reproductive capacity, and the direct effects of bomedemstat and the indirect effects of prior bomedemstat exposure on fetal development are also unknown. Every effort should be made to prevent pregnancy throughout the entire duration of participation in this study. All patients of reproductive potential involved in the study are required to use effective methods of contraception during the study and for 30 days after the last bomedemstat dose.

Pregnancy testing requirements for study inclusion are described in Section 9.2. Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding (spontaneously reported to the investigator or their designee) that occurs in a participant during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

11.2 Adverse Events

The Investigator is responsible for monitoring the safety of patients who have enrolled in the study and for accurately documenting and reporting information as described in this section. Patients will be instructed to report to the Investigator any AE that they experience. Investigators will ask about the occurrence of AEs at each visit. Investigators are required to document all AEs occurring during the clinical study, commencing from the time of consent through 30 days post last bomedemstat dose (through the EoS/ED visit). AE recording will continue for patients who

discontinue study treatment early but remain in follow-up, until their EoT, Pre-EoS, and EoS Visits have been completed.

AEs will be recorded on designated eCRF pages. Each AE is to be characterized (*i.e.*, verbatim term) and information provided regarding its seriousness, start and stop dates, severity, outcome, and causal relationship with the study drug.

An AE is any undesirable physical, psychological or behavioral effect experienced by a patient during participation in an investigational study, in conjunction with the use of the drug or biologic, whether or not product related. This includes any untoward signs or symptoms experienced by the patient from the time of first dose with bomedemstat until completion of the study.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient and/or observed by the Investigator or medical staff
- Findings at PEs
- Laboratory abnormalities of clinical significance
- [redacted] No specific information is available on the treatment of overdose of bomedemstat. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.
- Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an ALP laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

It is important Investigators record accurate AE terms in the eCRFs. Wherever possible, a specific disease or syndrome rather than individual associated signs, symptoms or laboratory parameter will be identified by the Investigator and recorded in the eCRF. However, if an observed or reported sign, symptom or laboratory parameter is not considered a component of a specific disease or syndrome by the Investigator, or is atypical, it should be recorded as a separate AE in the eCRF.

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the IP are not considered AEs after treatment unless they reoccur after the patient has recovered from the preexisting condition or in the opinion of the Investigator they represent a clinically significant exacerbation in severity or frequency.

Clinical significance is defined as any variation in signs, symptoms, or testing that has medical relevance and may result in an alteration in medical care. The Investigator will continue to monitor the patient until the assessment returns to baseline or until the Investigator determines that follow-up is no longer medically necessary.

11.2.1 Adverse Event Severity

AE severity will be evaluated using the NCI CTCAE version 5, published 27-NOV-2017. For AEs not included in the NCI CTCAE, the Investigator will be required to assess the severity of the adverse drug/biologic experience using the following categories and associated guidelines:

Grade	Guideline
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
4	Life-threatening consequences: urgent intervention indicated
5	Death related to AE

Note 1: A semi-colon indicates 'or' within the description of the grade.

Note 2: Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.2.2 Adverse Event Relatedness

The Investigator will make a judgment regarding whether or not, in his/her opinion, the AE was related to study drug. The Investigator will also evaluate any changes in laboratory values, make a determination as to whether the change is clinically significant, and whether or not the change(s) were related to study drug. However, even if the Investigator feels there is no relationship to the study drug, the AE or clinically significant laboratory abnormality MUST be recorded in the eCRF. Below are guidelines for relationship assessment:

- Unrelated: There was no relationship of the AE to the use of the drug or biologic. This may include, but is not limited to, the adverse experience being an expected outcome of a previously existing or concurrent disease, concomitant medication or procedure the subject experienced during their treatment period.
- Remote/Unlikely: AEs which are judged probably not related to the drug or biologic.
- Possible: There was no clear relationship of the AE to the use of the drug or biologic; however, one cannot definitively conclude that there was no relationship.
- Probable: While a clear relationship to the drug or biologic cannot be established, the event is associated with an expected AE (*per* the current Investigator Brochure or SAB findings) or there is no other medical condition or intervention which would explain the occurrence of such an experience.

- Definite: The relationship of the use of the drug or biologic to the experience is considered definitively established.

If a causal relationship is considered probable, possible, or definite by the Investigator or Sponsor (dependent on the regional reporting requirements), the AE is considered to be "related" for purposes of regulatory reporting. If a causal relationship is considered remote/unlikely or unrelated, the AE is considered "unrelated" for purposes of regulatory reporting.

11.2.3 Serious Adverse Events

SAEs will be reportable from the time of consent through the EoS Visit (scheduled for approximately 30 days post last bomedemstat dose) **or** until the Investigator and Sponsor determine that follow-up is no longer necessary. SAEs suspected to be drug related will be reported even if they occur when the patient is no longer on the study.

An SAE is any AE that results in any of the following outcomes:

- **Death**
- **Life-threatening experience**. Any AE that places the patient, in the view of the reporter, at immediate risk of death from the AE as it occurred, *i.e.*, does not include an AE that had it occurred in a more severe form, might have caused death.
- **Required or prolonged inpatient hospitalization**. The AE resulted in an initial inpatient hospitalization or prolonged an existing hospitalization of the patient. If a patient is hospitalized as part of the clinical use of the product, a period of normal hospitalization will be outlined in the protocol or by the judgment of the Investigator. Hospitalizations longer than this period will be prolonged hospitalizations.
- **Persistent or significant disability/incapacity**. An AE that resulted in a substantial disruption of a person's ability to conduct normal life functions.
- **Congenital Anomaly.** The exposure of the patient to the drug or biologic during pregnancy that is judged to have resulted in the congenital anomaly/birth defect.
- **Important medical events**. AEs that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Important medical events or interventions may be considered an SAE based upon medical judgment of the Investigator.

A hospitalization planned prior to time of consent is not considered an SAE. Surgeries or interventions requiring hospitalization under consideration but not performed prior to consent will not be considered serious if performed after consent **if** the condition has not changed in severity from its baseline level. If, however, the pre-planned hospitalization occurs after consent **and** an event occurs which prolongs hospitalization or meets any other SAE criteria, then the event will be considered an SAE.

11.2.4 Reporting Serious Adverse Events

SAEs will be reported promptly, using the SAE Report Form, once the Investigator determines that the event meets the protocol definition of an SAE. The Investigator or designee will report the SAE **within 24 hours of becoming aware of these events regardless of relationship of the SAE to the use of study drug**. A detailed SAE reporting procedure and contact information will be included in the SAE Report Form Completion Guidelines. The Investigator will always provide an assessment of relatedness at the time of the initial report as described in Section 11.2.2. The SAE Report will always be completed as thoroughly as possible with all available details of the event within the designated time frames. Copies of relevant patient records, autopsy reports, and other documents may be requested.

If the Investigator does not have all information regarding an SAE, they will not wait to receive additional information before reporting the SAE. The SAE Report will be updated when additional information is received **within 24 hours of receipt of such information**.

Important: For fatal and life-threatening events, the event should be reported in the EDC system immediately or within 24 hours of learning of the event. A death occurring during the study or information related to such occurrence that comes to the attention of the Investigator during the study must be reported immediately to the Sponsor. A detailed SAE reporting procedure and contact information will be included in the SAE Report Form Completion Guidelines and will be provided to the site before any patients are consented.

Additionally, the Institutional Review Board (IRB) and Independent Ethics Committee (IEC), as applicable, must be notified in writing of any SAEs that require expedited reporting to regulatory authorities. Depending upon regional requirements, it is the responsibility of the Investigator to notify the IRB/IEC. All SAEs meeting expedited reporting requirements will be reported to appropriate regulatory agencies by Sponsor or their designee as soon as possible and within the timeframes specified in the various regions in which the study is to be conducted.

11.2.5 For Participants Who Consent to An Extension Study

All AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol up to the time of consenting into a bomedemstat extension trial. Laboratory values that meet criteria for reporting as AEs performed during this study will be collected in this study.

Note: Once consented to an extension study, AEs/SAEs and other reportable safety events meeting the reporting criteria of the extension study, including those considered related to study intervention, will be collected in the extension study.

12 STATISTICAL METHODS

12.1 General Considerations

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a separate Statistical Analysis Plan (SAP). Additionally, a Pharmacokinetic Analysis Plan (PKAP) will be prepared. Baseline will be defined as the last non-missing observation closest to first dose and will be calculated in associated analysis. Descriptive statistics (arithmetic mean, standard deviation [SD], sample size, median, minimum, maximum, and number) will be calculated for continuous data, with frequency and percentages for categorical.

12.2 Power

This is a single-arm trial with a primary endpoint that is response rate as defined: incidence of patients who achieve a sustained reduction of Hct to <45% for 12 weeks without concomitant phlebotomy by Week 36.

In this study, approximately 20 participants will be enrolled and treated. With 15 observed responders, the estimated clinically meaningful response rate based on response rates for existing agents and its 95% CI are 75% (50.6%, 90.4%). All endpoints will be descriptive, and no formal hypothesis testing will be conducted. Table 3 shows the two-sided 95% CIs for the response rates with 20 participants for different observed response rates based on the method of Clopper and Pearson. (Clopper and Pearson, 1934). Since this study does not have formal hypotheses to be tested, no power calculations have been conducted.

Table 3: Confidence Intervals for Different Observed Response Rates

Total Sample Size	Observed # of Responders	Observed Response Rate	95% CI (%)
20	13	65	(40.9, 83.7)
	14	70	(45.7, 87.2)
	15	75	(50.6, 90.4)
	16	80	(55.7, 93.4)
	17	85	(61.1, 96.0)

CI, confidence interval.

12.3 Treatment Assignment and Blinding

This is an open-label study. The Investigators, other hospital personnel, patients and Sponsor will know the identity of the treatment.

Effort will be made, as appropriate, to maintain continuity of study staff who administer/evaluate various assessments at each site (*i.e.*, PE, morphology/fibrosis grade review, etc.), to facilitate consistency of assessments within a patient.

12.4 Study Populations

- The safety population will include all patients receiving at least one dose of study medication. The safety population will be used to analyze all safety data.
- The mITT population will include all patients receiving at least one dose of study medication and at least one post-baseline result of measure. This will be the primary study population.
- The PK population will include all patients in the safety population who have at least one post dose concentration observation collected.

12.5 Primary Analysis

Incidence of patients who achieve a sustained reduction of Hct <45% for 12 weeks without concomitant phlebotomy by Week 36 will be summarized with point estimate and its 95% CI using exact binomial method proposed by Clopper and Pearson (Clopper and Pearson, 1934). Patients not achieving a response by Week 36 or dropping from the trial but have at least one post-baseline observation will be included in the analysis as a nonresponder.

AE verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment emergent adverse event (TEAE), Serious TEAE, related TEAE, serious related TEAE, discontinued due to TEAE, TEAE by maximum toxicity grade. Patients will be counted once per unique preferred term and body system. TEAE is defined as any event that occurs on or after the first dose of study drug administration or any preexisting event which worsened in severity after dosing. Frequency and proportion of events will be summarized.

Changes in PEs, vital signs, and laboratory values will be analyzed over time where applicable. Shift tables to worst post-baseline may be produced for specific parameters as detailed in the SAP.

12.6 Secondary Analysis

Incidence of platelet count ≤450 × 10^9/L will be analyzed as a proportion. Frequency and percentage of patients achieving at least one result will be counted as a reduction. Similarly, WBC <10 × 10^9/L will be analyzed. Durability of hematocrit <45%, platelet count ≤ 450 × 10^9/L and WBC <10 × 10^9/L will be analyzed by frequency achieving at least 12, 24, 36, and 52 weeks durable responses.

New thrombotic or hemorrhagic events will be analyzed separately and combined using frequency and percentage. Each patient will be counted once per event. Reduction of spleen volume to Week 36 and Week 52 will be analyzed centrally using percent change from baseline. Change and percent change from baseline in spleen volume will be measured using a continuous measure as well. Frequency and proportion of progression will be analyzed within 36 weeks and 52 weeks. If enough events occur Kaplan-Meier estimates will be graphically displayed.

12.8 Interim Analysis

There is 1 planned interim analysis. Descriptive analysis for sustained reduction of Hct <45% for 12 weeks without concomitant phlebotomy will be provided to evaluate efficacy. Details will be provided in the SAP.

13 STUDY ADMINISTRATION

The names, titles, and addresses of the Investigators and study personnel are available from Sponsor.

13.1 Ethical Considerations

This research will be carried out in accordance with the protocol, US Code of Federal Regulations (CFR), GCP, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

13.2 Participation Information Sheet/Consent Form (PISCF)

A sample PISCF document will be provided to each site. No major deviations may be made from the sample PISCF other than country- or region-specific formatting or legal requirements. Sponsor and its advisors will review the site-specific draft PISCF before it is finalized, and the final IRB/IEC-approved document must be provided to Sponsor for regulatory purposes.

The PISCF must be signed by the patient before his or her participation in the study. A copy of the PISCF must be provided to the patient. If required by local procedure a second original of the PISCF may be provided to the patient. If applicable, it will be provided in a certified translation of the local language.

An original documented PISCF must remain in each patient's study file and must be available for verification by study monitors at any time.

13.3 Institutional Review Board (IRB) and Independent Ethics Committee (IEC)

This protocol, the PISCF, relevant supporting information and all types of patient recruitment or advertisement information must be submitted to IRB/IEC for review and must be approved before the study is initiated. Any amendments to the protocol must also be approved, where necessary, by the IRB/IEC prior to implementing changes in the study.

The Investigator is responsible for keeping the IRB/IEC apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, at least once a year. The Investigator must also keep the IRB/IEC informed of any AEs, according to the IRB/IEC policy.

13.4 Study or Site Termination

The EoT date is considered to be the date of Database Lock.

If Sponsor, an Investigator, or regulatory authorities discover conditions during the study that indicate that the study or related activities at a particular site should be terminated, this action may be taken after appropriate consultation between Sponsor and the Investigator. Conditions that may warrant study or site termination include but are not limited to:

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients

2. Patient recruitment is unsatisfactory
3. Data recording is inaccurate or incomplete
4. Investigator(s) do not adhere to the protocol or applicable regulatory guidelines in conducting the study
5. GCP is not being maintained or adequately followed
6. Administrative reasons
7. Reasons unrelated to the study.

Study or site termination and follow-up will be performed in compliance with the conditions set forth in 21 CFR Section 312 and/or other national and local regulations, as applicable, and in compliance with the principles set forth in ICH GCPs, including ICH E6, and ethical principles established by the Declaration of Helsinki.

13.5 Study Monitoring Requirements

Monitoring and auditing procedures developed by Sponsor will be followed in order to comply with ICH GCP guidelines. On-site checking of the eCRFs for completeness and clarity, cross checking with source documents, and clarification of administrative matters will be performed, when possible. Additionally, off-site or 'remote' monitoring visits may be conducted as needed. Remote monitoring may consist of centralized monitoring or remote data review. Centralized monitoring is the remote, cross-functional review and evaluation of accumulating in-house data conducted by data managers, central monitor associates, medical directors, the clinical team, and biostatisticians. The review of data within and across sites proactively identifies missing or inconsistent data, data trends, systematic or significant errors and enables site performance characteristics to be analyzed. Remote data review is intended to encompass as many activities performed in a routine on-site monitoring visit as is functionally possible, and as permitted by site policy and procedure. The remote review of data may be actioned *via* multiple pathways, often contingent on site's capabilities. Remote data review, specifically, has become critically important in the COVID-19 environment as a measure of safeguarding patient safety, while also minimizing risks to trial data integrity and facilitating GCP compliance. Please see Appendix 16.9 for additional information pertaining to remote data review.

Monitoring visits will consist of site qualification visits, periodic visits during the study period, and site close-out visits.

The Investigator will permit authorized representatives of Sponsor and the respective national or local authorities to inspect facilities and records relevant to this study.

Sponsor or its designee will monitor the study. Monitoring will be done by visits from representatives of Sponsor (monitors) who will review the eCRFs and source documents. The monitors will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, email, telephone, and fax). The monitor/representative of Sponsor will perform an Investigator Site File (ISF) review to confirm all documents required to reconstruct the conduct of the clinical trial are present. The

ISF supports the validity of the research, as well as the conduct and integrity of the data collected, and needs to be maintained by the Investigator (or designee) and inspection ready at all times.

All unused study materials are to be returned to Sponsor or its designee after the clinical period of the trial has been completed or be disposed of at the site according to institutional policies but not prior to the approval of the Sponsor and with appropriate documentation.

13.6 Quality Assurance

The study will be initiated and conducted under the sponsorship of Sponsor. Bomedemstat and clinical supplies will be provided by Sponsor. Representatives of Sponsor will monitor the study to verify study data, medical records, worksheets, and eCRFs are in accordance with current ICH GCPs and the respective local and national government regulations and guidelines.

The Investigator will contact the Sponsor immediately if contacted by a regulatory agency about an inspection at his or her center. The purpose of Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH/GCP guidelines, and any applicable regulatory requirements.

13.7 Confidentiality

The information obtained during the conduct of this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited.

The patient's identifying information will not leave the clinical site at which they are recruited. The patient will be identified on all study documentation using a code number and their initials (where it is lawful to collect such information).

Information obtained during the conduct of this study will be collected, processed, and transmitted to or for the benefit of Sponsor in accordance with the applicable regulations and principles of confidentiality for each participating country. Information contained therein will be maintained in accordance with applicable law protecting patient privacy, including the provisions of 46 CFR Part 164 promulgated under the Health Insurance Portability and Accountability Act (HIPAA) and may be inspected by the clinical researcher, the researcher's staff, Sponsor and its representatives, partners, advisors, affiliates, successors, and clinical research contractors and subcontractors to check, process, evaluate, and use the information collected during the study. The patient PISCF (or a separate data protection consent form if required locally) will be used to obtain participant consent to authorize transfer and processing of data consistent with applicable law. Processing, evaluation, or use of the information will be performed by a health professional for medical purposes and/or by those operating under a duty of confidentiality that is equivalent to that of a health professional. Information obtained from the study will likely be used by Sponsor or its affiliates or successors in connection with the development of study drug, including possible filing of applications with governmental authorities for marketing approval, and for other pharmaceutical and medical research purposes. The study Investigator is obliged to provide Sponsor with complete test results and all data developed in this study. This information may be disclosed to other physicians who are

conducting similar studies and to the applicable regulatory authorities as deemed necessary by Sponsor. Patient-specific information may be provided to other appropriate medical personnel only with the patient's permission, as necessary and in accordance with other applicable privacy laws and regulations protecting patient health information.

To ensure compliance with the ICH GCP guidelines, data generated by this study must be available for inspection upon request by representatives of the appropriate national and local authorities, Sponsor, and the IRB/IEC for each study site.

The raw dataset will be available to Sponsor on completion of the study. Sponsor will actively pursue publication of the results of the study in cooperation with the Lead Investigators subject to the terms and conditions of the clinical trial agreement between Sponsor and Investigators. The Lead/Coordinating Investigator will have the right to submit for publication any results arising from the study subject to the terms and conditions of the Clinical Trial and Confidentiality Disclosure Agreements. The Lead/Coordinating Investigator, with the agreement of Sponsor, will coordinate the principal publication of the data arising from the study. Patient names and other personal data relating to an identified or identifiable patient (such as photographs, audio, videotapes, or other factors specific to physical, physiological, mental, economic, cultural, or social identity), may not be disclosed in any publication without prior written authorization, in compliance with patient privacy law, from Sponsor and the patient.

14 INVESTIGATOR REQUIREMENTS

14.1 Protocol Adherence

Each Investigator must adhere to the protocol as detailed in this document and agrees that any changes to the protocol must be approved by Sponsor's authorized representative in writing prior to seeking approval, where necessary, from the IRB/IEC. Each Investigator will be responsible for allowing only those patients who have met all protocol eligibility criteria to be enrolled.

Modifications to the protocol should not be made without agreement among the Investigators and Sponsor. Changes to the protocol will require written IRB/IEC approval / favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide expedited review and approval/favorable opinion for minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC. The Investigator will submit all protocol modifications to the IRB/IEC in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact Sponsor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the eCRF and source documentation.

14.2 Source Documentation

The Investigator must maintain detailed records of all study participants who are enrolled in the study or who undergo Screening. Source documents include patient medical records and Investigator's patient study files, as well as all test results. Information required for study purposes and any data recorded in the eCRF must be supported by appropriate source documentation.

14.3 Direct Access to Source Documentation

The Investigator will ensure that the Sponsor, IRB/IEC and regulatory authorities will have direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). This includes electronic source data.

14.4 Case Report Forms

Case report forms (or an electronic data capture system) will be provided to each investigational site for the collection of all study data for enrolled patients, with the exception of data that may be captured externally to the site (*i.e.*, central laboratory data). Study site personnel will record the data in the source documentation and enter it in the eCRF within, on average, 5 business days of the study visit, while carefully reviewing all information recorded for accuracy and consistency. Any required data printouts should be filed in the patient's source data, *i.e.*, laboratory reports, etc. and signed/dated by appropriately designated site personnel as a true copy of the original.

A clinical study monitor will review the eCRFs and compare the content to the source data.

The eCRFs for each patient must be reviewed and signed by the Investigator. This should be done as soon as possible after the patient has completed the study and all data queries have been resolved.

14.5 Study Drug Accountability

Accountability for study drug at the trial site is the responsibility of the Investigator. The Investigator will ensure that study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the drugs' delivery date to the site, inventory at the site, use by each patient, and return to Sponsor (or disposal of the drug, if approved by Sponsor) will be maintained by the clinical site. These records will adequately document that the patients were provided the drugs and doses as specified in the protocol and should reconcile all study drugs received from Sponsor. Accountability records will include dates, quantities, batch/serial numbers, expiry dates (if applicable), and patient numbers. Sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

A *Per* Patient Dispensing Log must be kept current and contain the following information:

- The identification of the patient to whom the drug was dispensed;
- The date(s), lot numbers and quantity of the drug dispensed to the patient;
- The date(s), lot numbers and quantity of drug returned by the patient

A "*Per* Lot" Inventory must be maintained, and both the *Per* Patient and *Per* Lot Logs must be available for inspection by the study monitor during the study.

14.6 Disposal of Study Drug

All unused study drug will be retained at the site until inventoried by Sponsor / designee, unless otherwise agreed. All unused or expired study drug will be returned to Sponsor or its designee or, if authorized by Sponsor, will be disposed of at the study site and the disposal will be appropriately documented. Records shall be maintained by the Investigator of any such alternate disposition of the test drug. These records must show the identification and quantity of each unit disposed of, the method of destruction (taking into account the requirements of local law), and the person/company who disposed of the test substance. Such records must be submitted to the Sponsor and copies on file in the Investigator's Site File. All material containing study drug will be treated and disposed of as hazardous waste in accordance with governing regulations.

14.7 Training of Staff

The PI is responsible for the conduct of the study at this study site, including delegation of specified study responsibilities, and training of study staff. The PI shall ensure that the study is carried out in accordance with the protocol, ICH/GCP guidelines, and regulations.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

14.8 Clinical Study Report

The Coordinating or Lead Investigator will be designated to sign any interim clinical study reports and the final clinical study report at the end of this study. The signatory Lead Investigator will be identified by the Sponsor in advance of study completion.

14.9 Retention of Records

Records and documents pertaining to the conduct of this study, including eCRFs, source documents, consent forms, laboratory test results, medication inventory records and ISF, must be retained by the Investigator in accordance with locally applicable regulatory requirements, and in any event for a period of at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. No study records shall be destroyed without notifying Sponsor and giving Sponsor the opportunity to take such study records or authorizing in writing the destruction of records after the required retention period.

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16 APPENDICES

16.1 Schedule of Assessments

16.1.1 Pre-Treatment and Post Last Dose Visits

	Pre-Treatment		Suspected Disease Progression	Follow-up	
	Screening			EoT[h]	EoS **OR** ED
	Day -28 to Day -2	Day -1			EoT + 30 days
Informed Consent	X				
Inclusion/Exclusion	X				
Medical History, including: Demographics Confirmation of PV Diagnosis per WHO PV Disease History PV Treatment History Other Malignancy Treatment History Phlebotomy History	X				
ECOG Performance Status	X		X	X	X
Washout	X[b]				
Full PE (w/vitals, height, weight, **spleen palpation**)	X[f]				
Contact Patient with Fasting Reminder		X			
Limited PE (w/vitals, weight, **spleen palpation**)			X[f]	X[f]	X[f]
MFSAF Questionnaire[a]	X[a]		X[a]	X[a]	X[a]
PGIC Questionnaire			X	X	X[e]
Radiologic/Imaging Assessment of Spleen Volume			X[c]	X[c]	X[ce]
Bone Marrow Aspirate & Biopsy	X[d]		X[d]	X[d]	X[de]
Concomitant Medications[i]	←	—	—	—	→
Adverse Event Review & Evaluation	←	—	—	—	→
Local Laboratory Assessments					
Hematology w/Auto or Manual Differential[j]	X		X	X	X
Serum Chemistry	X[k]		X	X	X
Coagulation (PT/aPTT/INR)	X		X	X	X
Serum Pregnancy Test (POCBP)	X		X	X	X
Urinalysis	X		X	X	X
Central Laboratory Assessments					
Cytokines			X	X	X
BM Morphology Review	X[d]		X[d]	X[d]	X[de]
Correlative Research Sample (BM Aspirate)	X[d]		X[d]	X[d]	X[de]
Genomic Analysis (PB)			X	X	X
Correlative Research Sample (PB)			X	X	X
Genomic Analysis - Germline Samples	X[g]				
Bomedemstat Procedures and Assessments					
Returns and Accountability				X	X

aPTT, activated partial thromboplastin time; BM, bone marrow; CT, computerized tomography; ECOG, Eastern Cooperative Oncology Group; ED, Early Discontinuation; EoS, End of Study; EoT, End of Treatment; INR, international normalized ratio; MFSAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imaging; PB, peripheral blood; PE, physical examination; PGIC, Patient Global Impression of Change; POCBP, participant of childbearing potential; PT, prothrombin time; PV, polycythemia vera; SRM, Study Reference Manual; WHO, World Health Organization.

a Questionnaire to be completed during Screening as close to Day -7 as possible, and within the 2 days leading up to or on the day of every visit throughout the study except for any additional bi-weekly visits implemented after Week 12 for patients whose dose has not stabilized. Refer to Study Reference Manual (SRM) for additional instruction.
b Prior cytoreductive therapy for condition under study must be discontinued for 2 weeks (4 weeks for interferon) prior to study drug initiation. Phlebotomy may continue as clinically indicated.
c Day 1 visit window is ±2 days; visit window at all other time-points is ±7 days. Required at EoT and ED and upon suspicion of disease progression (unless performed within the prior 5 weeks). CT to be undertaken for patients not candidates for MRI.
d During Screening, UNLESS performed within the 3 months prior to the first dose of bomedemstat **AND** bone marrow biopsy slides or the formalin fixed paraffin embedded block are available from that sampling and can be provided to the central laboratory for review. Local laboratory generated fibrosis scores will be used at Screening to ensure eligibility. The visit window at all post-Screening time-points is ±7 days. Required at EoT, ED, upon suspicion of disease progression unless performed within the prior 5 weeks. Aspirate from the first pull whenever possible, but none beyond the second, is required (except in case of a dry tap).
e Required at ED only.
f Edge of spleen determined by palpation, measured in centimeters, using a soft ruler/tape, from the costal margin to the point of greatest splenic protrusion in the mid-clavicular line.
g Germline samples to be collected for genomics can be obtained at any time during the Screening period including pre-dose Day 1.
h Patients may commence alternative PV therapy 24 hours after stopping treatment with bomedemstat if deemed necessary by their treating physician.
i Includes any medication taken in the 15 days prior to Screening.
j Automated or manual differential (as needed to ensure all analytes are resulted).
k At Screening, Serum Chemistry includes erythropoietin (if test is available at institution).

16.1.2 Treatment Visits

	Initial 36-Weeks of Treatment					Post-Week 36 Treatment			
	Bi-Weekly Visits (±2 days)			Monthly Visits[a] (±2 days)		Monthly Visits[a] (±3 days)	Additional Assessments		
	Day 1	Weeks 2, 6, 10	Weeks 4, 8, 12	Weeks 16, 20, 24, 28, 32	Week 36	Weeks 40, 44, 48, 52, 56, 60, 64, 68, 72, etc	Every 3 Months (±3 days)	Every 6 Months (±14 days)	Every 12 Months (±28 days)
ECOG Performance Status	X	X	X	X	X	X			
Contact Patient with Reminders		X[k]	X[k]						
Limited PE (w/vitals, weight, **spleen palpation**)	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]			
MFSAF Questionnaire[c]	X[bc]	X[c]	X[c]	X[c]	X[c]	X[c]			
PGIC Questionnaire			X[gh]	X[gh]	X[h]	→→→	X[h]		
Radiologic/Imaging Assessment of Spleen Volume	X[d]		X[d]	X[d]	X[d]	→→→		X[d]	
Bone Marrow Aspirate & Biopsy					X[e]	→→→			X[e]
Concomitant Medications	←	—	—	—	—	—	—	—	→
Adverse Event Review & Evaluation	←	—	—	—	—	—	—	—	→
Enrollment	X								
Qualification Assessment					X[j]				
Local Laboratory Assessments									
Hematology w/Auto or Manual Differential[m]	X[b]	X[b]*	X[b]*	X[b]*	X[b]*	X[b]*			
Serum Chemistry	X[b]		X*	X*	X*	X*			
Coagulation (PT/aPTT/INR)	X[b]		X*	X*	X*	X*			
Serum Pregnancy Test (POCBP)	X[b]		X*	X*	X*	X*			
Urinalysis	X[b]		X[g]*	X[g]*	X*	→→→	X*		
Central Laboratory Assessments									
Cytokines	X[b]		X[g]*	X[g]*	X*	→→→	X*		
Pharmacokinetic Sampling	X[f]	X[f]	X[f]						
BM Morphology Review					X[e]	→→→			X[e]
Correlative Research Sample (BM Aspirate)					X[e]	→→→			X[e]
Genomic Analysis (PB)	X[b]		X[g]*	X[g]*	X*	→→→	X*		
Correlative Research Sample (PB)	X[b]		X[g]*	X[g]*	X*	→→→	X*		

	Initial 36-Weeks of Treatment					Post-Week 36 Treatment			
	Bi-Weekly Visits (±2 days)			Monthly Visits[a] (±2 days)		Monthly Visits[a] (±3 days)	Additional Assessments		
	Day 1	Weeks 2, 6, 10	Weeks 4, 8, 12	Weeks 16, 20, 24, 28, 32	Week 36	Weeks 40, 44, 48, 52, 56, 60, 64, 68, 72, etc	Every 3 Months (±3 days)	Every 6 Months (±14 days)	Every 12 Months (±28 days)
Genomic Analysis – Germline Samples	X[l]								
Bomedemstat Procedures and Assessments									
Dispensation & Dosing Instructions to Patient	X	X	X	X	X	X			
Dosing	X	←	—	—	—	—	—	—	→
Titration Assessment		X[bn]	X[bn]	X[bn]	X[bn]	X[bn]			
Returns and Accountability		X	X	X	X	X			

aPTT, activated partial thromboplastin time; BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; ED, Early Discontinuation; EoS, End of Study; EoT, End of Treatment; INR, international normalized ratio; MFSAF, Myelofibrosis Symptom Assessment Form; PB, peripheral blood; PE, physical examination; PGIC, Patient Global Impression of Change; POCBP, participant of childbearing potential; PT, prothrombin time; PV, polycythemia vera.

***Important:** may be performed up to 2 days ahead of the main visit to avoid delays in dispensation due to either pending lab results or pharmacy procedures and to facilitate all laboratory sampling occurring the same day as the hematology sampling needed for the titration assessment. For example, if a visit is scheduled on a Wednesday, these assessments can be performed Monday or Tuesday, if needed, to ensure bomedemstat is dispensed and available for collection at the Wednesday visit.

a It is anticipated that by Week 12 all patients will have achieved a stable dose, with bi-weekly visits no longer required. For the exceptional patient whose dose has not stabilized, bi-weekly visits may continue to be implemented at PI's discretion. For such patients, only the 'Hematology w/Auto or Manual Differential' and 'Titration Assessment' procedures are required. Refer to Section 7.2.2, Table 1 for dose titration and re-challenge rules.
b Assessment to be performed *prior* to dosing.
c Questionnaire to be completed during Screening as close to Day -7 as possible, and within the 2 days leading up to or on the day of every visit throughout the study except for any additional bi-weekly visits implemented after Week 12 for patients whose dose has not stabilized. Refer to Study Reference Manual (SRM) for additional instruction.
d Day 1 visit window is ±2 days; visit window at all other time-points is ±7 days. Required at Weeks 12, 24 and 36 only, and every 6 months ±14 days following Week 36 assessment as long as the patient qualifies for treatment. CT to be undertaken for patients not candidates for MRI.
e Week 36 visit window is ±7 days. Required every 12 months ±28 days following Week 36 assessment as long as the patient qualifies for treatment. Aspirate from the first pull whenever possible, but none beyond the second, is required (except in case of a dry tap).
f Three PK sampling sessions required: 1) Day 1, 2) Week 2 (Day 15) and 3) at either Week 4 (Day 29), Week 6 (Day 43) or Week 8 (Day 57). At each session, 5 samples each 4 mL in volume, will be drawn for a total of 20 mL blood. Sampling time-points are pre-dose (-60 minutes), then 1h (±15 minutes), 2h (±30 minutes), 4h (±30 minutes) and 6h (±60 minutes) post-dose.
g Required Weeks 12, 24 and 36 and every 12 weeks thereafter (Weeks 48, 60, 72, 84, etc.) as long as the patient qualifies for treatment.
h Refer to Study Reference Manual (SRM) for additional instruction on the PGIC.
i Edge of spleen determined by palpation, measured in centimeters, using a soft ruler/tape, from the costal margin to the point of greatest splenic protrusion in the mid-clavicular line.

j Assess whether the patient is deriving clinical benefit (defined as not meeting progressive disease criteria as *per* Appendix 16.5) and safely tolerating bomedemstat, thereby qualifying for continued treatment with bomedemstat beyond Week 36, with no interruption in dosing (Section 9.4). For patients not continuing beyond Week 36, the EoT visit (Section 9.5) will substitute for the Week 36 visit.

k Patient must be contacted on the day prior to PK sampling (required at Week 2/Day 15, and again at any regularly scheduled study visit from Week 4/Day 29 to Week 8/Day 57) to confirm the date and exact time of dose on the day prior to PK sampling to record in EDC and to remind the patient to fast overnight (at least 8 hours) prior to their visit and that bomedemstat will be administered in clinic.

l Germline samples to be collected for genomics, if not collected earlier in Screening.

m Automated or manual differential as needed to ensure all analytes are resulted.

n The first up-titration is not permitted before Week 6, and the second up-titration may occur no sooner than 6 weeks after the first up-titration (*e.g.*, if an up-titration occurs at Week 6, the next up-titration may not occur until Week 12). Beginning at Week 16, up-titrations are permitted no more frequently than every 4 weeks from the previous up- or down-titration. Down-titrations may be made (or the current dose maintained) at any time in the best interests of the patient (see Section 7.2).

16.2 The 2016 WHO Diagnostic Criteria for Polycythemia Vera (Arber *et al.*, 2016)

Polycythemia Vera	
Diagnosis of PV requires meeting either all 3 major criteria, OR the first 2 major criteria and the minor criterionΨ.	
Major criteria	1. Hemoglobin >16.5 g/dL in men, >16.0 g/dL in women OR Hematocrit >49% in men, OR >48% in women OR increased red cell mass (RCM)^
	2. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
	3. Presence of JAK2V617F or JAK2 exon 12 mutation
Minor criterion	Subnormal serum erythropoietin level

BM, bone marrow; PV, polycythemia vera; MF, myelofibrosis; RCM, red cell mass; WHO, World Health Organization.

^ More than 25% above mean normal predicted value.

Ψ Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dL in men (hematocrit, 55.5%) or >16.5 g/dL in women (hematocrit >49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).

16.3 Criteria for Grading Myelofibrosis (Arber *et al.*, 2016)*

Fibrosis grade	Definition
MF-0	Scattered linear reticulin with no intersections (crossovers) corresponding to normal bone marrow
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis[a]
MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis[a]

BM, bone marrow; MF, myelofibrosis.

* Slightly modified from the European Consensus Criteria as presented in Thiele *et al.*, 2005

Semiquantitative grading of BM fibrosis with minor modifications concerning collagen and osteosclerosis. Fiber density should be assessed only in hematopoietic areas.

[a] In grades MF-2 or MF-3 an additional trichrome stain is recommended.

16.4 Eastern Cooperative Group Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, *e.g.*, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

ECOG, Eastern Cooperative Oncology Group.

16.5 IWG Response Criteria for PV (Barosi *et al.*, 2013)

	Criteria
Complete Remission	
A	Durable* resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement† AND
B	Durable* peripheral blood count remission, defined as Hct lower than 45% without phlebotomies; platelet count ≤400 × 10^9/L, WBC count <10 × 10^9/L, AND
C	Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND
D	Bone marrow histological remission defined as the presence of age-adjusted normocellularity and disappearance of trilinear hyperplasia, and absence of > grade 1 reticulin fibrosis
Partial Remission	
A	Durable* resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement† AND
B	Durable* peripheral blood count remission, defined as Hct lower than 45% without phlebotomies; platelet count ≤400 × 10^9/L, WBC count <10 × 10^9/L, AND
C	Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND
D	Without bone marrow histological remission defined as persistence of trilinear hyperplasia.
No response	Any response that does not satisfy partial remission
Progressive Disease	Transformation into post-PV myelofibrosis, myelodysplastic syndrome or acute leukemia‡

Hct, hematocrit; IWG, International Working Group; IWG-MRT, IWG-for Myelofibrosis Research and Treatment; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; PV, polycythemia vera; WBC, white blood cell; WHO, World Health Organization.

* Lasting at least 12 wk.

† Large symptom improvement (≥10-point decrease) in MPN-SAF TSS.

‡ For the diagnosis of post-PV myelofibrosis, see the IWG-MRT criteria; for the diagnosis of myelodysplastic syndrome and acute leukemia, see WHO criteria.

Molecular response is not required for assignment as complete response or partial response. Molecular response evaluation requires analysis in peripheral blood granulocytes. Complete response is defined as eradication of a preexisting abnormality. Partial response applies only to patients with at least 20% mutant allele burden at baseline. Partial response is defined as ≥50% decrease in allele burden.

16.6 Intolerance/Resistance to Hydroxycarbamide (Hydroxyurea; HU) Modified from the ELN Criteria for PV (Barosi *et al.*, 2010)

Patients will be classified as either HU resistant or intolerant following HU administration *per* at least one of the criteria below:

- **HU Resistant:**
  - Need for phlebotomy to keep hematocrit <45% after 3 months of at least 2 g/day or maximum tolerated dose of HU, OR
  - Uncontrolled myeloproliferation, ***i.e.*** platelet count >400 × 10^9/L OR white blood cell count >10 × 10^9/l after 3 months of at least 2 g/day or maximum tolerated dose of HU, OR
  - Failure to reduce massive* splenomegaly by more than 50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly after 3 months of at least 2 g/day or maximum tolerated dose of HU, OR
  - Absolute neutrophil count <1 × 10^9/L OR platelet count <100 × 10^9/L or hemoglobin <100 g/L at the lowest dose of HU required to achieve a complete or partial clinico-hematological response Ω, OR
- **HU Intolerant:**
  - Absolute neutrophil count <1 × 10^9/L at any dose of HU
  - Platelet count <150 × 10^9/L at any dose of HU
  - Hemoglobin (Hb) <10 g/dL at any dose of HU
  - Presence of leg ulcers or other unacceptable HU-related non-hematological toxicities, including but not limited to mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HU defined as:
    - Common Terminology Criteria for Adverse Events (CTCAE) Grade 3–4 AE, or
    - >1 week of CTCAE Grade 2 AE, or
    - Any other unacceptable HU-related non-hematological toxicities leading to any of the below:
      - Permanent discontinuation of HU, or
      - Interruption of HU until toxicity resolved, or
      - Hospitalization

CTCAE, Common Terminology Criteria for Adverse Events; ELN, European Leukemia Network; HU, hydroxyurea; PV, polycythemia vera.

* Organ extending by more than 10 cm from the costal margin.

Ω Complete response was defined as: hematocrit <45% without phlebotomy, platelet count ≤400 × 10^9/l, white blood cell count ≤10 × 10^9/l, and no disease-related symptoms. Partial response was defined as: hematocrit <45% without phlebotomy, or response in three or more of the other criteria (Barosi *et al*, 2009).

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16.7 Strong CYP3A4 Inhibitors and Strong CYP3A4 Inducers

This table is included to provide examples of STRONG CYP3A4 *inhibitors and STRONG CYP3A4 Inducers and is not intended to be an exhaustive list.*

STRONG INHIBITORS	
CYP3A4	boceprevir cobicistat clarithromycin danoprevir and ritonavir elvitegravir and ritonavir grapefruit juice idelalisib indinavir and ritonavir itraconazole ketoconazole lopinavir and ritonavir nefazodone nelfinavir paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) posaconazole ritonavir saquinavir and ritonavir telaprevir tipranavir and ritonavir telithromycintroleandomycin voriconazole
STRONG INDUCERS	
CYP3A4	apalutamide carbamazepine enzalutamide ivosidenib lumacaftor mitotane phenytoin rifampin St. John's wort

16.8 Definitions of Thrombotic and Major Hemorrhagic Events

16.8.1 Definition of Thrombotic Events

Thrombotic Events
• **New or recurrent acute myocardial infarction** (Thygesen *et al.*, 2018) Acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cardiac troponin (cTN) values with at least one value above the 99th percentile upper reference limit (URL) and at least one of the following: o Symptoms of myocardial ischemia; o New ischemic ECG changes; o Development of pathological Q waves; o Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; o Identification of coronary thrombus by angiography or autopsy
• **Unstable angina** (Sandoval *et al.*, 2018) Clinical presentation consistent with unstable angina as defined below and cardiac biomarkers below the decision limit (i.e., cTN < 99th percentile URL) Rest angina: angina occurring at rest and prolonged, usually greater than 20 minutes New-onset angina: New-onset angina of at least Canadian Cardiovascular Society (CCS) class III severity (Marked limitations of ordinary physical activity. Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace.) Increasing angina: Previously diagnosed angina that has become distinctly more frequent, longer in duration, or lower in threshold
• **Stroke** (Sacco *et al.*, 2013) A stroke is a CNS infarction defined as brain, spinal cord or retinal cell death attributable to ischemia based on 1. Pathological, imaging, or other objective evidence of cerebral, spinal cord or retinal focal ischemic injury in a defined vascular distribution; or 2. Clinical evidence of cerebral, spinal cord or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded
• **Transient ischemic attack (TIA)** (Easton *et al.*, 2009) Transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia without acute infarction
• **Deep venous thrombosis (DVT)** A DVT is defined as a typical clinical picture with positive investigation: i.e., phlebography, ultrasonography, CT in unusual sites. In case of suspected recurrence in a site of previous DVT, diagnosis is accepted only if the investigation shows extension of recurrence of thrombosis compared to a previous test. Please refer to the American Society of Hematology (ASH) 2018 Guidelines for Diagnosis of VTE (Lim *et al.*, 2018) for diagnostic recommendations for DVT.

• **Pulmonary embolism (PE)** A PE is defined as a typical clinical picture with positive angiography or high-probability V/Q scanning. Please refer to the ASH 2018 Guidelines for Diagnosis of VTE (Lim *et al.*, 2018) for diagnostic recommendations for PE.
• **Thrombotic digital ischemia** Characterized by painful digital extremity (toes/fingers) with signs of ischemia (blue/purple discoloration), which may progress to infarction if untreated. Digital ischemia may occasionally be associated with erythromelalgia.
• **Other thrombotic event**, such as peripheral limb ischemia or Budd-Chiari syndrome that are assessed to be due to underlying PV
Other Vascular Occlusive Events
• Other occlusive events, such as symptoms of cardiac, abdominal or peripheral limb ischemia supported by objective evidence of vessel disease and/or ischemia.
ASH, American Society of Hematology; CCS, Canadian Cardiovascular Society; CNS, central nervous system; CT, computerized tomography; cTN, cardiac troponin; DVT, deep venous thrombosis; ECG, electrocardiogram; PE, pulmonary embolism; PV, polycythemia vera; TIA, transient ischemic attack; URL, upper reference limit; V/Q, ventilation-perfusion scan; VTE. Venous thromboembolism.

16.8.2 Definition of Major Hemorrhagic Events

Major Bleeding (MB) Events (Schulman *et al.*, 2005)
1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
3. Bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of 2 or more units of whole blood or red cells
Clinically Relevant Non-Major Bleeding (CRNMB) Events (adapted from Kaatz *et al.*, 2015)
• Leading to hospitalization or increased level of care (*i.e.*, requiring medical intervention by a health care professional)
• Clinically important, prompting a face-to-face medical evaluation (*i.e.*, not simply a telephonic or other form of electronic communication)
CRNMB, clinically relevant nonmajor bleeding; MB, major bleeding.

16.9 Remote Data Review

16.9.1 Risk Assessment

Given the rapidly evolving COVID-19 pandemic, Sponsor will remain responsive to the changing requirements of each individual site, globally, to determine whether and how patient visits and monitoring visits can occur with minimal risk and in accordance with site policy. A COVID-19 site management risk assessment form has been created to document site-specific issues that could impact patient safety and data integrity. This tool will be used to highlight risks and document contingency plans for both the patient, and the monitor, to mitigate such risks. As the patient population under study are those with a hematologic malignancy who require treatment for their disease and have failed at least one standard therapy, the benefit-risk is favorable for the patients to continue treatment during this pandemic, as long as the proper controls are in place and there is no government guidance to the contrary in individual countries.

16.9.2 Security Measures

Monitors are only permitted to undertake remote data review through the processes detailed below in Sections 16.9.3.1 and 16.9.3.2 (Electronic Medical Record [EMR] access or video call/conferencing) where the following security measures are in place:

- Location of Monitor: remote data review activities may be performed in locations that do not allow access/viewing by unauthorized third parties:
    - Acceptable locations include: closed room in a CRO office, at home in private area for home-based staff.
    - Examples of prohibited locations include: Open plan desk space in CRO offices, on public transportation, in airport lounge or other public areas.
- Internet connection: remote data review is permitted only through a secure internet connection *i.e.*, CRO office internet or secure personal internet after logging into CRO virtual private network (VPN). Use of a public internet, hot spot or hotel internet is prohibited.
- Device: remote data review is permitted only through CRO registered device (*e.g.*, laptop, iPad) or through a device provided by the site.
- While the EMR system is accessed or video call/conference are ongoing, the computer must be locked if left unattended.

16.9.3 Processes

As outlined in Section 13.5, remote data review is intended to encompass as many activities performed in a routine on-site monitoring visit as is functionally possible, and as permitted by site policy and procedure. Remote data review has become critically important in the COVID-19 environment as a measure of safeguarding patient safety, while also minimizing risks to trial data integrity and facilitating GCP compliance. The source documents/source data to be made

available for remote data review include those related to the primary endpoint and exploratory endpoints, safety, study drug dispensation and return and the reasons for exclusion of a subject from the trial.

The remote review of data may be actioned *via* multiple pathways, often contingent on site's capabilities. Examples include:

- Remote Source Data Review (via EMR)
- Remote Source Data Review (via video call/conferencing)
- Remote Data Verification (using redacted source documents)

Additionally, to facilitate continued interaction with and support of the site, phone monitoring visits may also periodically be conducted. Remote review of data will not occur during phone visits.

16.9.3.1 Direct, Controlled Remote Access to Site Systems Used to Manage Source Documents/Source Data

For data review whereby the monitor accesses the EMR system remotely, the following criteria are required to be met before this process can be implemented for any subject:

- An audit trail is available in the EMR system.
- There is unique password access to the EMR system assigned to each member of site staff.
- There is unique password, read-only access to the EMR system assigned to the Monitor.
- EMR access has been granted only to trial subjects' records and other patient data is not accessible to the Monitor (unless a procedure is in place to monitor the Monitor's activity following each session).
- US sites only: written procedure is in place for the use of EMR system.
- US sites only: If the EMR system is certified by the Office of the National Coordinator for Health Information Technology (ONC) at the Department of Health and Human Services, it is sufficient to confirm this on the COVID-19 Remote Source Data Monitoring Site Agreement.

16.9.3.2 Passive Access to Original Documents/Original Data via Live Image Transmission

The following controls will be applied for remote data review by video call/conferencing:

- The video call/conference may only occur using a CRO approved information and communication technology.
- Video review of documentation only is permitted.
- No recording of the interaction is permitted.
- No document upload is permitted.

- No Document storage is permitted.
- Usage must comply with applicable local regulations/regulatory guidance.
- During remote data review by video call/conferencing care will be taken to avoid inadvertent viewing of individuals who should not be part of the interaction.

16.9.3.3 Passing on Redacted Copies of Original Documents and Documents with Original Data

The following controls will be applied during for passing on redacted copies of original documents:

- Process must be allowed by local regulations and in compliance with applicable regulatory guidance
- Principal Investigator to document the delegation of creation of Pseudonymized Certified Copies of the source documents on the Study Personnel Signature and Delegation Form
- Site staff who will provide source documents to Monitor for remote data review will be trained on the role, responsibility, and process for providing pseudonymized Certified Copies of source documents to support remote review of data
- Certified Copies of all required original source documents will be prepared

  Certified Copy: *A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP) Revision 2).*

  Note: A copy is certified by signing and dating on the first page with a statement "certified copy" and adding a note on the first page that the certified copy package consists of # pages. Each page must be numbered so that, in total, the pages match the full # of pages documented on the first page of the package.
- All subject direct identifiers (*e.g.*, name, social security/national identification number, medical record number, initials, full date of birth, home address etc.) will be redacted/ obscured (*i.e.*, pseudonymized) on the copies to protect subject confidentiality and personal data.
- A quality check of the redacted Certified Copies will be performed by a second site staff member to confirm all subject directly identifiable information has been redacted, the correct subject identification code added and that the copies are legible.
  - The quality check will be documented by the second site staff member's initials, dating of the first page of the package and addition of the statement "QC'd/Checked"

- A transmittal form will be completed each time Pseudonymized Certified Copies of source documents are sent.
- The prepared source document package, including transmittal form, will be provided by one of the following methods:
    - Overnight Courier
    - Secure Fax Transmission
    - Scanned images via secure email (encrypted email or password protected email attachment. If the latter, the password will be provided to Monitor via telephone)
    - A secure platform for document exchange
- A set of the prepared source document package, including transmittal form, will be retained in the Investigator's Site File.

16.10 Contraceptive Guidance

16.10.1 Definitions

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile following menarche and capable of becoming pregnant until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (*e.g.*, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered POCBP:

- Premenarchal
- Premenopausal with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (*e.g.*, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
    - Participants assigned female sex at birth who are on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

16.10.2 Contraceptive Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol-defined time frame in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a POCBP who is not currently pregnant.
- The following are not acceptable methods of contraception:
    - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).
    - Male condom with cap, diaphragm, or sponge with spermicide.
    - Male and female condom cannot be used together.
- Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Female POCBP are eligible to participate if they agree to consistent and correct use of a highly effective method of contraception that has a low user dependency (as described in Table 4) during the protocol-defined time frame in Section 6.1.

Table 4: Highly Effective Contraception Methods

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency[a] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[a,b] • IUS[b,c] • Nonhormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with partner(s) capable of producing sperm during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study.
IUD, intrauterine device; IUS, progestin-releasing IUD; POCBP, participant of childbearing potential. [a] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [b] If hormonal contraception efficacy for a participant assigned female sex at birth is potentially decreased due to interaction(s) with study intervention(s) (*e.g.*, CYP3A4 inducers), penile/external condoms must be used in addition to POCBP's hormonal contraception. [c] IUS is a progestin-releasing IUD. Note: • Male and female condoms should not be used together (due to risk of failure with friction) • Tubal occlusion includes tubal ligation