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COVER PAGE

Official Study Title: AN INVESTIGATOR INITIATED PHASE 2 TRIAL OF THE LSD1 INHIBITOR IMG-7289 (BOMEDEMSTAT) IN ESSENTIAL THROMBOCYTHEMIA

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AN INVESTIGATOR INITIATED PHASE 2 TRIAL OF THE LSD1 INHIBITOR IMG-7289 (BOMEDEMSTAT) IN ESSENTIAL THROMBOCYTHEMIA

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INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Protocol "An Investigator Initiated Phase 2 Trial Of The LSD1 Inhibitor IMG-7289 (bomedemstat) In Essential Thrombocythemia" CTMS# 19-0078 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the study in accordance with current international conference on harmonization (ICH) guidance, Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, US Food and Drug Administration (FDA) regulations and local IRB and legal requirements.

Name of Investigator: Zohra Nooruddin, MD

Institution: Mays Cancer Center

See attached electronic signature

Investigator Signature

Date

Table of Contents

1 Abbreviations

AE	Adverse Event
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ATP	Additional Treatment Period
ATRA	all-*trans* retinoic acid
CBC	complete blood count
CR	complete remission
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
Dpi	dose of pharmacodynamic inhibition; the estimated dose of IMG-7289 needed in humans that provides sufficient exposure to inhibit normal hematopoiesis safely during a fraction of the 24-hour dosing cycle
DSM	Data Safety Monitoring
DSMB	Data Safety Monitoring Board
DSMC	Data Safety Monitoring Committee
DSMP	Data Safety and Monitoring Plan
Ds	starting dose
DQA	Director of Quality Assurance
ECOG	Eastern Cooperative Oncology Group
ELN	European Leukemia Net
EPO	erythropoietin
ET	early termination
ET	Essential Thrombocythemia
EoS	End of Study
EoT	End of Treatment
FDA	Food and Drug Administration
G-CSF	gram colony stimulating factor
GCP	Good Clinical Practice
GM-CSF	granulocyte-macrophage colony stimulating factor
GMP	Good Manufacturing Practice
H	histone
Hy	hypothesis
Hb	hemoglobin
HU	hydroxyurea; hydrea®, hydroxycarbamide
IB	Investigator's Brochure
IIT	Investigator Initiated Trial
IL	interleukin
IND	Investigational New Drug
INR	International normalized ratio
IPSET	International Prognostic Score for Thrombosis in Essential Thrombocythemia
IRB	Institutional Review Board
ITP	Initial Treatment Period
JAK	Janus kinase
K	lysine
KD	knockdown
KDM1A	lysine-specific demethylase 1
LPE	limited physical examination
LSD1	lysine-specific demethylase 1
MAOIs	monoamine oxidase inhibitors
MDS	myelodysplastic syndromes

MEP	megakaryocyte-erythroid progenitor
MF	myelofibrosis
MPN	myeloproliferative neoplasms, myeloproliferative diseases
MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment Form
NIH	National Institutes of Health
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect-level
NSAID	non-steroidal anti-inflammatory drug
OSP	Office of Sponsored Programs (UTHSA)
PALS	Priority of Audit Level Score
PD	pharmacodynamics
PE	physical examination
PI	Principal Investigator
PK	pharmacokinetics
PMF	primary myelofibrosis
PR	partial remission
PSD	Pharmacokinetic Sampling Department
PV	polycythemia vera
RNA	ribonucleic acid
SAE	Serious Adverse Event
STAT	Signal Transducer and Activator of Transcription
TSS	Total Symptom Score; is derived from the MPN-SAF
UPIRSO	Unanticipated Problem Involving Risks to Subjects or Others
UTHSA	UT Health San Antonio
WOCBP	Women of child-bearing potential

2 Study Synopsis

Protocol Title: AN INVESTIGATOR INITIATED PHASE 2 TRIAL OF LSD1 INHIBITOR IMG-7289 (BOMEDEMSTAT) IN ESSENTIAL THROMBOCYTHEMIA
Protocol No:CTMS#19-0078, NCT04081220
Investigator/Study Centers: Single site institutional study at the Mays Cancer Center in San Antonio, TX.
Study Objectives/Hypotheses: We propose to determine the effects of IMG-7289 (Imago BioSciences, Inc.'s bomedemstat), an irreversible inhibitor of the enzyme lysine-specific demethylase 1 (LSD1, or KDM1A) as a treatment of essential thrombocythemia (ET). ET is an indolent hematologic cancer characterized by reduced quality of life, thrombocytosis, elevated cytokines, and increased rates of thrombosis and bleeding that can evolve to myelofibrosis and/or acute myeloid leukemia. LSD1 is an enzyme that regulates the maturation of megakaryocytes from progenitor cells, as well as the function of mature megakaryocytes. In ET, acquired mutations cause JAK/STAT activation which results in an over-abundance of activated megakaryocytes that in turn produce an excess of platelets, growth factors and inflammatory cytokines. The primary hypothesis is that pharmacologic inhibition of LSD1 will reduce both the number of megakaryocytes and their capacity to secrete growth factors and inflammatory cytokines to the clinical benefit of ET patients. **Study Aims and Hypotheses (Hy):** **Aim 1.** To assess the hematologic effects of IMG-7289 in a population of ET patients requiring platelet control who are resistant to or intolerant of hydroxyurea per ELN criteria. **Hy1**: IMG-7289 will induce complete hematologic response in >10% of this study population by 24 weeks. **Aim 2:** To qualitatively examine markers of disease burden including patient-reported symptom burden, standard ARUP testing of mutant (variant) allele burden in granulocytes (baseline and Week 24), spleen size, and bone marrow histology. **Hy2**: ET patients treated with IMG-7289 will experience improved symptom burden, reduced mutation allele burden, improved spleen size if enlarged at baseline, and reduced megakaryocyte hyperplasia following the 24-week treatment course.
Investigational Drug: The active drug substance is identified as IMG-7289 (bomedemstat). IMG-7289 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. IMG-7289 will be supplied as capsules in multiple strengths. These strengths, based on IMG-7289 free base, i.e., the active substance, may include: 5 mg, 10 mg, 25 mg, and 50 mg. Capsule strengths provided may change throughout the duration of the study.
Study Population: Twenty patients eighteen years of age or older with hydroxyurea resistant or intolerant ET per ELN criteria will be treated.
Duration of Participation: Study participants will initially be treated in the study for 24 weeks. If participants are deriving clinical benefit from IMG-7289, the drug can be continued for an additional 24 weeks; this is an iterative process and may repeat indefinitely if there is clinical benefit in the absence of excess toxicity.
Methodology: This is a single-center, open-label investigator-initiated trial evaluating the effects of IMG-7289 administered orally once daily in patients with essential thrombocythemia. Preclinical testing of LSD1 inhibition in myeloproliferative neoplasm models induced apoptosis in mutant stem/progenitor cells, reduced inflammatory cytokines, reduced spleen length, decreased bone marrow fibrosis, and reduced extramedullary hematopoiesis. Additionally, LSD1 inhibition with IMG-7289 was shown in a *Jak2*^{V617F} mouse model of ET/polycythemia vera (PV) to selectively decrease the number of malignant megakaryocytes as well as reduce elevated platelets, red cells, and granulocytes (Jutzi *et al.* 2018). To date, IMG-7289 has been investigated in acute myeloid leukemia, myelodysplastic syndrome, and myelofibrosis patients, with notable changes in the myelofibrosis population including dose-dependent decreases in IL-8, platelets, and neutrophils. This Phase 2 prospective single arm study is the first proposed study to determine the hematologic effects of IMG-7289 in a population of ET patients. The primary aim of this study is to determine the effects of IMG-7289 in a population of ET patients requiring platelet control who are resistant to or intolerant of hydroxyurea, per ELN criteria, over a period of 24 weeks. Secondary aims are to explore

the effects of IMG-7289 on disease-related symptom burden, mutant (variant) allele burden in granulocytes, spleen size, and bone marrow histology. If successful, this study will help to meet an unmet need for therapeutic interventions that reduce thrombocytosis and improve symptom burden among individuals with HU-resistant or intolerant ET per ELN criteria.

The therapeutic goal for the treatment of ET 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 platelets and granulocytes 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 eighty-five patients who have received IMG-7289 to date in IMG-7289-CTP-101 and -102. Using all available information in conjunction with the therapeutic goal for the treatment of ET, the starting dose of IMG-7289 of 0.6 mg/kg QD has been selected to enable ET patients to reach the optimum dose sufficient to reduce platelets below 400 k/μL while still maintaining an adequate safety margin.

Study Conduct: This study consists of two treatment periods: the Initial Treatment Period (ITP), followed by the Additional Treatment Period (ATP). In the ITP, patients will be treated daily for 169 days. The ATP offers treatment to qualifying patients for additional 169 day cycles for those patients deriving clinical benefit, as determined by the Principal Investigator.

During the ITP, patients will initially return for study assessments weekly for the first 8 weeks (ITP Days 8, 15, 22, 29, 36, 43, 50 and 57), at least bi-weekly for 8 weeks with the start of video visits every other assessment point if deemed applicable by the Principal Investigator (ITP Days 71, 85, 99 and 113) and then monthly for 8 weeks (ITP Days 141 and 169). It is anticipated that by Week 8 (Day 57) patients will have achieved a stable dose, with weekly visits no longer necessary. For safety purposes, weekly visits may continue at the PI's discretion (note: bi-weekly visits may also continue post Week 16 (Day 113)) if necessary. On Day 169 bone marrow sampling is also required. At the Day 169 visit, a 'qualification' assessment will be made to determine whether the patient is deriving clinical benefit and safely tolerating IMG-7289. Such patients qualify for entry into the ATP, a transition which should occur without interruption in dosing. Patients not deriving clinical benefit, or who achieve complete remission (CR) or partial remission (PR) and subsequently relapse (Section 12.4) the equivalent of treatment failures, will discontinue IMG-7289 and undergo End of Treatment (EoT), pre-End of Study (pre-EoS) and End of Study (EoS) visits.

In the ATP, treatment may continue for an additional 169 days in those patients deriving clinical benefit, as determined by the Principal Investigator. Qualifying patients will return for study assessments monthly (ATP Days 1, 29, 57, 85, 113, 141 and 169). It is anticipated that patients continuing in the ATP will have already achieved a stable dose, with bi-weekly visits no longer necessary. For safety purposes, bi-weekly visits may continue at the PI's discretion, if necessary. Optional on *every other* Day 169 (i.e., ATP2 Day 169, ATP4 Day 169) for as long as the patient continues to qualify for treatment, patients will undergo bone marrow sampling. At the Day 169 visit, a 'qualification' assessment will be made to determine whether the patient is continuing to derive clinical benefit. Such patients thereby qualify for re-entry into the ATP, which is iterative; patients may continue to receive IMG-7289 for as long as they continue to qualify.

Patients will be followed closely throughout the study for both Adverse Events (AEs) and signs of toxicity by frequent monitoring of clinical signs and symptoms as well as safety labs. Pharmacodynamic effects will be closely monitored by frequent hematology assessments of peripheral blood, and optional requisite bone marrow aspirates (optional in the ATP period only) and biopsies. Throughout dosing, transfusions may be administered if needed in accordance with standard institutional guidelines.

IMG-7289 Dosing:

Initial Treatment Period (ITP): All patients will be treated daily, for up to 169 days of dosing. Treatment will begin on Day 1 at the starting dose (D_s) of 0.6 mg/kg QD. Details on the selection and rationale for the starting dose and dosing schedule can be found in Sections 3.4 and 3.5.

Through the use of dose titration, all patients will be dosed to the IMG-7289 D_{pi}; the dose needed to safely inhibit normal thrombopoiesis for a fraction of the dosing cycle. Dose-titration, both upward and downward, is contingent on the hematology assessment and comparison of hematology values from the prior study visit.

Up-titrations may begin on ITP Day 29 and occur no more frequently than every 4 weeks from the previous up- or down-titration. **Down-titrations** can be made at any time in the best interest of the patient. Up-titrations will be made in increments of 0.2 mg/kg/d and down-titrations in decrements of 0.1 or 0.15 mg/kg/d.

The dose of pharmacodynamic inhibition (D_{pi}) is anticipated to be approximately 2 mg/kg QD; however, this is not the upper limit for titration purposes as the dose needed to achieve a therapeutic effect will vary among patients and may change over time. The target platelet count range for dose titrations expected to be associated with a clinically significant therapeutic effect is: ≥ 200 to ≤ 400 k/μL (200-400 x 10^9/L).

Titration and re-challenge rules based on evaluation of platelet, absolute neutrophil (ANC) and hemoglobin (Hb) counts are noted below.

Titration and Re-challenge Rules

Important: ANC ≥0.5x10^9/L (500 neutrophils /μL) is needed for up-titration. For an ANC below this threshold, the current dose should be maintained or down-titrated in accordance with the rules detailed below.

Hematology Assessment		**Titration and Re-challenge Rules**		
Plt Count (x 10^9/μL)	**Hb Level (g/dL)**	**Titration?***	**Titration Rule***	**Re-challenge Rule¥**
> 400	≥ 10	Up-titrate¤	Increase by 0.2 mg/kg/d¤	N/A
≥ 200 - ≤ 400	≥ 10	Maintain current dose	N/A	N/A
50-199	≥ 10	Down-titrate	Decrease by 0.1 mg/kg/d	N/A
N/A	8.5 to <10	Down-titrate	Decrease by 0.15 mg/kg/d	N/A
< 50	**<8.5**	**HOLD DOSEΦ**	**N/A**	**At 50% of prior dose** when: - platelets return to ≥ 100 - Hb returns to ≥8***

¤ **Up-titrations may begin on ITP Day 29 and occur no more frequently than every 4 weeks from the previous up- or down-titration. Down-titrations can be made at any time in the best interest of the patient.**

ΦPatients requiring a dose hold should have complete blood counts monitored at least weekly for safety purposes and to enable re-challenge to commence as soon as counts return to the required level, if safe to do so.

*The PI may, upon review of individual patients and patient responses, recommend up- or down-titrations that are not in concordance with the above.

** Re-challenge at 50% of the previous mg/kg dose.

***PRBC transfusions allowed if at 0.15 mg/kg/d down-titrated dose level transfusions requirement remains stable within 2 units per month, and no more than 4 units total per 28 days, and patient otherwise has evidence of clinical benefit.

¥ Upon re-challenge, all of the above rules reapply.

Additional Treatment Period (ATP): Qualifying patients will 're-start' IMG-7289 on ATP Day 1, with dose titration continuing as *per* the Titration Rules table above; there should be no interruption in dosing (i.e., Day 169 = Day 1 of new ATP). Additional dose-titration may occur in consultation with the Principal Investigator.

Study Duration: Screening procedures may commence up to 28 days prior to the start of treatment. Patients may initially receive up to 24 weeks of dosing while on study. Patients will be followed for 28 days post last dose. Therefore, the anticipated duration of participation in the study is expected to be approximately 32 weeks from first patient-first visit to last patient-last visit. Additional treatment may be given, contingent on an assessment of patient benefit for multiple repeating ATPs

Study Assessments: The assessments outlined below are also summarized in Section 7 and in the Schedule of Assessments Sections 7.7 and 7.8.

The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) will be completed at Screening (as close to Day -7 as possible) and once weekly from Day 1 through the End of Study (EoS) Visit (Appendix 12.6). Multiple questionnaires will need to be provided to the patient for completion as visit schedule decreases over time.

ECOG Performance Status will be performed at Screening, and on Days 85 and 169 of the ITP, on Day 169 of the ATP for as long as the patient continues to qualify, at EoT, EoS/ET, and upon suspicion of relapse.

Adverse events (AEs) will be assessed at every visit post first IMG-7289 dose through the EoS visit.

Physical Examinations (PE): a **Full Physical Exam**, including height, weight, vital signs and spleen measurement will be performed at Screening. **Limited Physical Exams (LPE)** will be performed weekly for 8 weeksand then monthly throughout the study, unless deemed to be needed more frequently by PI. Limited PEs include weight, vital signs, a review of body systems to assess change from previous PE, and spleen measurement. The edge of the spleen shall be determined by palpation, measured in centimeters, using a soft ruler, from the costal margin to the point of greatest splenic protrusion. The spleen should be measured in the same manner at all visits ideally by the same examiner.

Serum pregnancy testing will be performed for women of child-bearing potential (WOCBP) at Screening and pre-dose on Day 1, and if pregnancy is suspected while the patient remains on-study.

Bone marrow aspirate* and biopsy will be performed**:

- At Screening (no more than 28 days prior to the first IMG-7289 dose).
- At ITP Day 169 visit.
- Optional at approximately every 12 months thereafter, at ATP Day 169 of *every other* Additional Treatment Period (i.e., ATP2, ATP4), for as long as the patient continues to qualify for treatment.

*Marrow from the first pull whenever possible, but no later than the second pull, is required.
**The total number of bone marrow evaluations required during the Initial Treatment Phase is 2 in ~32 weeks. Additional marrow evaluation is required only if the patient agrees to the optional time points in the Additional Treatment Phase.

Clinical laboratory measures: The following laboratory measures will be performed at Screening, pre-dose Day 1, upon suspicion of relapse, at the EoT, pre-EoS, and EoS/ET visits and in accordance with below:

- Biochemistry - monthly throughout the study (i.e., Days 29, 57, 85, 113, 141 and 169)
- Hematology with manual differential - at every clinic visit throughout the study
- C-Reactive Protein - monthly throughout the study (i.e., Days 29, 57, 85, 113, 141 and 169)

The following laboratory measures will be performed at Screening:

- Coagulation

The following laboratory measures will be performed at Screening, Week 24 and upon suspicion of relapse:

- Testing of mutant (variant) allele burden in granulocytes

Qualification Assessments:

- Initial Treatment Period Day 169: Assess whether the patient is eligible for the ATP. If it is determined that the patient is deriving clinical benefit and safely tolerating IMG-7289, then the patient qualifies for and may enter the ATP upon completion of the Day 169 visit
- Additional Treatment Period Day 169: Assess whether the patient continues to be eligible for the ATP. If it is determined that the patient is deriving clinical benefit and safely tolerating IMG-7289, then the patient qualifies for and may re-enter the ATP upon completion of the Day 169 visit.

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**.

- Up-titrations may occur no more frequently than every 4 weeks from the previous up- or down-titration
- Down-titrations are permitted at any time in the patient's best interest.

Eligibility Criteria: Patients must meet all applicable Inclusion and none of the Exclusion Criteria.

Inclusion criteria are as follows:

1. Age ≥18 years.
2. Diagnosis of Essential Thrombocythemia per World Health Organization (WHO) diagnostic criteria for myeloproliferative neoplasms (Arber *et al.*, 2016).
3. Patients who are intolerant or resistant to hydroxyurea per ELN criteria, or in the Investigator's judgment are not candidates for available approved therapy. The ELN definitions of resistance/intolerance to HU requires the fulfillment of at least one of the following criteria:
   a. Platelet count >600 × 10^9/L after daily dose of at least 2 g HU for at least 3 months (2.5 g/day in patients with a body weight over 80 kg);
   b. Platelet count >400 × 10^9/L and WBC <2.5 × 10^9/L at any dose of HU;
   c. Platelet count >400 × 10^9/L and hemoglobin <10 g/dL at any dose of HU;
   d. Presence of unacceptable HU-related non-hematologic toxicities, including fever, mucocutaneous manifestations or leg ulcers.
4. Requires treatment in order to lower platelet counts based on the Clinically Relevant IPSET-Thrombosis Guidelines.
5. Platelet count >450 x 10^9/L pre-dose Day 1.
6. Peripheral blast count ≤5% pre-dose Day 1.
7. ANC ≥0.5 x 10^9/L pre-dose Day 1.
8. Fibrosis Score <grade 2, as per a slightly modified version (Arber *et al.*, 2016) of the European Consensus Criteria for Grading Myelofibrosis, (Thiele *et al.*, 2005).
9. Life expectancy > 36 weeks.
10. Able to swallow capsules.
11. Amenable to spleen size determination, bone marrow evaluations (during the ITP only and optional in the ATP), and peripheral blood sampling during the study.
12. Must have discontinued ET therapy at least 2 weeks (4 weeks for interferon) prior to study drug initiation.
13. Agrees to use an approved method of contraception from Screening until 28 days after last administration of the study drug. Acceptable methods of birth control include: birth control pills, depo-progesterone injections, a vaginal hormonal contraceptive ring, a barrier contraceptive such as a condom with spermicide cream or gel, diaphragms or cervical cap with spermicide cream or gel, or an intrauterine device (IUD).
14. If male, agrees not to donate sperm or father a child for at least one month after the last dose of the study medication.

Exclusion criteria are as follows:

1. Greater than 3 separate transfusion episodes over the last 6 months and/or any transfusion over the last 4 weeks.
2. Eastern Cooperative Oncology Group (ECOG) questionnaire score of 3 or greater.
3. Currently pregnant or planning on being pregnant in the following 6 months or currently breastfeeding.
4. Currently residing outside the United States.
5. History of splenectomy.
6. Unresolved treatment related toxicities from prior therapies (unless resolved to ≤ Grade 1).
7. Uncontrolled active infection.
8. Known positive for HIV or infectious hepatitis, type A, B or C.
9. Current use of monoamine oxidase A and B inhibitors (MAOIs).
10. Evidence at the time of screening of increased risk of bleeding, including any of the following:
    a. Activated partial thromboplastin time (aPTT) > 1.3 x the upper limit of normal
    b. International normalized ratio (INR) >1.3 x the local upper limit of normal
    c. Known Acquired Von Willebrand's disorder.

GUIDELINES: These guidelines are for use by the Investigator, study staff and patient to safeguard patient safety while maintaining data integrity.

1. In general, supportive care (transfusions, administration of anti-fungals, etc.) should be maintained in accordance with institutional policy. Additionally:
    a. It is advised that patients with a platelet count ≤ 10 x 10^9/L (10,000/μL) be transfused.
2. Patients taking medications that have the potential to induce or inhibit CYP3A4 or CYP2D6 should be monitored closely for potential effects of co-administration; particular attention should be given to anti-infectives in the azole class.
3. Cessation of IMG-7289 is invariably associated with a rebound in thrombopoiesis and platelet counts may easily exceed the baseline value. When IMG-7289 is discontinued, the platelet count should be monitored closely and an alternative cytoreductive therapy to lower platelets should commence within 24-48 hours.

PROHIBITED MEDICATIONS/TREATMENTS: The PIs will contact Imago staff with any questions pertaining to prohibited medications.

1. All cytotoxic agents, including standard-of-care therapies for ET
2. All hematopoietic growth factors: romiplostim, eltrombopag, erythropoietin (EPO), granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF)
3. Monoamine oxidase A and B inhibitors
4. Anticoagulant and nonsteroidal anti-inflammatory drug (NSAID; including aspirin) use are prohibited in patients when their platelet count is < 50 x 10^9/L (50,000/μL)

Management of Study Toxicities: Adverse event intensity will be evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, published 27 November 2017. Please refer to Section 8.2 for additional detail on management of study toxicities, including reduction of the starting dose based on DLT.

Definitions: 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 IMG-7289 on normal myeloid hematopoiesis observed in non-clinical and clinical studies are expected in humans; these are pharmacodynamic effects of LSD1 inhibition by IMG-7289, thus are not regarded as adverse. These events, with the exceptions below, will not be considered DLTs.

Dose limiting toxicity (DLT): Any one of the following AEs that occurs through Day 7 of the Initial Treatment Period will be considered DLTs unless the Investigator deems the AE to be clearly unrelated to IMG-7289:

- Any Grade 3 or above thrombocytopenia associated with clinically significant bleeding*;
- Any Grade 4 thrombocytopenia associated with a requirement for platelet transfusion;
- Any Grade 4 or 5 non-hematologic adverse event;
- Any Grade 3 or above non-hematologic adverse event with the following exceptions:
    - Nausea, vomiting or diarrhea lasting 3 days or less
    - Aesthenia lasting less than 7 days
- Any Grade 3 electrolyte abnormality unrelated to the underlying malignancy and persisting greater than 24 hours.

*A clinically significant bleeding event is defined as an event that is life-threatening, cannot be controlled and/or results in hemodynamic instability.

Patients who experience a DLT may have their dose adjusted downward if the Sponsor Investigator (PI) deems it safe for the patient to continue on IMG-7289. Any patient that experiences DLT that results in discontinuation of IMG-7289 therapy may begin alternative cytoreductive therapy to lower platelets within 24-48 hours.

The SI will contact Imago medical staff to discuss IMG-7289 dose modifications for the management of clinically significant changes in platelets, neutrophil counts, or other hematologic parameters.

Stopping Rules:

IMG-7289 will be discontinued in the event of the following:

- Post DLT, the Principal Investigator deem it unsafe for the patient to continue on IMG-7289.
- Post dose reduction due to DLT, the patient either worsens at any time or fails to demonstrate significant improvement within 14 days.
- Post temporary interruption of IMG-7289 due to platelet counts below 50 x 10^9/L (50,000/µL), the patient's platelet counts don't return to > 150 x 10^9/L (150,000/µL) within 21 days.
- Any Grade 4 non-hematologic adverse event with failure to recover to Grade 3 within 7 days of drug cessation.

Study Design: This study will follow a Simon two-stage design with an anticipated lower limit response rate of 10% and a target response rate of >40%. With these parameters, the optimal Simon design with α=0.05 and 90% power would need 9 patients in the first stage and 11 patients in the second stage. After testing oral IMG-7289 on 9 patients in the first stage, the trial will be terminated if 1 or fewer respond. If the trial goes to the second stage, a total of 20 patients will be enrolled. If the total number responding is less than or equal to 4, oral IMG-7289 will be rejected; if the total number responding is more than 4, oral IMG-7289 will be considered worthy of further study.

3 Background

3.1 Background on the Disease to be Treated

The *BCR-ABL1*-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). 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).

ET is an indolent hematologic cancer characterized by reduced quality of life, thrombocytosis, elevated cytokines, an increased rate of thrombosis and bleeding and the potential to develop myelofibrosis and acute myeloid leukemia (Vannucchi *et al.* 2017). Transformation to post-ET myelofibrosis and post-ET acute leukemia occurs at a rate of 4–11% and 2.1–5.3% at 15 years, respectively (Cerquozzi and Tefferi, 2015). Risk factors for poor survival include age over 60, leukocytosis, and a prior history of thrombosis (Barbui *et al*., 2012). Indications for pharmacologic treatment in ET include extreme thrombocytosis, elderly age, $JAK2^{V617F}$ mutational status, and history of thrombosis or presence of cardiovascular risk factors (Rumi *et al*., 2017). Standard first-line pharmacologic treatment to reduce thrombocytosis is hydroxyurea (HU) which has a low incidence of acute toxicity but is regarded by some as mutagenic. However, approximately 20-25% of ET patients will be resistant or intolerant of HU per ELN criteria and treatment with HU has been demonstrated to worsen symptom burden (Sever *et al*., 2014; Geyer *et al.,* 2015). Thus, there remains **unmet need** for therapeutic interventions that reduce thrombocytosis and improve symptom burden among individuals with HU-resistant or intolerant ET per ELN criteria.

3.2 Study Rationale

This is an open-label, single-arm, single-site Investigator Initiated Trial (IIT) of the LSD1 inhibitor, IMG-7289. ET is characterized by a neoplastic process expanding myeloid lineages including the erythroid progenitor and megakaryocyte populations, platelet production and leukocytosis. Growth factors and cytokines synthesized by megakaryocytes and granulocytes contribute to symptoms and to bone marrow fibrosis. The disease is described as a clonal disorder of hematopoietic stem/progenitor cells that have acquired a somatic mutation activating the JAK/STAT pathway. As such, the activated, proliferating megakaryocyte-erythroid progenitor and its mature progeny are the pathologic seat of the disease.

LSD1, also known as KDM1A, is an enzyme that removes mono- and dimethyl groups from histone (H) H3 at critical lysines (K), K4 and K9 (Shi *et al*., 2004). Methylation of histone H3K4 and H3K9 is a post-translational modification associated with changes in the confirmation of chromatin (Bannister and Kouzarides, 2011; Beisel and Paro, 2011). Chromatin is a collective term for the association of nuclear macromolecules consisting of DNA, protein scaffolding, enzymes enhancing transcription and synthesis of RNA (Kornberg, 1974). The DNA and its protein scaffold of histones form an ordered complex called the nucleosome. Each nucleosome is composed of two copies of each of the four histone proteins, H2A, H2B, H3 and H4, forming an octamer around which DNA is wrapped. The rates of gene transcription are heavily influenced by the accessibility of transcription factors and the RNA polymerase complexes to template DNA at promoters (Bannister and Kouzarides, 2011; Beisel and Paro, 2011).

LSD1 enzyme activity is essential for the maturation of megakaryocytes and red blood cells from the megakaryocyte-erythrocyte progenitor (MEP) cell. In MEPs, LSD1 is recruited to chromatin *via* the transcription factor GFI1b, a protein also essential to MEP differentiation. Genetics studies have shown that interference with either *GFI1b* or *LSD1* has similar effects on the maturation of megakaryocytes and production platelets. Thus, therapeutically targeting LSD1 effectively reduces megakaryocyte numbers and the growth factors and cytokines that drive the secondary clinical effects observed in ET.

In myeloproliferative neoplasms including ET, LSD1 is overexpressed in myeloid cell lines including megakaryocytes and erythroid precursors (Niebel *et al.*, 2014). LSD1 inhibition has been found to be effective in inducing the apoptosis of human Janus kinase (*JAK*)*2*^{V617F} cell lines, reducing inflammatory cytokines, reducing spleen volumes, decreasing bone marrow fibrosis, and reducing extramedullary hematopoiesis in *Mpl*^{W515L} or *Jak2*^{V617F}-mutated murine models. Additionally, LSD1 inhibition with IMG-7289 was shown in a *Jak2*^{V617F} mouse model of ET/PV to selectively decrease the number of malignant megakaryocytes as well as reduce elevated platelets, red cells and granulocytes (Jutzi *et al.*, 2018). Toxicologic studies in rat and dog demonstrated a decreased red blood cell mass, platelet and neutrophil counts in a dose-dependent manner. LSD1 is known to participate in the maintenance of the self-renewal potential in stem/progenitor cells as well as enhance an interferon response in malignant cells. Whether the inhibition of LSD1 with IMG-7289 can gradually reduce the mutant cell burden as was observed in mice remains to be seen in patients.

Our proposed study is innovative in that it is the first study to determine the effects of IMG-7289 in a population of ET patients. This study will (a) provide data on the utility of IMG-7289 in the reduction of platelet counts in patients that have relapsed or are resistant to or intolerant of HU per ELN criteria, (b) determine the effects of IMG-7289 on disease-related markers including biomarkers and symptom burden with the aim of filling an unmet need in the management of ET.

At the doses proposed in this study, IMG-7289 is cleared in less than 24 hours allowing LSD1 activity to return and resume its function in normal hematopoiesis. Chronic daily administration of IMG-7289 in rat, dog and humans has been well tolerated. No safety signals have been observed in either the AML/MDS or myelofibrosis studies with IMG-7289 at doses up to 6 mg/kg/d.

3.3 Background on IMG-7289

LSD1 is a component of chromatin-modifying complex that alters the transcriptional activity of enhancers and transcription factors themselves (Rudolph *et al.*, 2013). Hematopoietic cells require LSD1 for stem cell maintenance and for progenitor differentiation in the granulopoietic, thrombopoietic, and erythropoietic lineages (Kerenyi *et al.*, 2013). In myeloproliferative neoplasms including ET, LSD1 is overexpressed in myeloid cells including megakaryocytes/ erythroid progenitors (Niebel *et al.*, 2014). LSD1 inhibition induced apoptosis in mutant stem/progenitor cells, reduced inflammatory cytokines, reduced spleen volumes, decreased bone marrow fibrosis, and reduced extramedullary hematopoiesis in *Mpl*^{W515L} *JAK2*^{V617F}-mutated murine models of MPNs (Imago Investigator Brochure). Long-term toxicologic studies in rat and dog demonstrated the expected pharmacodynamic effects of decreased red blood cell mass, platelet and neutrophil counts in a dose-dependent and reversible manner (Figure 1).

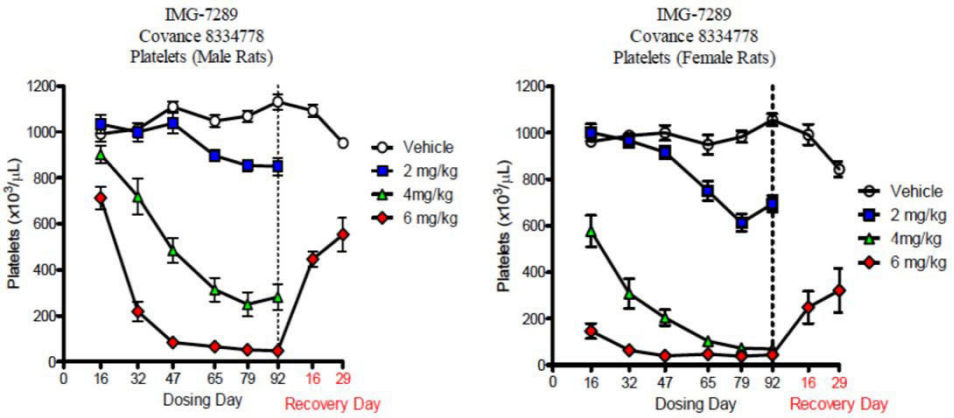

Figure 1. Dose-dependent decrease in platelet counts observed in male and female rats treated with IMG-7289 for 13 weeks.

3.4 Rationale for and Safety of the Proposed Starting Dose

The primary scientific goals of the study are to determine the hematologic effects of IMG-7289 in ET patients, and to establish the safety of dose titration based on periodic hematology evaluations and the impact of inhibiting LSD1 for a fraction of the dosing cycle (24 hours) sufficient to reduce the production of platelets.

The proposed protocol includes patients with ET who have failed at least one standard therapy (failure is the equivalent of inadequate response or intolerance). The therapeutic goal for the treatment of ET 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 platelets whose over-production characterizes the condition.

Considerations for a safe and therapeutic starting dose include chronic toxicology studies in conjunction with the clinical experience of the patients who have received IMG-7289 to date in IMG-7289-CTP-101 and -102. In the CTP-101 protocol, IMG-7289 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, 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 have been observed, was deemed 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 IMG-7289 required platelet transfusions. This sensitivity of thrombopoiesis to LSD1 inhibition in high-risk AML/MDS patients reflects 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 1039 k/μL 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 IMG-7289 needed by a majority of patients to achieve a platelet count in the target range (50-75 k/uL) 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 myelofibrosis was *not* correlated with the starting platelet count or the antecedent hematologic history. Platelet counts in patients with ET 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 ET treated with IMG-7289 are expected to be similar to those patients with myelofibrosis. Accordingly, to enable ET patients to reach the optimum dose sufficient to reduce platelets below 400 k/μL while still maintaining an adequate safety margin, an IMG-7289 starting dose of 0.6 mg/kg QD has been selected.

Collectively, these studies established some key points. First, inhibition of LSD1 for a fraction of the 24-hour dosing cycle can be achieved safely. Second, the platelet count can be targeted to a specific range by adjusting the dose of IMG-7289.

To meet the eligibility criterion for enrollment, ET patients must have a platelet count above 450 k/μL. The therapeutic target platelet count is between 200 and 400 k/μL. Based on previous clinical experience in patients (all with compromised hematopoiesis), a starting dose (Ds) of 0.6 mg/kg, or 42 mg QD for a 70 kg patient, is deemed safe in a patient population characterized by an excess of platelets. Dose adjustments in increments and decrements of between 0.2, 0.1 and 0.15 mg/kg will allow up- or down-titration of IMG-7289 to achieve the target platelet count (Table 1). Hematology assessments will ensure safety and guide dose adjustments, which may be made in accordance with the rules detailed in Section 6.2.

3.5 Justification of the Dose and Regimen

The phenotypic effects of LSD1 inhibition 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, include differentiation and, ultimately, cell death. In the primary pharmacology studies with IMG-7289, these changes take place over a period of days to weeks; in the assay for self-renewal potential (clonogenicity), these changes take days or weeks to observe. 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 less aggressive myeloid neoplasms such as ET, chronic treatment at doses that do not completely deprive the hematopoietic process of LSD1 activity is anticipated to be well tolerated while having a significant impact on disease. In mouse models of myelofibrosis, the gradual loss of cells bearing the MPN mutation (*Jak2* or *Mpl*) was observed over the course of modest LSD1 inhibition. What emerges from

these mouse studies is a therapeutic strategy that balances safety with clinical efficacy: inhibit the enzyme for only a fraction of the 24-hour dosing cycle to allow some normal thrombopoiesis to occur, thus preventing profound thrombocytopenia. At this stage of development, this optimal therapeutic dose must be identified in each patient because variations in the severity of disease and perhaps other factors will dictate the starting platelet count and hence, sensitivity to drug.

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 irreversible adverse effects on hematopoiesis. The primary effects of LSD1 inhibition are confined to the bone marrow with expected secondary effects a consequence of cytopenias at higher doses.

Observations regarding dose-response in patients with MF treated in the CTP-102 study have led to modifications of the titration schedule. As additional patients have been treated, it has been noted that for a given daily dose, the platelet count continues to fall beyond Day 7 of dosing, i.e., two successive weekly up-titrations caused the platelet count to fall more than expected and occasionally led to significant thrombocytopenia. In those patients who had received an identical dose for 3 consecutive weeks, each experienced a drop (mean -31%; N=20) in the platelet count between Day 7 and Day 14. The mean decrease in platelet counts from Day 14 and Day 21, however, was approximately -12%, suggesting that a steady state of drug exposure, LSD1 activity and platelet production occurs between Day 21 and Day 28. As such, it appears that two or three weeks between up-titrations is an insufficient amount of time for both the plasma concentrations of the drug and platelet production to reach a new steady-state necessary to achieve a stable platelet count. Therefore, up-titrations may occur no more frequently than every four weeks from the previous up- or down-titration. Down-titrations can occur at any time in best interest of the patient.

At the doses proposed in this study, the concentration of IMG-7289 is sufficient to inhibit hematopoiesis for a fraction of the 24-hour dosing period, thus allowing LSD1 activity to return and resume its function in normal thrombopoiesis. Chronic daily administration of IMG-7289 in rat, dog and humans has been well tolerated. No safety signals have been observed in either the AML/MDS or myelofibrosis studies with IMG-7289 at doses up to 6 mg/kg/d. Please refer to the Investigator's Brochure for additional information on the non-clinical and clinical studies conducted to date with IMG-7289.

4 Statement of Study Objectives

4.1 Study Aims and Hypotheses

Aim 1. To assess the hematologic effects of IMG-7289 in a population of ET patients requiring platelet control who are resistant to or intolerant of hydroxyurea per ELN criteria.
Hy1: IMG-7289 will induce complete hematologic response in >10% of this study population by 24 weeks.

Aim 2: To qualitatively examine markers of disease burden including patient-reported symptom burden, standard ARUP testing of mutant (variant) allele burden in granulocytes (baseline and Week 24), spleen size, and bone marrow histology.
Hy2: ET patients treated with IMG-7289 will experience improved symptom burden, reduced mutation allele burden, improved spleen size if enlarged at baseline, and reduced megakaryocyte hyperplasia following the 24-week treatment course.

4.2 Endpoints

4.2.1 Primary Endpoint

- Determine the proportion of patients who achieve complete hematologic remission at Week 24 using ELN response criteria for ET (Barosi *et al.,* 2013), as per protocol appendix 12.4.

4.2.2 Secondary Endpoints

- Determine the proportion of patients who achieve a reduction from baseline in TSS derived from the MPN-SAF at any time-point within the course of the 24-week study.
- Determine the proportion of patients who achieve a reduction in spleen length for patients with palpable splenomegaly (>5 cm below the left costal margin) at any time point over the course of the 24-week study.
- Among patients harboring a *JAK2*^{V617F} mutation, determine the proportion of patients who achieve a >25% change in mutant allele burden from baseline to Week 24.
- Assess if there are changes in bone marrow histology between bone marrow biopsies at baseline and Week 24.

5 Investigational Plan

5.1 Overview

This is a single-center, open-label, investigator-initiated trial evaluating the effects of IMG-7289 administered orally once daily in patients with essential thrombocythemia (ET). The therapeutic goal for the treatment of ET 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 platelets and granulocytes, respectively, whose over-production characterizes the condition. Considerations for a safe and therapeutic starting dose include chronic toxicology studies in conjunction with the clinical experience of the patients who have received IMG-7289 to date in IMG-7289-CTP-101 and -102. Using all of the information available in conjunction with the therapeutic goal for the treatment of myeloproliferative neoplasms, an IMG-7289 starting dose of 0.6 mg/kg QD has been selected. Refer to Sections 3.4 and 3.5 for additional detail on the rationale for the starting dose and dose regimen.

This study consists of two treatment periods: the Initial Treatment Period (ITP), followed by the Additional Treatment Period (ATP). In the ITP, patients will be treated daily for 169 days. The ATP offers treatment to qualifying patients for an additional 169 days. The ATP is iterative and may repeat as long as the patient continues to qualify. Patients not deriving clinical benefit, or who achieve complete remission (CR) or partial remission (PR) and subsequently relapse (Section 12.4) the equivalent of treatment failures, will discontinue IMG-7289 and undergo follow-up.

All patients will undergo follow-up period visits, including an End-of-Treatment (EoT) visit on the day of last dose or as soon as possible thereafter, a pre-End-of-Study (EoS) visit approximately 14 days post last dose, and an End-of-Study (EoS) visit approximately 28 days post last dose. Patients that do not enter the ATP, or discontinue early, will undergo follow-up beginning with an EoT visit. A patient will be considered to have completed the study if they have been dosed with IMG-7829 for the full 24 weeks.

Patients will be followed closely throughout the study for both Adverse Events (AEs) and signs of toxicity by frequent monitoring of clinical signs and symptoms as well as safety labs. Pharmacodynamic effects will be closely monitored by frequent hematology assessments of peripheral blood, and requisite bone marrow aspirates and biopsies. Throughout dosing, transfusions may be administered if needed in accordance with standard institutional guidelines.

5.2 Initial Treatment Period

Using dose titration, the dose of IMG-7289 will be adjusted in each patient to that dose that provides sufficient exposure to safely inhibit thrombopoiesis for a fraction of the dosing cycle (designated as the D_{pi}). Treatment will begin on Day 1 at the IMG-7289 D_s of 0.6 mg/kg QD for all patients, with dose-titration contingent on the comparison of hematology values from the prior visit. Up-titrations may begin on ITP Day 29 and occur no more frequently than every 4 weeks from the previous up- or down-titration. Down-titrations can be made at any time in the best interest of the patient. Up-titrations will be made in increments of 0.2 mg/kg/d, and down-titrations in decrements of 0.1 or 0.15 mg/kg/d.

The dose of IMG-7289 needed to reduce platelets to the target range is anticipated to be up to approximately 2 mg/kg QD; however, this is not the upper limit for titration purposes as the dose needed to achieve a therapeutic effect will vary among patients and may change over time. The platelet titration target expected to be associated with a clinically significant therapeutic effect is: ≥ 200 to ≤ 400 k/μL (200-400 x 10^9/L).

During the ITP, patients will initially return for study assessments weekly for the first 8 weeks (ITP Days 8, 15, 22, 29, 36, 43, 50 and 57), at least bi-weekly for 8 weeks (ITP Days 71, 85, 99 and 113) and then monthly for 8 weeks (ITP Days 141 and 169). It is anticipated that by Week 8 (Day 57) patients will have achieved a stable dose, with weekly visits no longer necessary. For safety purposes, weekly visits may continue at the PI's discretion (note: bi-weekly visits may also continue post Day 113), if necessary. On Day 169 bone marrow sampling is required. At the Day 169 visit, a 'qualification' assessment will be made to determine whether the patient is deriving clinical benefit and safely tolerating IMG-7289. Such patients qualify for entry into the ATP, a transition which should occur without interruption in dosing. Patients not deriving clinical benefit, or who achieve complete remission (CR) or partial remission (PR) and subsequently relapse (Section 12.4) the equivalent of treatment failures, will discontinue IMG-7289 and undergo End of Treatment (EoT), pre-End of Study (pre-EoS) and End of Study (EoS) visits.

5.3 Additional Treatment Period for Qualifying Patients Only

In the ATP, treatment may continue for an additional 169 days in those patients deriving clinical benefit, as determined by the Principal Investigator. Qualifying patients will return for study assessments monthly (ATP Days 1, 29, 57, 85, 113, 141 and 169). It is anticipated that patients continuing in the ATP will have already achieved a stable dose, with bi-weekly visits no longer necessary. For safety purposes, bi-weekly visits may continue at the PI's discretion, if necessary. On Day 169 of *every other* ATP (i.e., ATP2 Day 169, ATP4 Day 169) for as long as the patient continues to qualify for treatment, patients will undergo optional bone marrow sampling. At the Day 169 visit, a 'qualification' assessment will be made to determine whether the patient is continuing to derive clinical benefit. Such patients thereby qualify for re-entry into the ATP, which is iterative; patients may continue to receive IMG-7289 for as long as they continue to qualify. Patients not deriving clinical benefit will discontinue IMG-7289 and undergo EoT, pre-EoS and EoS visits.

5.4 Inclusion and Exclusion Criteria

5.4.1 Inclusion Criteria

Inclusion criteria are as follows:

1. Age ≥18 years.
2. Diagnosis of Essential Thrombocythemia per World Health Organization (WHO) diagnostic criteria for myeloproliferative neoplasms (Arber *et al*., 2016).
3. Patients who are intolerant or resistant to hydroxyurea per ELN criteria, or in the Investigator's judgment are not candidates for available approved therapy. The ELN definitions of resistance/intolerance to HU requires the fulfillment of at least one of the following criteria:
    - Platelet count >600 × 10^9/L after a daily dose of at least 2 g HU for at least 3 months (2.5 g/day in patients with a body weight over 80 kg);
    - Platelet count >400 × 10^9/L and WBC <2.5 × 10^9/L at any dose of HU;
    - Platelet count >400 × 10^9/L and hemoglobin <10g/dL at any dose of HU
    - Presence of unacceptable HU-related non-hematologic toxicities, including fever, mucocutaneous manifestations or leg ulcers.
4. Requires treatment in order to lower platelet counts based on the Clinically Relevant IPSET-Thrombosis Guidelines.
5. Platelet count >450 x 10^9/L pre-dose Day 1.
6. Peripheral blast count ≤5% pre-dose Day 1.
7. ANC ≥0.5 x 10^9/L pre-dose Day 1.
8. Fibrosis Score <grade 2, as per a slightly modified version (Arber *et al*., 2016) of the European Consensus Criteria for Grading Myelofibrosis, (Thiele *et al*., 2005).

9. Life expectancy > 36 weeks.
10. Able to swallow capsules.
11. Amenable to spleen size determination, bone marrow evaluations (in the ITP only, optional in the ATPs), and peripheral blood sampling during the study.
12. Must have discontinued ET therapy at least 2 weeks (4 weeks for interferon) prior to study drug initiation.
13. Agrees to use an approved method of contraception from Screening until 28 days after last administration of the study drug. Acceptable methods of birth control include: birth control pills, depo-progesterone injections, a vaginal hormonal contraceptive ring, a barrier contraceptive such as a condom with spermicide cream or gel, diaphragms or cervical cap with spermicide cream or gel, or an intrauterine device (IUD).
14. If male, agrees not to donate sperm or father a child for at least one month after the last dose of the study medication.

5.4.2 Exclusion Criteria

Exclusion criteria are as follows:

1. Greater than 3 separate transfusion episodes over the last 6 months and/or any transfusion over the last 4 weeks.
2. Eastern Cooperative Oncology Group (ECOG) questionnaire score of 3 or greater.
3. Currently pregnant or planning on being pregnant in the following 6 months or currently breastfeeding.
4. Currently residing outside the United States.
5. History of splenectomy.
6. Unresolved treatment related toxicities from prior therapies (unless resolved to ≤ Grade 1).
7. Uncontrolled active infection.
8. Known positive for HIV or infectious hepatitis, type A, B or C.
9. Current use of monoamine oxidase A and B inhibitors (MAOIs).
10. Evidence at the time of screening of increased risk of bleeding, including any of the following:
    - Activated partial thromboplastin time (aPTT) > 1.3 x the upper limit of normal
    - International normalized ratio (INR) >1.3 x the local upper limit of normal
    - Known Acquired Von Willebrand's disorder.

5.5 Guidelines

These guidelines are for use by the Investigator, study staff and patient to safeguard patient safety while maintaining data integrity.

1. In general, supportive care (transfusions, administration of anti-fungals, etc.) should be maintained in accordance with institutional policy. Additionally:

    a. It is advised that patients with a platelet count ≤ 10 x 10^9/L (10,000/μL) be transfused.

2. Patients taking medications that have the potential to induce or inhibit CYP3A4 or CYP2D6 should be monitored closely for potential effects of co-administration; particular attention should be given to anti-infectives in the azole class.

3. Cessation of IMG-7289 is invariably associated with a rebound in thrombopoiesis and platelet counts may easily exceed the baseline value. When IMG-7289 is discontinued, the platelet count should be monitored closely and an alternative cytoreductive therapy to lower platelets should commence within 24-48 hours.

5.6 Prohibited Medications/Treatments

Investigators will contact Imago staff with any questions pertaining to prohibited medications.

1. All cytotoxic agents, including standard-of-care therapies for ET

2. All hematopoietic growth factors: romiplostim, eltrombopag, erythropoietin (EPO), granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF)

3. Monoamine oxidase A and B inhibitors

4. Anticoagulant and nonsteroidal anti-inflammatory drug (NSAID; including aspirin) use are prohibited in patients when their platelet count is < 50 x 10^9/L (50,000/µL)

6 Study Treatment

IMG-7289, is an irreversible inhibitor of the enzyme LSD1 being developed by Imago BioSciences, Inc. For pre-clinical, clinical and formulation information see the most recent Investigator's Brochure (IB) for IMG-7289.

The drug product is IMG-7289, a bis-tosylate salt. The free base of IMG-7289 is the active moiety. IMG-7289 will be supplied to the site pharmacy department by Imago BioSciences (or designee) in bottles containing capsules in accordance with all applicable regulatory requirements. The capsule strengths to be provided, based on IMG-7289 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. Such details will be included *via* updates to ancillary study documents and not the study protocol.

The capsules will be manufactured in accordance with Annex 13 and principles of cGMP at:
Xcelience LLC
4910 Savarese Circle
Tampa, FL 33634 USA

Upon supply to site, labels will be in accordance with all applicable regulatory requirements for the labeling of active pharmaceutical ingredients and with Annex 13 of GMP.

The recommended long-term storage conditions for IMG-7289 is for the storage temperature not to exceed 25°C. IMG-7289 must be stored in a secure area with access limited to the Investigator and authorized staff and under the physical conditions that are consistent with IMG-7289-specific requirements.

6.1 Dosing and Administration

Participants will be initiated on a daily oral dose of 0.6 mg/kg/day of IMG-7289. Dose escalation and de-escalation rules are detailed below targeting a platelet count of 200 to 400 x 10^9/L and a hemoglobin of 10-13 g/dL *via* hematology evaluations (evaluations are weekly for the first 8 weeks, bi-weekly for the next 8 weeks, and then monthly). **Up-titrations** may begin on ITP Day 29 and occur no more frequently than every 4 weeks from the previous up- or down-titration. **Down-titrations** can be made at any time in the best interest of the patient.

Trained personnel will provide instruction pertaining to IMG-7289 administration and supervise the administration of IMG-7289 on any day that it is taken in the clinic. With the exception of ITP Day 1 it is not required that IMG-7289 be taken in the clinic; this will be determined based on the patient's regular daily dosing time. When applicable, the date and time of each administration in the clinic will be recorded in the source notes.

IMG-7289 dosing will be based on the patient's ITP Day 1 weight. If during the study, the patient's weight differs from ITP Day 1 by more than 10%, the amount of IMG-7289 dispensed should be corrected per the dose chart provided. In cases where using the ITP Day 1 weight is impractical for dispensing, a weight taken as close to ITP Day 1 as possible (e.g., Screening) may be used; weight at a current visit may also occasionally need to be used. The source data must clearly document the weight used.

Patients will be provided supply of IMG-7289 capsules at the time of their visits throughout the study (weekly for the first 8 weeks, followed by monthly). There is no additional preparation required.

Patients should be instructed to:

- Take their IMG-7289 orally once daily, at approximately the same time
- When possible, take IMG-7289 on an empty stomach (fast for 1 hour prior to and 30 minutes after dose). If needed, and at the discretion of the PI, IMG-7289 may be taken with food.
- Swallow their IMG-7289 capsules whole, with an 8oz glass of water

Patients may have clear liquids prior to and after the fasting periods have been completed.

6.2 Dosage: Initial Treatment Period

In the Initial Treatment Period, all patients will be treated daily, for up to 169 days of dosing. Dosing will begin on Day 1 at the starting dose, 0.6 mg/kg/d IMG-7289 free base. Details on the selection of and rationale for the starting dose and dosing schedule can be found in Section 3.4 and Section 3.5.

Through the use of dose titration, all patients will be dosed to the IMG-7289 D_{pi}; the dose needed to safely inhibit normal hematopoiesis for a fraction of the dosing cycle. Dose-titration, both upward and downward, is contingent on the hematology assessment and comparison of hematology values from the prior visit. **Up-titrations** may begin on ITP Day 29 and occur no more frequently than every 4 weeks from the previous up- or down-titration. **Down-titrations** can be made at any time in the best interest of the patient.

The D_{pi} is anticipated to be approximately 2 mg/kg QD; however, this is not the upper limit for titration purposes as the dose needed to achieve a therapeutic effect will vary among patients and may change over time. The platelet titration target expected to be associated with a clinically significant therapeutic effect is:

- A platelet count of ≥ 200 to ≤ 400 k/μL (200-400 x 10^9/L)

Titration and re-challenge rules based on periodic evaluation of platelet, absolute neutrophil (ANC) and hemoglobin (Hb) counts are noted below.

Table 1: Titration and Re-challenge Rules

Titration and Re-challenge Rules				
Important: ANC ≥0.5x10^9/L (500 neutrophils/μL) is needed for up-titration. For an ANC below this threshold, the current dose should be maintained or down-titrated in accordance with the rules detailed below.				
Hematology Assessment		**Titration and Re-challenge Rules**		
Plt Count (x 10^9/L)	**Hb Level (g/dL)**	**Titration?***	**Titration Rule***	**Re-challenge Rule¥**
> 400	≥ 10	Up-titrate¤	Increase by 0.2 mg/kg/d¤	N/A
≥ 200 to ≤ 400	≥ 10	Maintain current dose	N/A	N/A
50-199	≥ 10	Down-titrate	Decrease by 0.1 mg/kg/d	N/A
N/A	8.5 to <10	Down-titrate	Decrease by 0.15 mg/kg/d	N/A
< 50	**< 8.5**	**HOLD DOSEΦ**	**N/A**	**At 50% of prior dose** when: - platelets return to ≥ 100 - Hb returns to ≥8***

¤**Up-titrations may begin on ITP Day 29 and occur no more frequently than every 4 weeks from the previous up- or down-titration. Down-titrations can be made at any time in the best interest of the patient.**

ΦPatients requiring a dose hold should have complete blood counts monitored at least weekly for safety purposes and to enable re-challenge to commence as soon as counts return to the required level, if safe to do so.

*The PI may, upon review of individual patients and patient responses, recommend up- or down-titrations that are not in concordance with the above.

** Re-challenge at 50% of the previous mg/kg dose.

Titration and Re-challenge Rules

***PRBC transfusions allowed if at 0.15 mg/kg/d down-titrated dose level transfusions requirement remains stable within 2 units per month, and no more than 4 units total per 28 days, and patient otherwise has evidence of clinical benefit.
¥ Upon re-challenge, all of the above rules reapply.

Please consult the Principal Investigator regarding dose modifications of IMG-7289 should an adverse event (AE) requiring a dose reduction occur, and also for the management of clinically significant changes in platelets, neutrophil counts, or other hematologic parameters.

6.3 Dosage: Additional Treatment Period

Those patients demonstrating clinical benefit in the absence of toxicity qualify for continued treatment in the Additional Treatment Period, which repeats iteratively. For qualifying patients, dose titration will continue as per the Titration Rules table (**Table 1**) above. Additional dose-titration may occur in consultation with the Principal Investigator.

6.4 Missed Doses

Patients who do not take their IMG-7289 dose at the usual required time should take it immediately upon noting that 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 their study coordinator and continue with their normal daily dose the following day.

6.5 Dose Modification Guidelines

Adverse event intensity will be evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, published 27 November 2017.

Expected IMG-7289 toxicities based on non-clinical and clinical studies are reported in the latest available edition of the Investigator's Brochure.

6.5.1 Hematologic Toxicities

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.

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. LSD1 inhibition 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 LSD1 inhibition, as observed in animals treated with IMG-7289, reflect primary pharmacodynamic effects. The kinetics of anemia, thrombocytopenia, and neutropenia following complete LSD1 inhibition are a function of the lifespan of the individually affected cell types. Over the course of LSD1 inhibition, 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 LSD1 inhibition as well as the degree of inhibition are critical to the pharmacodynamic effects on myeloid lineages.

The intended dosing plan for ET 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. The concentrations of IMG-7289 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 ET patients will require treatment at doses sufficient to reduce platelet counts and hemoglobin counts, respectively, and, to a lesser degree, absolute neutrophil counts. 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.

The effects of IMG-7289 on normal myeloid hematopoiesis observed in non-clinical studies are expected in humans; these are pharmacodynamic effects of LSD1 inhibition by IMG-7289, thus are not regarded as adverse. These events, with the exceptions below, will not be considered DLTs.

6.5.2 Dose Limiting Toxicities

DLT is defined as any one of the following AEs per CTCAE version 5.0 criteria that occurs through Day 7 of the Initial Treatment Period will be considered DLTs unless the Investigator deems the AE to be clearly unrelated to IMG-7289:

- Any Grade 3 or above thrombocytopenia associated with clinically significant bleeding*;
- Any Grade 4 thrombocytopenia associated with a requirement for platelet transfusion;
- Any Grade 4 or 5 non-hematologic adverse event;
- Any Grade 3 or above non-hematologic adverse event with the following exceptions:
  - Nausea, vomiting or diarrhea lasting 3 days or less
  - Aesthenia lasting less than 7 days
- Any Grade 3 electrolyte abnormality unrelated to the underlying malignancy and persisting greater than 24 hours.

**A clinically significant bleeding event is defined as an event that is life-threatening, cannot be controlled and/or results in hemodynamic instability.*

Patients who experience DLT will have their dose adjusted downward by 50% if the Principal Investigator deems it safe for the patient to continue on IMG-7289; the titration rules will subsequently be followed. Any patient that experiences DLT that results in discontinuation of IMG-7289 therapy may begin alternative therapy within 24-48 hours of discontinuation if their physician deems this safe and appropriate regarding the resolution of the DLT.

Please consult the Principal Investigator for IMG-7289 dose modifications for the management of clinically significant changes in platelets, neutrophil counts, or other hematologic parameters.

6.5.3 Stopping Rules

IMG-7289 will be discontinued in the event of the following:

- Post DLT, the Investigator deems it unsafe for the patient to continue on IMG-7289.
- Post dose reduction due to DLT, the patient either worsens at any time or fails to demonstrate significant improvement within 14 days.
- Post temporary interruption of IMG-7289 due to platelet counts below 50 x 10^9/L (50,000/µL), the patient's platelet counts don't return to > 150 x 10^9/L (150,000/µL) within 21 days.
- Any Grade 4 non-hematologic adverse event with failure to recover to Grade 3 within 7 days of drug cessation.

Patients who discontinue IMG-7289 will enter follow-up assessments beginning with EoT visit.

6.5.4 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 to commence as soon as counts

return to the required level, if it safe to do so. During these visits, patients are required to undergo complete blood counts only.

7 Study Assessments and 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 Events (Sections 7.7 and 7.8) contains these details in schematic form and is provided for use in a supportive/reference capacity only.

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.

7.1 Informed Consent

Patients must provide written informed consent before undergoing any study-related procedures. The Principal Investigator (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.

7.2 Screening (Day -28 to Day -1)

- Review of all Inclusion and Exclusion Criteria
- Complete medical/medication history including:
    - History of their current disease (see Section 12.2)
    - Calculate ECOG performance status (Section 12.5)
    - History of all treatments for their current disease [including clinical course with hydroxyurea (see Section 12.3) and/or other ET therapy] or any previous oncologic conditions; including chemical, surgical and/or radiotherapeutic
    - All concomitant medication, in addition to any used in the 15 days prior to Screening
    - Transfusion history, including: the average number of transfusions per month and average volume of each transfusion over a 6-month period; and, any transfusions received (RBC, platelets, etc.), with approximate volumes, within 30 days prior to Screening
- Full PE, including Vital Signs – review of all body systems as indicated by signs/symptoms
- Spleen length in centimeters for subjects with palpable splenomegaly
- Collect blood for the following Local Laboratory assessments:
    - CBC with manual differential
    - Chem-12
    - Coagulation (PT/INR/aPTT)
    - C-reactive protein
    - Testing of mutant (variant) allele burden in granulocytes
    - Serum pregnancy test for WOCBP
- Bone Marrow Sampling, including additional aspirate for storage
- Collect MPN-SAF as close to Day -7 as possible and provide patient with questionnaire for completion on Day 1, prior to or at the start of the visit (i.e., pre-dose)

7.3 Initial Treatment Period

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

7.3.1 ITP Day 1 - Treatment Start

7.3.1.1 ITP Pre-dose Day 1

- Update medical/medication history with any changes since Screening
- Limited PE, including weight, vital signs, spleen measurement and a review of body systems to assess change from previous PE
- Collect MPN-SAF and provide patient with questionnaire for completion on Day 8, prior to or at the start of the visit
- Blood samples for the following Local Laboratory assessments:
    - CBC with manual differential
    - Chem-12
    - C-reactive protein
- Serum pregnancy test for WOCBP
- Dispense doses sufficient until the next visit and provide Dosing Card/Diary
- Ensure patient continues to meet eligibility criteria prior to dosing

7.3.1.2 ITP Dosing Day 1

- Administer IMG-7289

7.3.1.3 ITP Post-dose Day 1

- Patients should remain in clinic for at least 2 hours (plus or minus one hour) post first dose
- Query for Adverse Events, using non-directive questions (i.e., “How are you feeling?”)
- Update concomitant medications if needed
- Schedule Day 8 clinic visit

7.3.2 ITP Weekly Visits - Days 8, 15, 22, 29, 36, 43, 50 and 57 (± 1 day*)

***Important:** The ±1 day visit window applies to the visit (e.g., ‘Day 8’ visit may be conducted on Day 7, Day 8 or Day 9 as dictated by site and patient schedule), and not to individual assessments, unless otherwise noted for a specific assessment. 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.

- Limited PE, including weight, vital signs, spleen measurement and a review of body systems to assess change from previous PE
- Adverse Events and Concomitant Medications
- Pre-dose: Blood samples for the following Local Laboratory assessments:
    - CBC with manual differential and hematology assessment to determine if dose titration is required** (note: up-titrations may occur no more frequently than every 4 weeks from the previous up- or down-titration; down-titrations may occur at any time in the best interest of the patient)

      Important: may be performed up to 2 days ahead of the main visit to avoid the need for IMG-7289 dispensation on the day of blood sampling. For example, if a visit is scheduled on a Wednesday,

the hematology panel and associated titration assessment can be performed Monday or Tuesday, if needed, to ensure IMG-7289 is dispensed and available for collection at the Wednesday visit.

- Collect MPN-SAF and provide questionnaire for completion on the day of the next visit, prior to or at the start of the visit
- Pre-dose: Perform drug accountability and collect study medication
- Dispense doses sufficient until the next visit and provide Dosing Card/diary
- Schedule next clinic visit

**If a patient requires a dose hold, complete blood counts should be monitored at least weekly for safety and to enable re-challenge to commence as soon as counts return to the required level, if safe to do so.

7.3.2.1 ITP Days 29 and 57 Only

- Blood samples for the following Local Laboratory assessments
    - Chem-12
    - C-reactive protein

7.3.2.2 ITP Day 57 Only

- Provide extra MPN-SAF questionnaire to patient for completion during the 'off' week (Day 64)
- Dispense doses sufficient for 14 days (this is the last weekly visit; the patient will now be seen every 14 days)

7.3.3 ITP Bi-Weekly Visits - Days 71, 85, 99 and 113 (± 2 days*)

***Important:** The ±2 day visit window applies to the visit (e.g., 'Day 71' visit may be conducted on Day 69, Day 70, Day 71, Day 72 or Day 73 as dictated by site and patient schedule), and not to individual assessments, unless otherwise noted for a specific assessment. 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 8 patients will have achieved a stable dose, with weekly visits no longer necessary. For the exceptional patient whose dose has not stabilized, weekly visits may continue at the PI's discretion. For such patients, the following is required at each weekly visit:

- Pre-dose: Blood samples for the following Local Laboratory assessments:
    - CBC with manual differential and hematology assessment to determine if dose titration is required** (note: up-titrations may occur no more frequently than every 4 weeks from the previous up- or down-titration; down-titrations may occur at any time in the best interest of the patient)

      Important: may be performed up to 2 days ahead of the main visit to avoid the need for IMG-7289 dispensation on the day of blood sampling. For example, if a visit is scheduled on a Wednesday, the hematology panel and associated titration assessment can be performed Monday or Tuesday, if needed, to ensure IMG-7289 is dispensed and available for collection at the Wednesday visit.

All other patients will undergo the following at bi-weekly visits:

- Limited PE*, including weight*, vital signs*, spleen measurement* and a review of body systems to assess change from previous PE
    - (*) assessments may be omitted on Days 71 and 99 as these visits may be conducted utilizing telemedicine/video visit option at PI discretion.
- Adverse Events and Concomitant Medications
- Pre-dose: Blood samples for the following Local Laboratory assessments:

- CBC with manual differential and hematology assessment to determine if dose titration is required** (note: up-titrations may occur no more frequently than every 4 weeks from the previous up- or down-titration; down-titrations may occur at any time in the best interest of the patient)

  Important: may be performed up to 2 days ahead of the main visit to avoid the need for IMG-7289 dispensation on the day of blood sampling. For example, if a visit is scheduled on a Wednesday, the hematology panel and associated titration assessment can be performed Monday or Tuesday, if needed, to ensure IMG-7289 is dispensed and available for collection at the Wednesday visit.

- Collect MPN-SAF and provide questionnaires for completion on the day of the next visit, prior to or at the start of the visit (including one for completion during each 'off' week, i.e., Days 78, 92 and 106)
- Pre-dose: Perform drug accountability and collect study medication
- Dispense doses sufficient for 14 days and provide Dosing Card/Diary
- Schedule next clinic visit

**If a patient requires a dose hold, complete blood counts should be monitored at least weekly for safety and to enable re-challenge to commence as soon as counts return to the required level, if safe to do so.

7.3.3.1 ITP Day 85 Only

- Calculate ECOG performance status (Section 12.5). ECOG must be <3 to continue on study drug.

7.3.3.2 ITP Days 85 and 113 Only

- Blood samples for the following Local Laboratory assessments
  - Chem-12
  - C-reactive protein

7.3.3.3 ITP Day 113 only

- Provide extra MPN-SAF questionnaires to patient for completion during the 'off' weeks (i.e., Days 120, 127 and 134)
- Dispense doses sufficient for 28 days (this is the last bi-weekly visit; the patient will now be seen every 28 days).

7.3.4 ITP Monthly Visits Days 141 and 169 (± 3 days*)

***Important:** The ± 3 day visit window applies to the visit (e.g., 'Day 141' visit may be conducted on Day 138, Day 139, Day 140, Day 141, Day 142, Day 143 or Day 144 as dictated by site and patient schedule), and not to individual assessments, unless otherwise noted for a specific assessment. 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 16 patients will have achieved a stable dose, with bi-weekly visits 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 samples for the following Local Laboratory assessments:
  - CBC with manual differential and hematology assessment to determine if dose titration is required** (note: up-titrations may occur no more frequently than every 4 weeks from the previous up- or down-titration; down-titrations may occur at any time in the best interest of the patient)

    Important: may be performed up to 2 days ahead of the main visit to avoid the need for IMG-7289 dispensation on the day of blood sampling. For example, if a visit is scheduled on a Wednesday, the hematology panel and associated titration assessment can be performed Monday or Tuesday, if needed, to ensure IMG-7289 is dispensed and available for collection at the Wednesday visit.

All other patients will undergo the following at monthly visits:

- Limited PE*, including weight*, vital signs*, spleen measurement* and a review of body systems to assess change from previous PE
    - (*) assessments may be omitted on Day 141 as this visit may be conducted utilizing telemedicine/video visit option at PI discretion. (In person visit is required on Day 169 with all assessments needed).
- Adverse Events and Concomitant Medications
- Blood samples for the following Local Laboratory assessments:
    - Pre-dose: CBC with manual differential and hematology assessment to determine if dose titration is required** (note: up-titrations may occur no more frequently than every 4 weeks from the previous up- or down-titration; down-titrations may occur at any time in the best interest of the patient)

      Important: may be performed up to 2 days ahead of the main visit to avoid the need for IMG-7289 dispensation on the day of blood sampling. For example, if a visit is scheduled on a Wednesday, the hematology panel and associated titration assessment can be performed Monday or Tuesday, if needed, to ensure IMG-7289 is dispensed and available for collection at the Wednesday visit.
    - Chem-12
    - C-reactive protein
- Collect MPN-SAF and provide questionnaires for completion on the day of the next visit, prior to or at the start of the visit
- Pre-dose: Perform drug accountability and collect study medication
- Dispense doses sufficient for 28 days and provide Dosing Card/Diary (Day 141 only)
- Schedule next clinic visit

**If a patient requires a dose hold, complete blood counts should be monitored at least weekly for safety and to enable re-challenge to commence as soon as counts return to the required level, if safe to do so.

7.3.4.1 ITP Day 141 Only

- Provide extra MPN-SAF questionnaires to patient for completion during the 'off' weeks (i.e., Days 148, 155 and 162)

7.3.4.2 ITP Day 169 Only

- Calculate ECOG performance status (Section 12.5)
- Blood sample for testing of mutant (variant) allele burden in granulocytes
- Bone marrow sampling, including additional aspirate for storage **(-14/+7 days)**
- **Qualification:** Assess whether the patient is eligible for the ATP. If it is determined that the patient is deriving clinical benefit and safely tolerating IMG-7289, then the patient qualifies for and may enter the ATP upon completion of the Day 169 visit. If the patient is entering the ATP, please proceed to Section 7.4 below. If the patient is not entering the Additional Treatment Period, please proceed to Follow-up Period Section 7.6 below.

7.4 Additional Treatment Period (ATP; for qualifying patients only)

Those patients deriving clinical benefit that enter the Additional Treatment Period will "re-start" IMG-7289. For the purposes of clarity and efficiency, rather than continuing to present chronological days/weeks, visits are presented as 'ATP Day 1', followed by, 'ATP Days 29, 59, 85,' etc.

The visits and procedures contained herein may repeat as long as the patient continues to qualify for additional treatment. Continued treatment in the ATP should occur without interruption in dosing; Day 1 assessments may be performed on the same day as Day 169 of the prior treatment period.

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

7.4.1 ATP Day 1 Treatment 're-start' (± 3 days)

All assessments should ideally be performed pre-dose; however, with the exception of the hematology blood test and determination of the need for a dose titration, the assessments may be performed post-dose if needed.

The below assessments do not need to be repeated if performed on the same or calendar day prior.

- Verify patient meets the criteria for additional treatment
- Adverse Events and Concomitant Medications
- Limited PE, including weight, vital signs, spleen measurement and a review of body systems to assess change from previous PE
- Collect MPN-SAF and provide patient with questionnaires for completion on the day of the next visit, prior to or at the start of the visit (including one for completion during each 'off' week, i.e., Days 8, 15, 22, etc.)
- Blood samples for the following Local Laboratory assessments:
    - Pre-dose: CBC with manual differential and hematology assessment to determine if dose titration is required** (note: up-titrations may occur no more frequently than every 4 weeks from the previous up- or down-titration; down-titrations may occur at any time in the best interest of the patient)

      Important: may be performed up to 2 days ahead of the main visit to avoid the need for IMG-7289 dispensation on the day of blood sampling. For example, if a visit is scheduled on a Wednesday, the hematology panel and associated titration assessment can be performed Monday or Tuesday, if needed, to ensure IMG-7289 is dispensed and available for collection at the Wednesday visit.
    - Chem-12
    - C-reactive protein
- Dispense doses sufficient for 28 days and provide Dosing Card/Diary

**If a patient requires a dose hold, complete blood counts should be monitored at least weekly for safety and to enable re-challenge to commence as soon as counts return to the required level, if safe to do so.

7.4.2 ATP Monthly Visits Days 29, 57, 85, 113, 141 and 169 (± 3 days*)

***Important:** The ± 3 day visit window applies to the visit (e.g., 'Day 29' visit may be conducted on Day 26, Day 27, Day 28, Day 29, Day 30, Day 31 or Day 32 as dictated by site and patient schedule), and not to individual assessments, unless otherwise noted for a specific assessment. 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 in the ATP will have already achieved a stable dose, with bi-weekly visits 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 samples for the following Local Laboratory assessments:
    - CBC with manual differential and hematology assessment to determine if dose titration is required** (note: up-titrations may occur no more frequently than every 4 weeks from the previous up- or down-titration; down-titrations may occur at any time in the best interest of the patient)

Important: may be performed up to 2 days ahead of the main visit to avoid the need for IMG-7289 dispensation on the day of blood sampling. For example, if a visit is scheduled on a Wednesday, the hematology panel and associated titration assessment can be performed Monday or Tuesday, if needed, to ensure IMG-7289 is dispensed and available for collection at the Wednesday visit.

All other patients will undergo the following at monthly visits:

- Limited PE*, including weight*, vital signs*, spleen measurement* and a review of body systems to assess change from previous PE
    - (*) assessments may be omitted on Days 29, 85, and141 as these visits may be conducted utilizing telemedicine/video visit option at PI discretion.
- Adverse Events and Concomitant Medications
- Blood samples for the following Local Laboratory assessments:
    - Pre-dose: CBC with manual differential and hematology assessment to determine if dose titration is required** (note: up-titrations may occur no more frequently than every 4 weeks from the previous up- or down-titration; down-titrations may occur at any time in the best interest of the patient)

      Important: may be performed up to 2 days ahead of the main visit to avoid the need for IMG-7289 dispensation on the day of blood sampling. For example, if a visit is scheduled on a Wednesday, the hematology panel and associated titration assessment can be performed Monday or Tuesday, if needed, to ensure IMG-7289 is dispensed and available for collection at the Wednesday visit.
    - Chem-12
    - C-reactive protein
- Collect MPN-SAF and provide questionnaires for completion on the day of the next visit, prior to or at the start of the visit (including one for completion during each 'off' week, i.e., Days 36, 43, 50, etc.)
- Pre-dose: Perform drug accountability and collect study medication
- Dispense doses sufficient for 28 days and provide Dosing Card/Diary
- Schedule next clinic visit

**If a patient requires a dose hold, complete blood counts should be monitored at least weekly for safety and to enable re-challenge to commence as soon as counts return to the required level, if safe to do so.

7.4.2.1 ATP Day 169 Only

- Calculate ECOG performance status (per Section 12.5).
- Optional bone marrow sampling, including additional aspirate for storage **(-14/+7 days)**, may be collected *every other* ATP (ATP2 Day 169, ATP4 Day 169, etc.) for as long as the patient continues to qualify for treatment
- **Qualification:** Assess whether the patient continues to be eligible for the ATP. If it is determined by the Investigator that the patient is deriving clinical benefit and safely tolerating IMG-7289, then the patient qualifies for and may re-enter the ATP upon completion of the Day 169 visit. If the patient is re-entering the ATP, please revert back to Section 7.4 for the ATP visit schedule and associated procedures and assessments. If the patient is not re-entering the ATP, please proceed to Section 7.6 below.

7.5 Suspected Relapse

If at any time during the study a patient is suspected to have relapsed, *which can only occur post remission*, then a Suspected Relapse visit should be performed with the following assessments:

- Limited PE, including weight, vital signs, spleen measurement and a review of body systems to assess change from previous PE

- Adverse Events and Concomitant Medications
- Blood samples for the following Local Laboratory assessments:
    - CBC with manual differential
    - Chem-12
    - C-reactive protein
    - Testing of mutant (variant) allele burden in granulocytes
- Collect MPN-SAF and provide questionnaire for completion on the day of the next visit, prior to or at the start of the visit
- Calculate ECOG performance status (per Section 12.5)
- Schedule next clinic visit

7.6 Follow-up Period Visits

7.6.1 End of Treatment Visit

For patients completing the study at the end of a 168-day treatment period, the Day 169 visit will substitute for the EoT visit. For patients discontinuing before completing a 168-day treatment period but agreeing to enter the Follow-Up Period, the EoT visit should be conducted on the day of last dose or as soon as possible thereafter.

Patients should return to the clinic for the following assessments:

- Limited PE, including weight, vital signs, spleen measurement and a review of body systems to assess change from previous PE
- Adverse Events and Concomitant Medications
- Blood samples for the following Local Laboratory assessments:
    - CBC with manual differential
    - Chem-12
    - C-reactive protein
    - Testing of mutant (variant) allele burden in granulocytes
- Collect MPN-SAF and provide questionnaire for completion on the day of the next visit, prior to or at the start of the visit (including one for completion during each ‘off’ week)
- Perform drug accountability and collect study medication
- Calculate ECOG performance status (per Section 12.5)
- Schedule the Pre-End of Study visit 14 days post last dose

7.6.2 Pre-End of Study Visit

The Pre-EoS visit should be conducted 14 days (± 3 days) post last dose.

Patients should return to the clinic for the following assessments:

- Limited PE, including weight, vital signs, spleen measurement and a review of body systems to assess change from previous PE
- Adverse Events and Concomitant Medications
- Blood samples for the following Local Laboratory assessments:

- CBC with manual differential
- Chem-12
- C-reactive protein
- Schedule the End of Study Visit in 14 days' time

- Collect MPN-SAF and provide patient with questionnaires for completion on the day of the next visit, prior to or at the start of the visit (including one for completion during each 'off' week)

7.6.3 End of Study / Early Termination Visit

Early Termination: patients should be seen in the 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: patients should be seen in the clinic 28 days (± 3 days) after the last dose of study drug. The following assessments are required at the End of Study/Early Termination visit:

- Limited PE, including weight, vital signs, spleen measurement and a review of body systems to assess change from previous PE
- Adverse Events and Concomitant Medications
- Blood samples for the following Local Laboratory assessments:
  - CBC with manual differential
  - Chem-12
  - C-reactive protein
- Collect MPN-SAF

7.7 Schedule of Events – Initial Treatment Period

INITIAL TREATMENT PERIOD		Weekly Visits (±1 day)									Bi-Weekly Visits (±2 days)[a]				Monthly Visits (±3 days)[a]		Follow-up (±3 days)	
Procedures	Screen	Day 1	Day 8 Week 1	Day 15 Week 2	Day 22 Week 3	Day 29 Week 4	Day 36 Week 5	Day 43 Week 6	Day 50 Week 7	Day 57 Week 8	Day 71 Week 10	Day 85[k] Week 12	Day 99 Week 14	Day 113[k] Week 16	Day 141[k] Week 20	Day 169 or EOT Week 24	Pre-EOS	EOS/ ET
Informed Consent	1																	
Inclusion/Exclusion	1																	
Demographics	1																	
Physical Exam[eg]	1	1	1	1	1	1	1	1	1	1	1	1k	1	1k	1k	1	1	1
MPN-SAF[h]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Adverse Events	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Concomitant Medications	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
ECOG	1											1				1		
Bone Marrow Biopsy and Aspirate (and pathology)[i]	1															1[c]		1[c]
Titration Assessment			1[j]	1[j]	1[j]	1[j]	1[j]	1[j]	1[j]	1[j]	1[j]	1[j]	1[j]	1[j]	1[j]			
Qualification Assessment																1[d]		
Dispense IMG-7289		1	1[f]	1[f]	1[f]	1	1	1	1	1	1	1	1	1	1			
Administer IMG-7289		◄	———	———	———	———	———	———	———	———	———	———	———	———	———	——►		
Clinical Laboratory																		
CBC with manual Diff	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Chem-12 (CMP)	1	1				1				1		1		1	1	1	1	1
C-reactive protein	1	1				1				1		1		1	1	1	1	1
Testing of mutant allele burden in granulocytes	1															1		
PT/INR/aPTT	1																	
Pregnancy Test- Serum[b]	1	1																

Data collection may begin after subject has consented to participation; % NCI-CTCAE v5.0 will be used to document adverse events. Adverse events should only be collected starting on Day 1 of treatment.

a: It is anticipated that by Week 8 all patients will have achieved a stable dose, with weekly visits no longer required. For safety purposes, weekly (or bi-weekly, as appropriate) visits may continue to be implemented at PI's discretion, if necessary. CBC with manual diff only is required at weekly visits; at bi-weekly visits, titration assessment is also required.

b: Serum pregnancy test for women of childbearing potential (women who are not post-menopausal for 1 year or more) also performed if pregnancy suspected while patient remains on-study.

c: Optional not required .

d: Assess whether patient is deriving clinical benefit and safely tolerating IMG-7289, thereby qualifying for entry into the ATP upon completion of the Day 169 visit.

e: All physical exams done after screening will be a limited PE

f: Up-titrations are not permitted at these visits. Please see 'j' below for additional details.

g: Spleen measurements should be taken during physical exam

h: MPN-SAF completed once per week from Day 1 through End of Study. Provide multiple questionnaires to patient for completion during weeks there are no clinic visits.

i: Additional aspirate to be collected and stored for potential single-cell metabolism, inflammatory signaling, or other future studies.

j: Up-titrations may begin at ITP Day 29 and occur no more frequently than every 4 weeks from the previous up- or down-titration. Down-titrations can be made at any time in the best interest of the patient. Patients requiring a Dose Hold according to the Titration and Re-challenge Rules, or due to an (S)AE, should be monitored at least weekly for safety purposes and to enable re-challenge to commence as soon as counts return to the required level, if it safe to do so. During these visits, patients are required to undergo complete blood counts only.

k: Visit may be conducted utilizing telemedicine/video visit if deemed appropriate by PI. Limited PE, weight, VS, spleen measurement assessments will be omitted if this option is utilized.

7.8 Schedule of Events – Additional Treatment Period

ADDITIONAL TREATMENT PERIOD	Monthly Visits (±3 days)[a]			Suspected Relapse	Follow-up (±3 days)	
Procedures	Days 1, 29[i], 57, 85[i], 113 Weeks 1, 4, 8, 12, 16	Day 141[i] Week 20	Day 169 or EOT Week 24		Pre-EOS (EOT + 14 days)	EOS (Pre-EOS +14 days)/ ET
Physical Exam[d]	1i	1i	1	1	1	1
MPN-SAF[e]	1	1	1	1	1	1
Adverse Events	1	1	1	1	1	1
Concomitant Medications	1	1	1	1	1	1
ECOG			1	1		1
Bone Marrow Biopsy and Aspirate (and pathology)[f]			1[h]			
Titration Assessment	1[g]	1[g]				
Qualification Assessment			1[c]			
Dispensation of IMG-7289	1	1				
Administration of IMG-7289	◄	———	►			
Clinical Laboratory						
CBC with manual Diff	1	1	1	1	1	1
Chem-12 (CMP)	1	1	1	1	1	1
C-reactive protein	1	1	1	1	1	1
Testing of mutant allele burden in granulocytes				1		

Data collection may begin after subject has consented to participation; % NCI-CTCAE v5.0 will be used to document adverse events. Adverse events should only be collected starting on day 1 of treatment

a: It is anticipated that all patients continuing in the Additional Treatment Period will have achieved a stable dose, with bi-weekly visits no longer required. For safety purposes, bi-weekly visits may be implemented at the PI's discretion, if necessary. CBC with manual diff and titration assessment are required.

b: Only if not performed in the prior 5 weeks.

c: Assess whether patient is deriving clinical benefit and safely tolerating IMG-7289, thereby qualifying for entry into the ATP upon completion of the Day 169 visit.

d: Spleen measurements should be taken during physical exam

e: MPN-SAF completed once per week from Day 1 through End of Study. Provide multiple questionnaires to patient for completion during weeks there are no clinic visits.

f: Additional aspirate to be collected and stored for potential single-cell metabolism, inflammatory signaling, or other future studies.

g: Up-titrations may occur no more frequently than every 4 weeks from the previous up- or down-titration. Down-titrations can be made at any time in the best interest of the patient. Patients requiring a Dose Hold according to the Titration and Re-challenge Rules, or due to an (S)AE, should be monitored at least weekly for safety purposes and to enable re-challenge to commence as soon as counts return to the required level, if it safe to do so. During these visits, patients are required to undergo complete blood counts only.

h: Optional *every other* Day 169 (i.e., ATP2 Day 169, ATP 4 Day 169) for as long as the patient continues to qualify for treatment.

i: Visit may be conducted utilizing telemedicine/video visit if deemed appropriate by PI. Limited PE, weight, VS, spleen measurement assessments will be omitted if this option is utilized

8 Study Design/Data Collection

Study Design: This study will follow a Simon two-stage design with an anticipated lower limit response rate of 10% and a target response rate of >40%. With these parameters, the optimal Simon design with α=0.05 and 90% power would need 9 patients in the first stage and 11 patients in the second stage. After testing oral IMG-7289 on 9 patients in the first stage, the trial will be terminated if 1 or fewer respond. If the trial goes to the second stage, a total of 20 patients will be enrolled. If the total number responding is less than or equal to 4, oral IMG-7289 will be rejected; if the total number responding is more than 4, oral IMG-7289 will be considered worthy of further study.

Engagement Approach: Enrollment will be *via* MPN Hematology investigators the Mays Cancer Center (Dr. Nooruddin) as well as by members of the Mays Cancer Center hematology team.

Study Population and Setting: See previous section for eligibility criteria. This investigation will identify, recruit, enroll and treat through MPN investigators the Mays Cancer Center.

Intervention: Participants will be initiated on a daily oral dose of 0.6 mg/kg/day of IMG-7289. Dose escalation and de-escalation algorithms will be similar to the IMG-7289 CTP-102 protocol for MF targeting a platelet count of 200 to 400 x 10^9/L.

Outcomes: Outcomes for Aims 1 - 2 will be collected pre- and post-intervention.

Duration: Study participants will be initially be treated in the study for 24 weeks. If participants are deriving clinical benefit from IMG-7289, the drug can be continued for an additional 24 weeks; this is an iterative process and may repeat indefinitely.

Prior Relevant Experience: Our team has extensive experience recruiting and retaining study participants in clinical trials. The Mays Cancer Center at UT Health SA is an NCI designated cancer center widely recognized for Phase I clinical trials and drug development discovery. Dr. Nooruddin will be the study PI and was formerly Deputy Director of the Cancer Center at Mayo Arizona and continues to collaborate closely between both institutions. Dr. Nooruddin has worked investigating QOL and symptom burden in MPNs since 2010. Dr. Joel Michalek is the project biostatistician and has over 40 years' experience in the analysis and reporting of clinical and epidemiological studies.

9 Minority Accrual

9.1 Purpose

To assist the Principal Investigators (PIs) conducting Investigator Initiated Trials (IIT) in determining whether or not they are meeting the NIH and NCI guidelines and recommendations for the inclusion of minorities in Clinical Trials.

Preliminary information that Principal Investigators should consider include:

- Overall Representation of Minorities in the target catchment area
- The ethnic/racial distribution of the specific type of cancer that is being targeted
  The following resources can be utilized to determine target sample sizes for ethnic groups:
  - Texas Health Data http://soupfin.tdh.state.tx.us/txhd.htm
  - Texas Cancer Registry www.dshs.tx.us/tcr/
  - SEER Cancer Statistics Review www.seer.cancer.gov
  - ACS Cancer Statistics www.cancer.org

***Estimated Target Accrual (Total)**
This section asks for a **projection** of the total ethnic/racial and gender mix of the subjects

Breakdown of subjects - Indicate the **total** targeted/planned accrual by **Race & Gender**		
Race	**% Male**	**% Female**
Black or African American	10	10
American Indian or Alaskan Native	0	0
Asian	0	0
Native Hawaiian or Other Pacific Islander	0	0
White	30	30
More Than One Race (Multiracial)	60	60
Total	100	100

Breakdown of subjects - Indicate the **total** targeted/planned accrual by **Ethnicity & Gender**.		
Ethnicity	**% Male**	**% Female**
Hispanic or Latino	10	10
Not Hispanic or Latino	40	40
Total	50	50

Section 2: Clinical Investigator Tools for Recruitment of Minorities

Tool included in study	LIST OF TOOLS AND ACTIONS FOR INCREASING MINORITY ACCRUAL TO CLINICAL TRIALS ***For assistance with submitting IRB documents, developing materials in English and Spanish, and scheduling public service announcements, please contact MAtools@uthscsa.edu***
Yes ☒ No ☐	1. Include Clinical Trial information on Mays Cancer Center website in both English and Spanish *(Please notify MAtools@uthscsa.edu).*
Yes ☒ No ☐	2. Use of Bilingual Research Team Member or Translation services
Yes ☐ No ☒	3. Identification of bilingual Patient Navigator representative of the Target Population Please Specify:
Yes ☒ No ☐	4. Informed Consent available in Spanish
Yes ☐ No ☒	6. Information Brochures in English and Spanish** *(IRB approval required)*
Yes ☐ No ☒	7. Flyers in English and Spanish (two sided, printed in English on one side and Spanish on the other).** *(IRB approval required)*
Yes ☐ No ☒	8. Public Service Announcements (PSAs) or Advertisements- Spanish Radio** *(IRB approval required)*
Yes ☐ No ☒	9. PSA's or Advertisements -Spanish newspapers (e.g., La Prensa)** *(IRB approval required)*
Yes ☐ No ☒	10. PSA's or Advertisements -Spanish Television (e.g., Univision)** *(IRB approval required)*
Yes ☐ No ☒	11. Patient Friendly Fast Facts in English and Spanish ** *(IRB approval required)*
Yes ☒ No ☐	12. Outreach to advocacy or community organizations (including presentations or awareness campaigns). Please specify: We will contact MPN- Research Foundation, MPN forum, and other MPN Specific resources to advertise this study. These websites do not target any Specific Hispanic or latino populations.
Yes ☐ No ☒	13. Other. Please Specify:

** - It is recommended to submit any patient materials to the IRB as an amendment after the initial IRB approval has been granted

Translational Research Component

Translational components of the study include the analysis of bone marrow histology.

10 Statistical Analysis

Analytic Plan: This will be a one arm Simon 2-stage design with up to N=20 subjects. Complete hematologic remission (primary outcome) and overall symptom burden (secondary outcomes) will be assessed at weeks 20 and 24 (response at Week 24 only).

Sample Size and Power: This study will follow a Simon two-stage design with an anticipated lower limit response rate of 10% and a target response rate of >40%. With these parameters, the optimal Simon design with α=0.05 and 90% power would need 9 patients in the first stage and 11 patients in the second stage. After testing oral IMG-7289 on 9 patients in the first stage, the trial will be terminated if 1 or fewer respond. If the trial goes to the second stage, a total of 20 patients will be enrolled. If the total number responding is less than or equal to 4, oral IMG-7289 will be rejected; if the total number responding is more than 4, oral IMG-7289 will be considered worthy of further study.

Publications:
All protocol- and amendment-related information, with the exception of the information provided by Imago on public registry websites, is considered confidential information. Study results may also be presented at one or more medical congresses and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Eligibility for external authorship, as well as selection of first authorship, will be determined by the study Principal Investigator(s).

11 Data and Safety Monitoring Oversight

A Data and Safety Monitoring Plan is required for all individual protocols conducted at Mays Cancer Center. All protocols conducted at Mays Cancer Center are covered under the auspices of the Mays Cancer Center Institutional Data Safety Monitoring Plan (DSMP).

The Mays Cancer Center Institutional DSMP global policies provide individual trials with:

- institutional policies and procedures for institutional data safety and monitoring,
- an institutional guide to follow,
- monitoring of protocol accrual by the Mays Cancer Center Protocol Review Committee,
- review of study forms and orders by the Forms Committee,
- tools for monitoring safety events,
- independent monitoring and source data verification by the Mays Cancer Center QA Monitor/Auditor
- monitoring of UPIRSO's by the Director of Quality Assurance and DSMC,
- determining level of risk (Priority of Audit Level Score – PALS),
- oversight by the Data Safety Monitoring Committee (DSMC), and
- verification of protocol adherence via annual audit for all Investigator Initiated Studies by the Mays Cancer Center Quality Assurance Division.

Monitoring Progress and Safety
Due to the risks associated with participation in this protocol, the Mays Cancer Center DSMB in conjunction with the Principal Investigator will perform assessment of adverse events, adverse event trends and treatment effects on this study. The Mays Cancer Center DSMB acts as an independent Data Safety Monitoring Board (DSMB) for IIS conducted at Mays Cancer Center. The Mays Cancer Center DSMB will monitor data throughout the duration of a study to determine if continuation of the study is appropriate scientifically and ethically. An additional layer of review is provided by the Mays Cancer Center Data Safety Monitoring Committee (DSMC) who will review DSMB quarterly reports.

Baseline events and adverse events will be captured using the Mays Cancer Center Master Adverse Events Document for each patient using CTCAE V.5.0 or most current version for the grading and attribution of adverse events. Usage of the Mays Cancer Center Master Adverse Events Document centrally documents:

- the event and evaluates the seriousness, and grades the severity of the event,
- if the event was a change from baseline,
- the determination of the relationship between the event and study intervention,
- if the event was part of the normal disease process, and
- what actions were taken as a result of the event.

Safety Definitions:
For this study, the following safety definitions will be applicable:

Adverse Event Definition: An adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research For this study, all adverse events will be documented starting with day 1 of treatment and ending 28 days after the last dose of study drug is received. Events occurring pre-first dose are baseline events and not AEs.

Serious Adverse Event Definition: is any adverse event that:

1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. results in inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

Adverse event intensity will be evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, published 27 November 2017. For adverse events (AEs) not included in the CTCAE, the following guidelines will be used to describe severity.

> **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
> **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
> **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- Unrelated: There was no relationship of the adverse event 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: Adverse events which are judged probably not related to the drug or biologic.
- Possible: There was no clear relationship of the adverse event 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 adverse event (per the current Investigator Brochure or DSMC 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, 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.

Unanticipated Problems Involving Risks to Subjects or Others Definition: Unanticipated problem involving risk to subjects or others includes any incident, experience or outcome that meets all of the following criteria:

A. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied (note: the unfounded classification of a serious adverse event as "anticipated" constitutes serious non-compliance);
B. definitely related or probably related to participation in the research; and
C. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Reporting Requirements

For this study, the Master Adverse Events Documents collected on patients for this protocol will be reviewed by the Principal Investigator on a continuous basis to determine if a serious safety problem has emerged that result in a change or early termination of a protocol such as:

- suspending enrollment due to safety or efficacy, or
- termination of the study due to a significant change in risks or benefits.

The PI will provide the DSMB with the quarterly findings for discussion and review during their meetings.

The PI (or designee) is responsible for notifying sub-investigators regarding recommendations to modify the dosage (dose escalate, dose decrease – outside of the per patient defined titration plan) to ensure that subsequent subjects are treated at the currently approved dose level. As per the protocol, the PI will contact Imago medical staff to discuss protocol modifications for the management of clinically significant changes in platelets, neutrophil counts, or other hematologic parameters. Discussions with Imago staff will be documented and decisions shared with the DSMB and all sub-investigators. In the event starting doses are modified, the PI may delegate the study coordinator to notify other Mays staff, including the Investigational Drug Section to ensure that orders are modified timely and appropriately.

Additionally, this study will have an interim analysis after the first 9 patients to review for response rate. The results of the first 9 patients should be shared with the DSMB to approve extending the study to an additional 11 subjects. The PI is responsible to for notifying sub-investigators of the hold on enrollment until the DSMB has recommended continuance of the study.

Stopping rules for this study include 2 DLT's in the first cohort of 9. A DLT is defined as any one of the following AEs that occurs through Day 7 of the Initial Treatment Period unless the event is considered by the Investigator to be clearly unrelated to IMG-7289:

- Any Grade 3 or above thrombocytopenia associated with clinically significant bleeding*;
- Any Grade 4 thrombocytopenia associated with the requirement for platelet transfusion;
- Any Grade 4 or 5 non-hematologic adverse event;
- Any Grade 3 or above non-hematologic adverse event with the following exceptions:
    - Nausea, vomiting or diarrhea lasting 3 days or less

    - Aesthenia lasting less than 7 days
- Any Grade 3 electrolyte abnormality unrelated to the underlying malignancy and persisting greater than 24 hours.

*A clinically significant bleeding event is defined as an event that is life-threatening, cannot be controlled and/or results in hemodynamic instability.

As per the Mays Cancer Center DSMP, any protocol modifications, problematic safety reports, unanticipated problems, and suspension or early termination of a trial must be reported to the DSMB and all members of the research team. Furthermore, the PI of this study will promptly notify all study affiliates, the UT Health SA IRB, the Mays Cancer Center DSMB, and the FDA via a FDA Form 3500Aa written IND safety report of any serious adverse events that are unexpected and also suspected by the Investigator to be related to the use of the study treatment (deemed possibly, probably or definitely related). Suspension and early termination of a trial must also be reported immediately to the Director of Quality Assurance who will promptly notify the sponsor and the UT Health SA IRB.

The PI will review the Master Adverse Events documents to determine the significance of the reported events and will provide findings using the Investigator Initiated Study Quarterly DSMB Report Form on a quarterly basis with the DSMB. The DSMB will review the information provided by the PI and report to the Mays Cancer Center DSMC on a quarterly basis, unless an emergent issue has been identified. The Investigator Initiated Study Quarterly DSMB Report Form includes information on adverse events, current dose levels, number of patients enrolled, significant toxicities per the protocol, patient status (morbidity and mortality) dose adjustments with observed response, and any interim findings. Any trend consisting of three or more of the same event will be reported to the Mays Cancer Center DSMB for independent review outside of the quarterly reporting cycle, which begins the quarter after the first patient is enrolled on the protocol. The DSMB will also provide its findings to the Mays Cancer Center's Regulatory Affairs Division so that it may be provided to the UT Health SA IRB with the protocol's annual progress report. Conflict of interest is avoided by the independent reviews of the Mays Cancer Center DSMB, Mays Cancer Center DSMC, and by ongoing independent review of UPIRSO trends by the Director of Quality Assurance.

All SAE and UPRISO's will be reported following Mays Cancer Center, UT Health SA institutional and FDA guidelines.

UT HEALTH SA SAE/UPRISO REPORTING REQUIREMENTS For IIS that the PI holds the IND		
Type Event	Report to	Timeframe
All, SAE and UPIRSO	Regulatory Affairs, Imago BioSciences and DQA	ASAP
All SAEs deemed both unexpected and 'related*' to study treatment and UPIRSO	FDA on form 3500A	within 7 calendar days by telephone and 15 calendar days using the Form 3500A
SAE	PI at UT Health SA	within 24 hours
SAE	UT Health SA IRB	Annually
UPIRSO – all	PI at UT Health SA	within 24 hours
UPIRSO – all	FDA	within 7 days
UPIRSO - life threatening	UT Health SA IRB/UT Health SA OCR	within 48 hours
UPIRSO - non-life threatening	UT Health SA IRB/UT Health SA OCR	within 7 days

*deemed possibly, probably or definitely related

SAEs that are unexpected and also suspected by the Investigator to be related to the use of the study treatment (deemed possibly, probably or definitely related) that occur during clinical trials with or without an Investigational New Drug (IND) application are mandatory reports submitted to FDA via Medwatch FDA F3500A *within 15 days for events that have at least a possible relationship with the drug.*

Assuring Compliance with Protocol and Data Accuracy

As with all studies conducted at Mays Cancer Center, the PI has ultimate responsibility for ensuring protocol compliance, data accuracy/integrity and responding to recommendations that emanate from monitoring activities. Source to data monitoring will occur after 9 subjects have been enrolled with periodic data quality checks. Protocol compliance, data accuracy and reporting of events is further ensured by an annual audit conducted by the Quality Assurance Division, whose audit report is shared with the PI, the research team, and will be reviewed by the Mays Cancer Center DSMC.

Mays Cancer Center DSMB Membership

This Protocol will utilize the Mays DSMB that consists of UT Health SA faculty and staff.

As per NCI guidelines and to eliminate conflict of interest (financial, intellectual, professional, or regulatory in nature), the Mays Cancer Center DSMB specific to this study will not treat patients on this protocol. Usage of the Mays DSMB has been created to ensure that experts are represented on the DSMB assembled for this protocol, but may be expanded, at the PI's discretion, to include other members which may include:

- experts in the fields of medicine and science that are applicable to the study (if not currently represented on the DSMB),
- statistical experts,
- lay representatives,
- multidisciplinary representation, from relevant specialties including experts such as bioethicists, biostatisticians and basic scientists, and
- others who can offer an unbiased assessment of the study progress.

Additional or alternate membership of the DSMB is selected by the DSMC chair, in conjunction with the PI of this protocol.

Mays Cancer Center DSMB Charter and Responsibilities

The Mays Cancer Center DSMB will provide information on the membership composition, including qualifications and experience to both the UT Health SA IRB and Mays Cancer Center PRC for review. The Mays Cancer Center DSMB for this study will act as an independent advisory board to the PI and will report its findings and recommendations to the PI, the UT Health SA IRB and the Mays Cancer Center DSMB. Mays Cancer Center DSMB reports will utilize the Investigator Initiated Study Quarterly DSMB Report Form and meetings will occur on a quarterly basis to review any updates from the prior meeting.

Once the protocol is activated, if not already established elsewhere in the protocol the Mays Cancer Center DSMB will establish and provide:

- procedures for maintaining confidentiality;
- statistical procedures including monitoring guidelines, which will be used to monitor the identified primary, secondary, and safety outcome variables;
- consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;
- plans for changing frequency of interim analysis as well as procedures for recommending protocol changes;
- recommendation of dose escalation, MTD recommendation of early termination based on efficacy results;
- recommendation of termination due to unfavorable benefit-to-risk or inability to answer study questions;
- recommendation of continuation of ongoing studies;
- recommend modification of sample sizes based on ongoing assessment of event rates; and
- review of final results and publications.

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12 Appendices

Appendix Item
12.1 Revision History
12.2 WHO Diagnostic Criteria for ET
12.3 Criteria for Intolerance/Resistance to Hydroxyurea
12.4 ELN Response Criteria
12.5 Performance Status Scale (ECOG or Zubrod)
12.6 MPN-SAF Symptoms/Quality of Life
12.7 Bone Marrow Fibrosis Grading
12.8 Adverse Event Tracking Log
12.9 Data Collection and Submission

12.1 Revision History

Version 12 to Version 13

Please see summary of Changes document.

Version 11 to 12

Changed Principal Investigator to Zohra Nooruddin, MD

Version 10 to 11

Please see Summary of Changes document.

Version 9 to 10

Please see Summary of Changes document.

Version 8 to 9

Changed Principal Investigator to Ruben Anthony Mesa, MD

Version 7 to 8

Section 7.7 Schedule of Events table was updated to delete dispensing of IMG-7289 on Day 169.

Version 6 to Version 7 Updated information is bolded.

7.3.4 ITP Monthly Visits Days 141 and 169 (± 3 days)

Note: It is anticipated that by Week 16 patients will have achieved a stable dose, with bi-weekly visits 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:

- Blood samples for the following Local Laboratory assessments:
    - CBC with manual differential
- Pre-dose: Perform hematology assessment and determine if dose titration is required

All other patients will undergo the following at monthly visits:

- Limited PE, including weight, vital signs, spleen measurement and a review of body systems to assess change from previous PE
- Adverse Events and Concomitant Medications
- Blood samples for the following Local Laboratory assessments:
    - CBC with manual differential
    - Chem-12
    - C-reactive protein
- Collect MPN-SAF and provide questionnaires for completion on the day of the next visit, prior to or at the start of the visit
- Pre-dose: Perform hematology assessment and determine if dose titration is required.

- Pre-dose: Perform drug accountability and collect study medication
- Dispense doses sufficient for 28 days and provide Dosing Card/Diary **(Day 141 only)**

Rationale: Clarification of IP dispensing at Day 141, IP is not dispensed on Day 169.

Version 5 to Version 6 Updated information is bolded.

Capitalization errors corrected throughout protocol.

7.3.2.3 ITP Day 57 Only

- Provide extra MPN-SAF questionnaire to patient for completion during the 'off' week (Day 64)
- **Dispense doses sufficient for 14 days (this is the last weekly visit; the patient will now be seen every 14 days)**

Rationale: Clarification from the sponsor on the change in the number of days study medication is to be dispensed. Additional comment added in the protocol at the specific time point indicating the correct number of doses to be dispensed – 14 days.

7.3.3.3 ITP Day 113 only

- Provide extra MPN-SAF questionnaires to patient for completion during the 'off' weeks (i.e., Days 120, 127 and 134)
- **Dispense doses sufficient for 28 days (this is the last bi-weekly visit; the patient will now be seen every 28 days).**

Rationale: Clarification from the sponsor on the change in the number of days study medication is to be dispensed. Additional comment added in the protocol at the specific time point indicating the correct number of doses to be dispensed – 28 days.

12.2 The 2016 WHO Diagnostic Criteria for ET (Arber *et al*., 2016)

		Essential Thrombocythemia†
Major criteria	1	Platelet count ≥450 x 10^9/L
	2	BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant left-shift of neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibersϕ
	3	Not meeting WHO criteria for BCR-ABL1 + CML, PV, PMF, MDS or other myeloid neoplasms
	4	Presence of *JAK2*, *CALR* or *MPL* mutation
Minor criteria	1	Presence of a clonal marker (e.g., abnormal karyotype) or absence of evidence for reactive thrombocytosis

WHO indicates World Health Organization; PV, polycythemia vera; ET, essential thrombocythemia; PMF, primary myelofibrosis; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome.
† ET requires meeting all 4 major criteria or first three major criteria and one minor criterion.
ϕGrading of BM fibers (Thiele *et al*., 2005)
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)

12.3 Criteria for Intolerance/Resistance to Hydroxyurea

Intolerance/resistance to hydroxyurea defined using the ELN criteria for ET (Barosi *et al*., 2007)

For patients with ET, intolerance / resistance to HU is defined as one of the following criteria:

- Platelet count >600 ×10^9/L after a daily dose of at least 2g HU for at least 3 months (2.5g/day in patients with a body weight over 80kg)
- Platelet count >400 × 10^9/L and WBC < 2.5 ×10^9/L at any dose of HU
- Platelet count >400 × 10^9/L and hemoglobin <10g/dl at any dose of HU
- Presence of unacceptable HU-related non-hematologic toxicities, including fever, mucocutaneous manifestations or leg ulcers

Note: Updated based on Erratum published 25April2007.

12.4 ELN Response Criteria for ET (Barosi *et al*, 2013)

Response Categories	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: platelet count ≤400 x 10^9/L, WBC count <10 x 10^9/L, absence of leukoerythroblastosis, AND
C	Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND
D	Bone marrow histological remission defined as disappearance of megakaryocyte hyperplasia and absence of >grade 1 reticulin fibrosis.
Partial Remission	
A	Durable* resolution of disease-related signs including palpable hepatosplenomegaly, and large symptoms improvement, AND
B	Durable* peripheral blood count remission, defined as: platelet count ≤400 x 10^9/L, WBC count <10 x 10^9/L, absence of leukoerythroblastosis, AND
C	Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND
D	Without bone marrow histological remission, defined as the persistence of megakaryocyte hyperplasia.
No Response	Any response that does not satisfy partial remission
Progressive Disease	Transformation into PV, post-ET myelofibrosis, myelodysplastic syndrome or acute leukemia‡

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.

WBC, white blood cell.
*Lasting at least 12 wk.
†Large symptom improvement (≥10-point decrease) in MPN-SAF TSS.
‡For the diagnosis of PV see World Health Organization criteria (WHO);for the diagnosis of post-ET myelofibrosis, see the IWG-MRT criteria; for the diagnosis of myelodysplastic syndrome and acute leukemia, see WHO criteria.

12.5 Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

The ECOG scale (Oken, 1982) is used to assess a subject's quality of life in an evaluation by a health professional of the daily activities and how the activities are affected by the disease of the subject.

Eastern Cooperative Oncology Group (ECOG) 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, eg, light house work, office work.
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5 - Dead.

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J. Clin Oncol 1982;5(6):649-55.

12.6 MPN-SAF Symptoms/Quality of Life

Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)

Instructions: Please fill out all questions, as best able, reflecting how these symptoms affected you over the **LAST WEEK** unless directed otherwise. Complete forms until the STOP instruction toward the end of the packet.

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

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

12.7 Bone Marrow Fibrosis Grading

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]

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

12.8 Adverse Event Tracking Log

Subject Initials ☐☐☐ **Subject ID#** ☐☐☐☐☐ **Page** ☐☐ **of** ☐☐

Adverse Event Tracking Log

Check box if there were no adverse events to be recorded ☐

Insert question to ask participant (e.g. Were there any adverse events? Y/N)

#	Date Reported	Adverse Event Description	Adverse Event** *(Select from Safety Profiler)*	Start Date	End Date	Ongoing (Y or N)	Outcome[1]	Severity/ Grade[2]	Serious (Y or N)	AE Treatment[3]	Expected (Y or N)	Study Attribution[5]	Action Taken[4]	Drug/Device Attribution[5^]	PI Initials	Date of PI Initials

- AE number. "1" indicates the first adverse event documented on the form, 2 = the second, etc. If the adverse event changes in severity, enter it as a separate adverse event row on the paper form using the same AE number as the one that ended.

**look up corresponding AE at: https://safetyprofiler-ctep.nci.nih.gov/

Outcome[1]
0 – Fatal
1 – Not recovered/not resolved
2 – Recovered w/sequelae
3 – Recovered w/o sequelae
4 – Recovering/Resolving

Severity/Grade[2]
1 – Mild
2 – Moderate
3 – Severe
4 – Life Threatening
5 – Death (Fatal)

AE Treatment[3]
0 – None
1 – Medication(s)
2 – Non-medication TX

Action Taken[4] with Study Intervention
0 – None
1 – Interrupted
2 – Discontinued
3 – Dose reduced
4 – Dose increased
5 – Not Applicable

Attribution/ Relatedness[5]
0 – Definite
1 – Probable
2 – Possible
3 – Unlikely
4 – Unrelated
^5 – Not Applicable (did not receive intervention)

12.9 Data Collection and Submission

Study specific instructions for data entry into REDCap will be provided to the study team during the site initiation training prior to study activation.

The Mays Cancer Center IIS and Multi-site Compliance policies and Data Safety Monitoring Plan will be strictly enforced.

Protocol Title: AN INVESTIGATOR INITIATED PHASE 2 TRIAL OF THE LSD1 INHIBITOR IMG-7289 (BOMEDEMSTAT) IN ESSENTIAL THROMBOCYTHEMIA

Version 12 to Version 13 Summary of Changes (7/27/23)

Protocol Change and Location	Justification
Allowing telemedicine visits, decreasing the frequency of visits **Page 28, 30, 32, 35, 36, 37** - Video/Telemedicine visit during ITP phase post Day 57, may occur every other assessment timepoint (Days 71/99/141); In person visits will continue on (Days 85/113/169) -In ATP, video/telemedicine visits may occur at every other assessment timepoint (Days 29/85/141) **Page 11**- clarified language to reflect above changes.	Drug is moving into the Phase 3 with a published safety profile.
Remove Spleen measurement from all timepoints post 24 week. -Spleen measurement to be completed during the initial 24 week period at every physical visit.	Endpoint for evaluation per study requirement is complete at the 24-week timepoint.
MPN-SAF to be done at every visit (removing extra “at home” questionnaires)	Endpoint for collection of the MPN-SAF data concludes at 24-week.
Page 9- clarification of Study Conduct time frame to more accurately reflect paragraphs below and original study intended length.	Clerical correction.
Page 22- Dispense language adjusted to Monthly/28-day supply after Q1week for first 8-weeks of ITP and all of ATP phases	Dispensing will coincide with all physical/In-person visit for the ITP phase which also correlates with titration time-points. ATP phase dispensing will remain at monthly/28-day visits to correspond with potential titration. This will reduce the need for mail/ship of drug.
Pg 9	Made a change for language to clarify video assessments to be started.
Pg 22	Made a change in language to clarify dosing/dispensing moving to monthly.