Official Protocol Title:	A Phase 2 Multi-Center, Open Label Study to Assess the Safety, Efficacy and Pharmacodynamics of IMG-7289 in Patients With Essential Thrombocythemia
NCT number:	NCT04254978
Document Date:	September 9, 2020

Protocol Title:	A Phase 2 Multi-Center, Open Label Study to Assess the Safety, Efficacy and Pharmacodynamics of IMG-7289 in Patients with Essential Thrombocythemia
Protocol No.:	IMG-7289-CTP-201
Investigational Product:	IMG-7289 (Bomedemstat)
Indication:	Essential Thrombocythemia
Study Phase:	Phase 2b
EudraCT Number:	2019-003659-13
IND Number:	130,789
Sponsor:	Imago BioSciences, Inc. 2729 Debbie Court San Carlos, CA 94070 - USA PPD
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Version and Date:	11 November 2019 Amendment 1: 03 December 2019 Amendment 2: 09 September 2020

The clinical trial protocol has been reviewed and approved by the Sponsor:

PPD

Signature

10 Sept 2020

Date

INVESTIGATOR SIGNATURE PAGE

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Declaration of Investigator

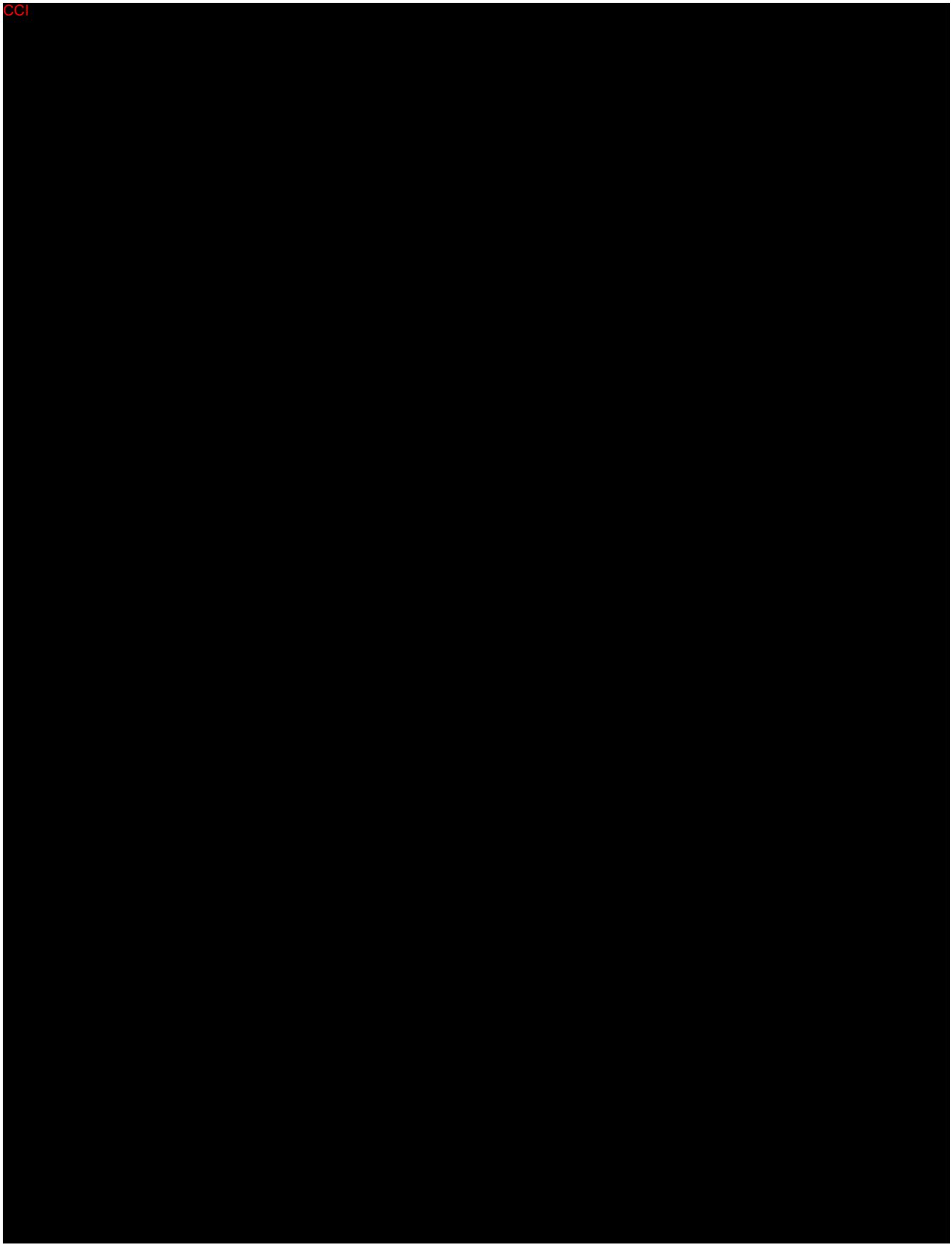
I confirm that I have read and understood this protocol and agree to conduct the study as outlined in the protocol and other information supplied to me. I agree to conduct the study in compliance with: all local legal and regulatory requirements, good clinical practice as described in the International Council on Harmonization document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance"; and the Declaration of Helsinki.

_____ _____

Investigator Signature Date

_____

Investigator Name (Print)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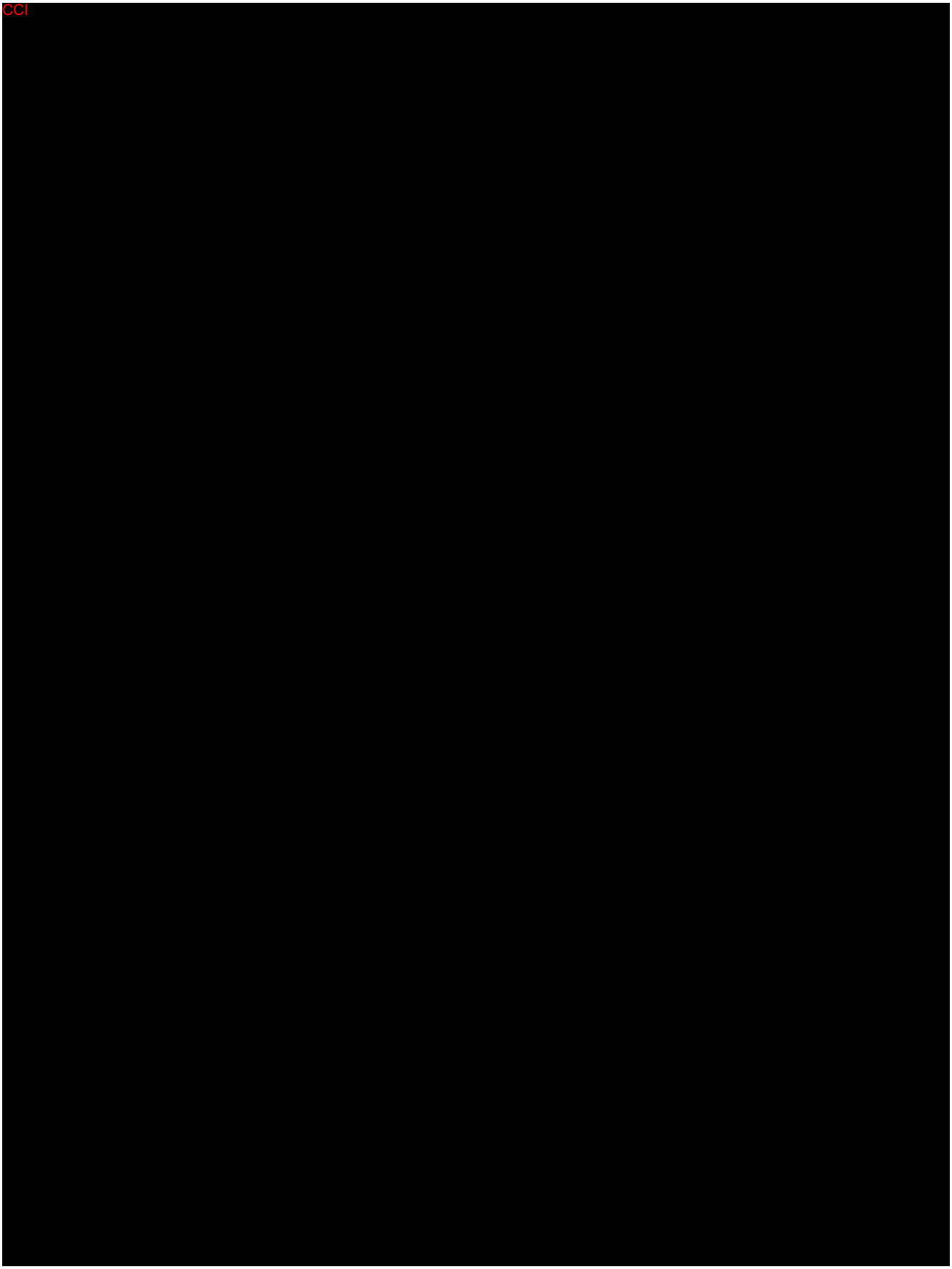

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2 PROTOCOL SYNOPSIS

Protocol Title: A Phase 2 Multi-Center, Open Label Study to Assess the Safety, Efficacy and Pharmacodynamics of IMG-7289 in Patients with Essential Thrombocythemia

Protocol No: IMG-7289-CTP-201

Sites: Approximately 25 sites in Australia, Italy, Germany, New Zealand, UK and US with additional sites and countries as needed.

Study Objectives:

Hypothesis: IMG-7289 is a safe and tolerable orally available agent when administered to patients with essential thrombocythemia; inhibition of LSD1 by IMG-7289 will reduce both the number of megakaryocytes and their capacity to secrete growth factors and inflammatory cytokines to the clinical benefit of patients with ET.

Primary Objectives: To evaluate in ET patients the effect of IMG-7289 on:

- Safety and tolerability
- Reduction of platelet counts to ≤ 400 k/μL (400 x 10^9/L) in the absence of new thromboembolic events

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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*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4- methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, 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. Such details will be included *via* updates to the Pharmacy Manual.

Study Population: Approximately 60 patients eighteen years of age or older in a population of ET patients requiring platelet control that have failed at least one standard therapy (failure is the equivalent of inadequate response or intolerance).

Methodology: This is a Phase 2 multi-center, open-label study evaluating the safety, efficacy and pharmacodynamics of IMG-7289 administered orally once daily in patients with essential thrombocythemia (ET).

Preclinical testing of LSD1 inhibition in mouse models of myeloproliferative neoplasm induced apoptosis in mutant stem/progenitor cells, reduced inflammatory cytokines, reduced spleen length and weight, decreased bone marrow fibrosis if present, and reduced extramedullary hematopoiesis. Additionally, LSD1 inhibition with 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 patients with 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.

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 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. 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. Refer to Section 3.6 for additional detail on the rationale for the starting dose and dose regimen.

To ensure patient safety, a Safety Advisory Board (SAB) will perform reviews at least quarterly of safety parameters and pharmacodynamic markers to draw conclusions around the safety and pharmacodynamic effect of IMG-7289. The SAB will also review patient dose titrations and may recommend adjustments.

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 an additional 169 days.

During the ITP, patients will initially return for study assessments every other week (bi-weekly) for the first 12 weeks (ITP Days 15, 29, 43, 57, 71 and 85) and then monthly for 12 weeks (ITP Days 113, 141 and 169). It is anticipated that by Week 12 (Day 85) the great majority of patients will have achieved a stable dose. For safety purposes, bi-weekly visits may continue at the PI's discretion post Day 85 if necessary. On Day 169, bone marrow sampling is also required. Additionally, at the Day 169 visit a 'qualification' assessment will be made to determine whether the patient is deriving clinical benefit (defined as not meeting "progressive disease" criteria as per Appendix 16.5) and safely tolerating IMG-7289. For the patients who qualify for entry into

the ATP, transition should occur without interruption in dosing. Patients not deriving clinical benefit 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 every other week visits no longer necessary. For safety purposes, every other week visits may continue at the PI's discretion, if necessary. On Day 169 of every other ATP (i.e., ATP 2, ATP 4, etc.), the equivalent of yearly, bone marrow sampling is also required. 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 requisite bone marrow aspirates and biopsies. Throughout dosing, transfusions may be administered if needed in accordance with standard institutional guidelines.

IMG-7289 Dosing: Through the use of dose titration, the dose of IMG-7289 will be adjusted for 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}).

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 3.6.1 and 3.6.2. 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 28 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.

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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 14 days post last dose. Therefore, the anticipated duration of participation in the study is expected to be approximately 30 weeks from first patient visit to last patient visit. Additional treatment may be given, contingent on an assessment of patient benefit.

Study Assessments: The assessments outlined below are also summarized in Study Assessments Section 9 and in the Schedule of Assessments Sections 16.1.

The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF; Appendix 16.6) will be completed during Screening (as close to Day -7 as possible), pre-dose Day 1, weekly from Day 7 through the EoS Visit, and upon suspicion of relapse. Multiple questionnaires will need to be provided to the patient at each visit for completion during each 'off week'.

ECOG Performance Status (Appendix 16.4) 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.

Patient Global Impression of Change (PGIC; Appendix 16.7) will be performed at 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 dose through the EoS visit.

Note for UK: Non-serious events occurring pre-first IMG-7289 dose will be recorded as Medical History; those occurring post first IMG-7289 dose through the EoS visit will be recorded as AEs. Serious AEs (SAEs) will be recorded from time of consent through the EoS/ET visit or until the Investigator and Imago determine follow-up is no longer necessary.

Physical Examinations (PE): a **Full Physical Exam**, including vital signs, and height will be performed at Screening. **Limited Physical Exams (LPE)**, including vital signs, will be performed on Day 1 and at every study visit throughout the study (noted exception: if patient's dose has not stabilized and more frequent visits than detailed in the visit schedule are deemed necessary, LPEs are not required at these additional visits). CCI [redacted]

Serum pregnancy testing will be performed for women of child-bearing potential (WOCBP) at Screening, pre- dose Day 1, monthly (i.e., Days 29, 57, 85, 113, 141 and 169) throughout the study, upon suspicion of relapse, at the EoT, pre-EoS, and EoS/ET visits, 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 Day 169 visit (±7 days).
- Approximately every 12 months thereafter, at Day 169 (±7 days) of every other Additional Treatment Period (i.e., ATP 2, ATP 4, etc.), the equivalent of yearly, for as long as the patient continues to qualify.
- At EoT, EoS/ET, and upon suspicion of relapse, unless performed within the prior 5 weeks.

*Aspirate from the first pull whenever possible, but no later than the second, is required (except in case of dry tap).
**The total number of bone marrow evaluations required during the Initial Treatment Period is 2 in ~30 weeks. Additional marrow evaluation is required only if the patient qualifies for the Additional Treatment Period, is suspected to have relapsed after demonstrating response, or upon evidence of progressive disease.

Clinical laboratory measures: The following laboratory measures will be performed at Screening, pre-dose Day 1, then as described below for individual panels, upon suspicion of relapse, and at the EoT, pre-EoS, and EoS/ET visits:

- Hematology with automated differential – at every visit throughout the study
- Chemistry – monthly (i.e., Days 29, 57, 85, 113, 141 and 169) throughout the study
- Coagulation – Days 85 and 169 throughout the study
- Urinalysis – Days 85 and 169 throughout the study
- **Note:** In Italy, HIV, HAV, HBsAg, HBsAb, HBcAb and HCV testing must also be performed at Screening and EoT/ET.

Mutant (variant) allele burden: The following laboratory samples will be collected at the time-points noted:

- Germline samples for genomic analysis - Screening
- Peripheral blood for genomic analysis
    - Screening, Day 169, and at Day 169 of *every* ATP (i.e., ATP 1, ATP 2, etc.) for as long as the patient continues to qualify
    - At EoT, EoS/ET and upon suspicion of relapse*
- Bone marrow for genomic analysis
    - Screening, Day 169, and at Day 169 of *every other* ATP (i.e., ATP 2, ATP 4, etc.), the equivalent of yearly, for as long as the patient continues to qualify
    - At EoT, EoS/ET and upon suspicion of relapse*

*Required at EoT, EoS/ET and upon suspicion of relapse unless performed within the prior 5 weeks.

Future Correlative Studies: Blood will be collected in conjunction with each genomic blood sampling time-point, as detailed above, for the purposes of potential correlative studies

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 are permitted 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.

Cytokines: Sample collection time-points are below.

- Pre-dose Day 1, Days 15, 29, 57, 85 and 169, and at Day 169 of the ATP for as long as the patient continues to qualify
- At EoT, and at ET (ET required only if the patient discontinues during the ITP)

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. Refer to ITP Day 169 above, as the process is the same.

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

Inclusion Criteria:

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 have failed at least one standard therapy (failure is the equivalent of inadequate response or intolerance). European Leukemia Net (ELN) criteria for intolerance / resistance to hydroxyurea (Appendix 16.8) may be used in association with Investigator discretion. Ruxolitinib refractoriness or intolerance will be left to the discretion of the Investigator.
4. Requires treatment in order to lower platelet counts based on patient age over 60 or history of thrombosis.
5. Platelet count > 450 k/μL (450 x 10^9/L) pre-dose Day 1.
6. Peripheral blast count < 1% 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 bone marrow evaluations and peripheral blood sampling during the study.
12. Must have discontinued ET therapy at least 1 week (4 weeks for interferon) prior to study drug initiation.
13. Women of childbearing potential (WOCBP) and fertile men (see Section 6.1) must agree to use an approved method of contraception from Screening until 14 days* after last IMG-7289 dose. Methods of contraception include: estrogen and progestogen combined hormonal contraception which inhibits ovulation; progestogen-only hormonal contraception associated with inhibition of ovulation; intrauterine device (IUD); bilateral tubal occlusion; vasectomized partner in a monogamous sexual relationship (vasectomy or tubal ligation at least six months prior to dosing); and, complete sexual abstinence (defined in Section 6.1). Males with a pregnant partner must agree to use a condom to avoid exposure to the developing child. Patients practicing abstinence must agree to use an approved method of contraception should they become sexually active during the study.

*The risk of embryofetal toxicity is fully mitigated by 28 days which is >10 half-lives of the drug at the doses used in this study.

Exclusion Criteria

1. Hemoglobin < 10 g/dL prior to dosing on Day 1.
2. Transfusion dependency, defined as requiring 2 or more units of pack red blood cells per month for more than 3 months, or a hemoglobin level of ≤8g/dL in the preceding 8 weeks before the start of dosing.
3. Eastern Cooperative Oncology Group (ECOG) questionnaire score of 3 or greater at Screening.
4. History of splenectomy.

5. Has undergone major surgery ≤4 weeks prior to starting study drug or has not recovered from side effects of such surgery.
6. Unresolved treatment related toxicities from prior therapies (unless resolved to ≤ Grade 1).
7. Uncontrolled active infection.
8. Known positive for HIV if not well-controlled (i.e., undetectable viral load) or infectious hepatitis, type A, B or C.

   Note for Italy: Active infection with hepatitis A virus, B virus (positive hepatitis B surface antigen; **note:** positive hepatitis B surface antibody and positive hepatitis B core antibody are not exclusionary provided disease is not active, which should be clearly documented in the patient's medical history) or C virus (patients with positive hepatitis C antibody result would require confirmation of active disease with a positive hepatitis C polymerase chain reaction (PCR) test), seropositivity for human immunodeficiency virus (HIV).
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
    - History of severe thrombocytopenia or platelet dysfunction unrelated to a myeloproliferative disorder or its treatment
    - Known bleeding disorder (e.g., dysfibrinogenaemia, factor IX deficiency, hemophilia, Von Willebrand's disorder, Disseminated Intravascular Coagulation [DIC], fibrinogen deficiency, or other clotting factor deficiency)
11. Evidence at the time of Screening of significant renal or hepatic insufficiency (unless due to hemolysis, or leukemic infiltration) as defined by any of the following local lab parameters:
    - Calculated glomerular filtration rate (GFR; using the Cockcroft-Gault equation) <40 mL/min or serum creatinine > 1.5 x the local upper limit of normal
    - Aspartate transaminase (AST) or alanine aminotransferase (ALT) ≥2 x the local upper limit of normal
12. Current use of a prohibited medication (e.g., romiplostim) or expected to require any of these medications during treatment with the investigational drug.
13. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to IMG-7289 or LSD1 inhibitors (i.e., monoamine oxidase inhibitors; MAOIs) that contraindicates their participation.
14. History of any illness/impairment of gastrointestinal (GI) function that might interfere with drug absorption (e.g., chronic diarrhea), confound the study results or pose an additional risk to the patient by participation in the study; patients with gastric bypass surgery.

15. Use of an investigational agent within less than 14 days, or the equivalent of at least 7 half-lives of that agent, whichever is the longer, prior to the study Day 1.
16. Females who are pregnant or breastfeeding or plan to become pregnant or breastfeed during the study.
17. A concurrent second active and non-stable malignancy (patients with a concurrent second active but stable malignancy, such as non-melanoma skin cancers, are eligible).

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.

2. Patients taking medications with the potential to induce or inhibit CYP_3A_4 or CYP_2D_6 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.

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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, 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 dose limiting toxicity (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; 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 and is considered by the Investigator to be possibly, probably or definitely related to IMG-7289:

- Any Grade 2 or above thrombocytopenia associated with clinically significant bleeding*
- Any Grade 3 or above thrombocytopenia;
- Any Grade 4 or 5 non-hematologic adverse event;
- Any Grade 3 or above non-hematologic adverse event with failure to recover to Grade 2 within 7 days of drug cessation, with the following exceptions:
    - nausea, vomiting or diarrhea that responds to standard medical care
    - aesthenia lasting less than 14 days
- Any Grade 3 electrolyte abnormality unrelated to the underlying malignancy (for example, hyperkalemia *is* related to thrombocytosis and would therefore not qualify as DLT) and persisting greater than 24 hours.

*Clinically significant bleeding 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 Medical Monitor and Principal Investigator (PI) deem 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.

Please contact the Imago medical monitor 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 Medical Monitor and Principal Investigator deem it unsafe for the patient to continue on IMG-7289.
- Post dose reduction due to DLT, the patient fails to demonstrate significant improvement within 21 days.
- Post temporary interruption of IMG-7289 due to platelet counts below 50 k/μL (50 x 10^9/L), the patient's platelet counts don't return to >150 k/μL (150 x 10^9/L) within 21 days.

3 INTRODUCTION

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). There are no specific treatments for ET. Treatments principally manage symptoms but do not alter the natural history of the disease (Spivak 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). Low-dose pegylated interferon-α2a early in the course of the disease reduces splenomegaly and can produce molecular remissions but is associated with cytopenias and neurotoxocities and is not approved for this indication in many countries (Kiladjian *et al*., 2008).

Thus, there remains unmet need for therapeutic interventions that reduce thrombocytosis and improve symptom burden in patients with ET.

3.2 Background on the Drug Target

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 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).

Epigenetics refers to the regulation of gene expression resulting from chemical modifications of histones, the DNA bases such as cytosine or RNA, changes that do not alter the actual DNA sequence (Bird, 2002). Enzymes that modify these substrates by the addition or removal of these chemical changes are called epigenetic regulators. Histone and nucleic acid modifications provide binding sites for proteins and components of the transcriptional machinery that affect transcriptional gene silencing or activation (Kouzarides, 2007). Histone modifications include acetylation (Ac), methylation (Me), phosphorylation (Ph) and ubiquitination (Ub). By virtue of altering the local state of chromatin, LSD1 is an epigenetic regulator of gene expression. The primary therapeutic effects of LSD1 inhibition in the treatment of essential thrombocythemia come from the down regulation of megakaryopoiesis and thrombopoiesis, functions that require LSD1 activity.

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

LSD1 is unique among the many histone demethylases in that it coordinates flavin adenine dinucleotide (FAD) to oxidatively remove one or two methyl groups, in the process producing H_2O_2 and formaldehyde. As such, FAD is an essential co-factor for LSD1 activity (Shi *et al.*, 2004). The other 34 histone lysine demethylases, collectively termed the Jumonji demethylases, employ an iron-dependent mechanism to remove methyl groups from histone lysines (Klose *et al.*, 2006).

LSD1 is an essential gene; loss of LSD1 activity leads to early embryonic lethality (Wang *et al.*, 2009; Foster *et al.*, 2010). The protein is also needed for regulating the balance between self-renewal and proliferation (Wang *et al.*, 2007). A conditional *in vivo LSD1* knockdown (KD) using a doxycycline-inducible short hairpin *LSD1* (*shLSD1*) established LSD1 as a central regulator of hematopoietic stem cells (HSCs) and progenitor cells (Sprussel *et al.*, 2012). An inducible *LSD1* KD resulted in profound but reversible thrombocytopenia, neutropenia and anemia; monocyte numbers were increased as monopoiesis does not require LSD1 activity. *LSD1* KD for 27 days led to an increase in circulating multipotent progenitors (MPPs) and HSCs with a concomitant down-regulation of chemokine (C-X-C motif) receptor 4 (CXCR4) without affecting the size of the quiescent long-term HSC pool (Sprussel *et al.*, 2012).

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

3.3 Background on LSD1 in Myeloid Neoplasia and Essential Thrombocythemia

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

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

LSD1 may play a direct role in regulating pathogenic signaling from the activated JAK-STAT pathway. The JAK-STAT signaling pathway is activated by the canonical MPN mutations in *MPL*, *JAK2* and *CALR* *via* the phosphorylation of STAT3 and STAT5, transcription factors that activate specific sets of genes with pleiotropic effects (Chen and Mullally, 2014). STAT3 activity as a transcription factor is modulated by methylation on lysine (K140) and is one of many reported non-histone substrates for

LSD1 (Yang *et al*., 2010).

Proof-of-concept studies of the therapeutic activity of LSD1 inhibition were performed in well established, pre-clinical mouse models of MPNs (*Jak2*^{V617F}, *Mpl*^{W515L}). Compared to mice treated with vehicle, LSD1 inhibition (LSDi) in *Mpl*^{W515L} mice markedly suppressed myeloproliferation reducing granulocyte and platelet counts, thus establishing therapeutic efficacy. Spleen weights in treated animals showed a dose-proportional decrease. Histopathological analysis of bone marrow and spleen confirmed a marked reduction in myeloproliferation, as well as a reversal of extramedullary hematopoiesis (EMH). Most notably, there was near-complete resolution of reticulin fibrosis in the bone marrow in the LSDi treatment arm. LSD1 inhibition had a significant impact on serum inflammatory cytokine concentrations as exemplified by a very marked reduction in the plasma concentration of the Chemokine (C-X-C Motif) Ligand 5 (Cxcl5 or IL-8 in humans), a key participant in the pathologic inflammatory state of MPN.

LSD1 inhibition also reduced the mutant cell burden. In mice treated with vehicle, 74.6% of circulating cells were green fluorescent protein cell-positive (GFP$^+$), while only 43.2% of circulating cells were GFP$^+$ in LSDi-treated mice. Flow cytometry analysis of spleen and bone marrow revealed reduced numbers of CD11b$^+$/Gr1$^+$ myeloid cells and CD41$^+$ megakaryocytes. The numbers of mutant GFP$^+$ myeloid cells and megakaryocytes in these tissues were also significantly reduced by LSDi treatment. The decrease in platelet counts and mutant clone burden, and the resolution of fibrosis after 28 days of LSD1 inhibition supports targeting LSD1 in patients with MPN.

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

The treatment effects with an LSD1 inhibitor (LSDi) are distinct from treatment with standard cytotoxic agents or with Janus Kinase (JAK) inhibitors. LSD1 inhibition has specific effects on each myeloid lineages. LSD1 activity is needed for the differentiation of progenitors to red cells, platelets

and granulocytes; LSD1 activity is not needed for monopoiesis. Hence, LSD1 inhibition changes the cellular composition in the marrow and the morphology of these cells. Likewise, distribution of blood cells based on lineage is also affected with an increase in the production of monocytes and a decreasing in the other myeloid cell types; the production of platelets appears to be more sensitive to LSD1 inhibition and red cell production the least. There is no evidence to suggest that inhibition of LSD1 has any effect on the proper function of platelets or neutrophils. In the treatment of ET, the intent is *not* to inhibit LSD1 completely; the treatment thesis is to titrate drug exposure to that which lowers platelets into the desired range. The sensitivity to a given exposure of IMG-7289 in ET patients, however, may be variable and understanding that dose-response is one of the objectives of this study.

The morphologic and clinical pathology changes may not be familiar to clinicians and hematopathologists. As such, there is potential for confusion in the interpretation of peripheral hematologic parameters and the morphology of bone marrow cells. Outlined below are some of the anticipated clinical scenarios that might be observed in ET patients treated with IMG-7289 based on non-clinical and clinical studies conducted by Imago BioSciences and published reports of the effects of inhibiting LSD1:

1. With *complete* pharmacologic inhibition of LSD1, the red cell, platelet and neutrophil counts can be expected to decrease as a function of the lifespan of each cell type, that is, with zero order kinetics; hence, a linear decrease over time. Human platelets circulate for an average of seven to ten days; if LSD1 were to be inhibited completely, the platelet count would be predicted to fall below 10 x 10^9/L (10 k/μL) within a week. The time to observe these drug-induced effects on blood cell production may be less for a patient starting out with a lower granulocyte or red cell mass or platelet count. In this study, the goal is to safely reduce platelet production. Notwithstanding, as thrombopoiesis appears most sensitive to LSD1 inhibition, severe thrombocytopenia represents the greatest clinical risk.

2. The effects of LSD1 inhibition on normal hematopoiesis are fully reversible. IMG-7289 is an irreversible inhibitor of LSD1 but as drug is cleared and the amount of active LSD1 enzyme increases, megakaryocyte maturation and platelet production return to normal. These changes are manifest as early as 24-48 hours. (N.B. Platelet counts, as well as granulocyte counts, can exceed baseline values after several days-to-weeks of no drug exposure, owing, in part, to the rise in the plasma concentration of growth factors such as GM-CSF and thrombopoietin that accompanies LSD1 inhibition.)

3. Cessation of IMG-7289 is invariably associated with a rebound in thrombopoiesis, hence 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 after the cessation of IMG-7289.

4. As a consequence of inhibition of LSD1 in both rat and dog, megakaryocytes appear dysplastic and form syncytia in proportion to the degree of LSD1 inhibition. Platelet volumes also increase dramatically as LSD1 inhibition reaches a maximum and platelet counts fall. These effects are reversible after cessation of drug exposure.

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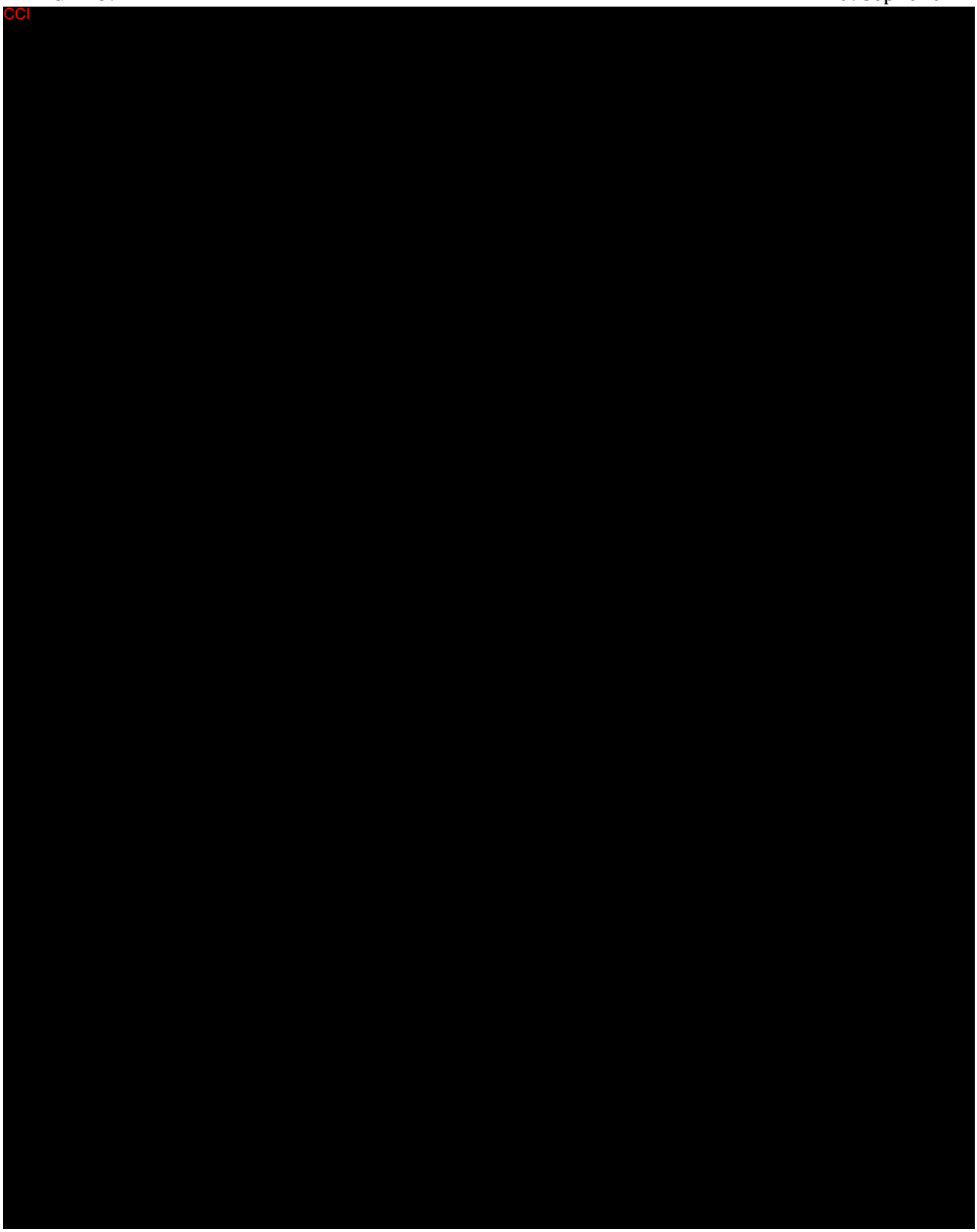

4 HYPOTHESIS AND OBJECTIVES

This trial will study the effects of IMG-7289, an irreversible inhibitor of the enzyme LSD1 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 in hematopoietic stem cells 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.

4.1 Hypothesis

IMG-7289 is a safe and tolerable orally available agent when administered to patients with ET; inhibition of LSD1 by IMG-7289 will reduce both the number of megakaryocytes and their capacity to secrete growth factors and inflammatory cytokines to the clinical benefit of patients with ET.

4.2 Objectives

The following primary and exploratory objectives will be evaluated in patients with essential thrombocythemia (ET) treated with IMG-7289:

4.2.1 Primary

- Safety and tolerability
- Reduction of platelet counts to ≤ 400 k/μL (400 x 10^9/L) in the absence of new thromboembolic events

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5 INVESTIGATIONAL PLAN

5.1 Overview

This is a Phase 2 multi-center, open-label study evaluating the safety, efficacy and pharmacodynamics 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, whose over-production characterizes this condition. Considerations leading to the choice of a safe starting dose include chronic toxicology studies in conjunction with the clinical experience of the patients who have received IMG-7289 to date. Using all of the information available in conjunction with the therapeutic goal for the treatment of ET, an IMG-7289 starting dose of 0.6 mg/kg QD has been selected. Refer to Section 3.6 for additional detail on the rationale for the starting dose and dose regimen.

To ensure patient safety, a Safety Advisory Board (SAB) will perform reviews at least quarterly of safety parameters and pharmacodynamic markers to draw conclusions around the safety and pharmacodynamic effect of IMG-7289. The SAB will also review patient dose titrations and may recommend adjustments.

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. In the ATP, which is iterative, treatment may continue for an additional 169 days in those patients deriving clinical benefit (defined as not meeting "progressive disease" criteria as per Appendix 16.5) and safely tolerating IMG-7289; this definition applies throughout the document and will not be repeated with each reference to clinical benefit), as determined by the Principal Investigator.

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 7 days post last dose, and an End-of-Study (EoS) visit approximately 14 days post last dose. Patients that do not enter the ATP, or discontinue early, will undergo follow-up beginning with an EoT visit.

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. Efficacy and 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.

5.1.1 Initial Treatment Period

Through the use of 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 28 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. CCI [redacted]

During the ITP, patients will initially return for study assessments every other week (bi-weekly) for the first 12 weeks (ITP Days 15, 29, 43, 57, 71 and 85) and then monthly for 12 weeks (ITP Days 113, 141 and 169). It is anticipated that by Week 12 (Day 85) the majority of patients will have achieved a stable dose. For safety purposes, bi-weekly visits may continue at the PI's discretion post Day 85 if necessary. On Day 169 bone marrow sampling is also required. Additionally, 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. For the patients who qualify for entry into the ATP, transition should occur without interruption in dosing. Patients not deriving clinical benefit will discontinue IMG-7289 and undergo End of Treatment (EoT), pre-End of Study (pre-EoS) and End of Study (EoS) visits.

5.1.2 Additional Treatment Period (ATP) 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. 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, 57, 85', etc. Qualifying patients will 're-start' IMG-7289 on ATP Day 1, with dose titration continuing as per the Titration Rules table (Section 7.2.3); there should be no interruption in dosing (Day 169 = Day 1 of the next ATP). Additional dose-titration may occur in consultation with the Medical Monitor.

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 every other week visits no longer necessary. For safety purposes, every other week visits may continue at the PI's discretion, if necessary. On Day 169 of every other ATP (i.e., ATP 2, 4, etc.), the equivalent of yearly, 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 not deriving clinical benefit will discontinue IMG-7289 and undergo EoT, pre-EoS and EoS visits.

6 STUDY POPULATION

6.1 Study Entry Criteria

For purposes of eligibility, the following definitions apply:

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

6.1.1 Inclusion Criteria

Patients must meet <u>all</u> of the applicable criteria to be eligible for enrollment in this study:

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 have failed at least one standard therapy (failure is the equivalent of inadequate response or intolerance). European Leukemia Net (ELN) criteria for intolerance / resistance to hydroxyurea (Appendix 16.8) may be used in association with Investigator discretion. Ruxolitinib refractoriness or intolerance will be left to the discretion of the Investigator.
4. Requires treatment in order to lower platelet counts based on patient age over 60 or history of thrombosis.
5. Platelet count > 450 k/μL (450 x 10^9/L) pre-dose Day 1.
6. Peripheral blast count < 1% 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 bone marrow evaluations and peripheral blood sampling during the study.
12. Must have discontinued ET therapy at least 1 week (4 weeks for interferon) prior to study drug initiation.
13. Women of childbearing potential (WOCBP) and fertile men (see Section 6.1.) must agree to use an approved method of contraception from Screening until 14 days* after last IMG-7289 dose. Methods of contraception include: estrogen and progestogen combined hormonal contraception which inhibits ovulation; progestogen-only hormonal contraception associated with inhibition of ovulation; intrauterine device (IUD); bilateral tubal occlusion; vasectomized partner in a monogamous sexual relationship (vasectomy or tubal ligation at least six months prior to dosing); and, complete sexual abstinence (defined in Section 6.1). Males with a pregnant partner must agree to use a condom to avoid exposure to the developing child. Patients practicing abstinence must agree to use an approved method of contraception should they become sexually active during the study.

*The risk of embryofetal toxicity is fully mitigated by 28 days which is >10 half-lives of the drug at the doses used in this study.

6.1.2 Exclusion Criteria

Patients will be excluded from the study if they meet <u>any</u> of the following criteria:

1. Hemoglobin < 10 g/dL prior to dosing on Day 1.
2. Transfusion dependency, defined as requiring 2 or more units of pack red blood cells per month for more than 3 months, or a hemoglobin level of ≤8g/dL in the preceding 8 weeks before the start of dosing.
3. Eastern Cooperative Oncology Group (ECOG) questionnaire score of 3 or greater at Screening.
4. History of splenectomy.
5. Has undergone major surgery ≤4 weeks prior to starting study drug or has not recovered from side effects of such surgery.
6. Unresolved treatment related toxicities from prior therapies (unless resolved to ≤ Grade 1).
7. Uncontrolled active infection.
8. Known positive for HIV if not well-controlled (i.e., undetectable viral load) or infectious hepatitis, type A, B or C.

   Note for Italy: Active infection with hepatitis A virus, B virus (positive hepatitis B surface antigen; **note:** positive hepatitis B surface antibody and positive hepatitis B core antibody are not exclusionary provided disease is not active, which should be clearly documented in the patient's medical history) or C virus (patients with positive hepatitis C antibody result would require confirmation of active disease with a positive hepatitis C polymerase chain reaction (PCR) test), seropositivity for human immunodeficiency virus (HIV).
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
    - History of severe thrombocytopenia or platelet dysfunction unrelated to a myeloproliferative disorder or its treatment
    - Known bleeding disorder (e.g., dysfibrinogenaemia, factor IX deficiency, hemophilia, Von Willebrand's disorder, Disseminated Intravascular Coagulation [DIC], fibrinogen deficiency, or other clotting factor deficiency).
11. Evidence at the time of Screening of significant renal or hepatic insufficiency (unless due to hemolysis, or leukemic infiltration) as defined by any of the following local lab parameters:
    - Calculated glomerular filtration rate (GFR; using the Cockcroft-Gault equation) <40 mL/min or serum creatinine > 1.5 x the local upper limit of normal
    - Aspartate transaminase (AST) or alanine aminotransferase (ALT) ≥2 x the local upper limit of normal
12. Current use of a prohibited medication (e.g., romiplostim) or expected to require any of these medications during treatment with the investigational drug.
13. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to IMG-7289 or LSD1 inhibitors (i.e., monoamine oxidase inhibitors; MAOIs) that contraindicates their participation.
14. History of any illness/impairment of gastrointestinal (GI) function that might interfere with drug absorption (e.g., chronic diarrhea), confound the study results or pose an additional risk to the patient by participation in the study; patients with gastric bypass surgery.
15. Use of an investigational agent within less than 14 days, or the equivalent of at least 7 half-lives of that agent, whichever is the longer, prior to the study Day 1.
16. Females who are pregnant or breastfeeding or plan to become pregnant or breastfeed during the study.
17. A concurrent second active and non-stable malignancy (patients with a concurrent second active but stable malignancy, such as non-melanoma skin cancers, are eligible).

6.2 Patient Enrollment

A sufficient number of patients who fulfil the inclusion/exclusion criteria documented in Section 6.1 will be screened to ensure approximately 60 patients are enrolled and treated in this study.

6.3 Patient Withdrawal

In accordance with the Declaration of Helsinki, Good Clinical Practice (GCP), and International Council on Harmonization (ICH) Guidelines and applicable regulations governing human subject protection, a subject has the right to withdraw from the study at any time for any reason. Subjects may also be removed from the study by the Sponsor or Investigator. CCI [redacted] Patients will be requested to return for follow-up beginning with an End of Treatment visit as per Section 9.6.1.

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

- Taking another investigational medicinal agent during their involvement in the study;
- Use of a prohibited medication;
- Major violation of, or deviation from, study protocol procedures which, in the judgment of the Medical Monitor, could adversely affect the patient or the integrity of the study including missing an extended duration of IMG-7289 doses or other evidence of major non-compliance;
- Withdrawal from the study is, in the Investigator's judgment, in the patient's best interest;
- Experiencing a Dose Limiting Toxicity (DLT), as per Section 8.2.2.

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6.5 Guidelines

Patient safety is paramount. The guidelines provided below are intended to provide some consistency across sites by providing guidance to be used by the Investigator, the study staff and the patient to safeguard patient safety while maintaining data integrity. The guidelines are not intended to supersede best clinical judgment by the Investigator. Please contact the Medical Monitor with questions or with planned/known divergences from these guidelines.

1. In general, supportive care (transfusions, administration of anti-fungals, etc.) should be maintained in accordance with institutional policy.
2. Patients taking medications with the potential to induce or inhibit CYP_3A_4 or CYP_2D_6 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.

6.6 Prohibited Medications

Please consult the Medical Monitor 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, granulocyte and granulocyte-macrophage colony stimulating factor (G-CSF and GM-CSF) and erythropoietin (EPO)
3. Monoamine oxidase A and B inhibitors
4. Anticoagulant and nonsteroidal anti-inflammatory drug (NSAID; including aspirin) use are only prohibited in patients when their platelet count is < 50 k/µL (50 x 10^9/L)

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7.2 Dispensing, Administration, Dosage and Missed Doses

7.2.1 Dispensing

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

The Investigator is responsible for IMG-7289 accountability, reconciliation and record maintenance (Section 14.5). CCI [redacted]

7.2.2 Administration

Appropriately trained personnel of the study site 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.

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CCI [redacted]: **Initial Treatment Period**

In the ITP, all patients will be treated daily for 169 days. Dosing will begin on Day 1 at the starting dose (D_s) of 0.6 mg/kg/d IMG-7289, free base, for all patients. Details on the selection of and rationale for the starting dose and dosing schedule can be found in Section 3.6.

Through the use of dose titration, the dose of IMG-7289 will be adjusted for 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}). 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 28 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. CCI

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Please consult the medical monitor 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.

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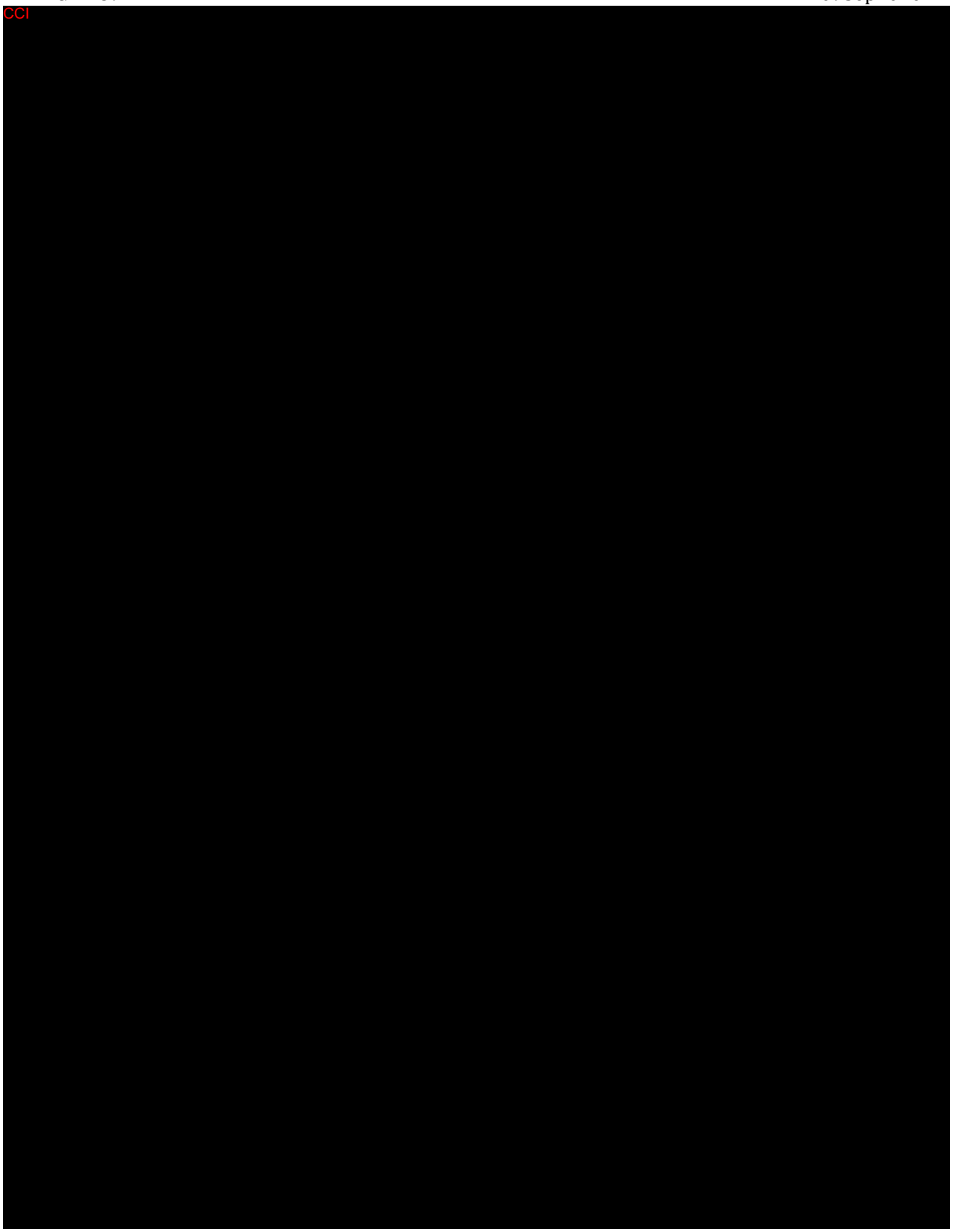

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8.2 Management of Study Toxicities

Adverse event intensity will be evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5, published 27 November 2017.

Dose-limiting toxicity and stopping rules are defined in Sections 8.2.2 and 8.2.3 below. Expected IMG-7289 toxicities based on non-clinical and clinical studies are reported in the latest available edition of the Investigator's Brochure.

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8.2.2 Dose Limiting Toxicity (DLT)

DLT is defined as any one of the following AEs that occurs through Day 8 of the ITP and is considered by the Investigator to be possibly, probably or definitely related to IMG-7289:

- Any Grade 2 or above thrombocytopenia associated with clinically significant bleeding*
- Any Grade 3 or above thrombocytopenia;
- Any Grade 4 or 5 non-hematologic adverse event;
- Any Grade 3 or above non-hematologic adverse event with failure to recover to Grade 2 within 7 days of drug cessation, with the following exceptions:
    - nausea, vomiting or diarrhea that responds to standard medical care
    - aesthenia lasting less than 14 days
- Any Grade 3 electrolyte abnormality unrelated to the underlying malignancy (for example, hyperkalemia *is* related to thrombocytosis and would therefore not qualify as DLT) and persisting greater than 24 hours.

*Clinically significant bleeding 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 if the Medical Monitor and Principal Investigator deem 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 therapy within 24-48 hours of discontinuation if their physician deems this safe and appropriate regarding the resolution of the DLT.

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

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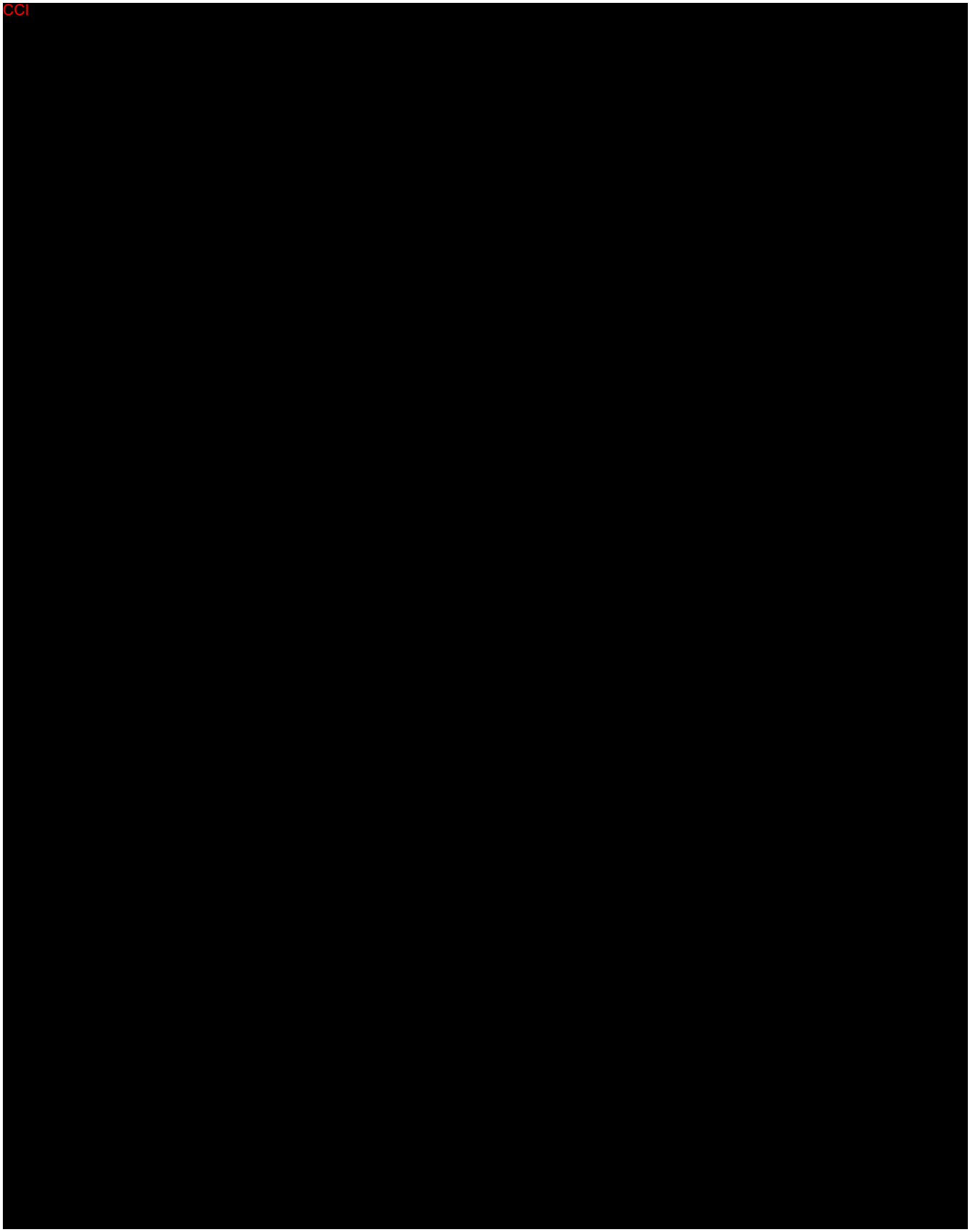

Term	Protocol Meaning
Collect MPN-SAF	MPN-SAF is to be completed by the patient in their native language and in the format provided. The MPN-SAF will be completed during Screening (as close to Day -7 as possible), pre-Dose Day 1 and weekly from Day 7 through the EoS Visit. Ideally, the MPN-SAF will be completed at the same time and day each week for consistency. On visit days, the MPN-SAF should be completed prior to the study visit, and if the patient arrives without a completed MPN-SAF, then it will be completed during the visit and collected prior to the patient departing. Importantly, multiple MPN-SAF forms will need to be provided to the patient for completion between visits, during each 'off week'. Date of completion should be documented on each MPN-SAF completed.
Full Local Lab Assessment	Assessment consisting of the following test panels performed locally (see Section 10.1.1 for specific analytes required): • Hematology with automated differential • Biochemistry • Serum pregnancy test for women of child-bearing potential (WOCBP); results to be reviewed prior to dosing, if applicable
Bone Marrow Sampling	CCI [redacted]
Dosing Instructions	• Instruct patients to refer to their Dosing Card every day for details on IMG-7289 dosing and what to do if a dose is missed • Take their IMG-7289 in accordance with Section 7.2.2 • Handle any missed IMG-7289 doses as per Section 7.2.5 • Bring all medication to every clinic visit, including empty bottles
Administer IMG-7289	Administer IMG-7289 with a glass of water, instruct patient to continue to fast for at least 30 minutes, and, if dosed in clinic, record the exact time of dosing.
Adverse Events and Concomitant Medications	Use non-directive questions (i.e., "How are you feeling") to query patient re: any AEs that may have occurred. Also, inquire about medication changes since the last visit.

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.

9.1 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.

9.2 Screening Period, Including Enrollment

The Screening period is comprised of a Screening visit at which all assessments may be performed on the same day or multiple days, as needed, throughout the 28 day screening period. If the patient screen fails, document the reason(s) in the source data and on the Screening & Enrollment log.

Note for UK: AEs will be assessed at every visit. Non-serious events occurring pre-first IMG-7289 dose will be recorded as Medical History; those occurring post first IMG-7289 dose through the EoS visit will be recorded as AEs. Serious AEs (SAEs) will be recorded from time of consent through the EoS or until the Investigator and Imago determine that follow-up is no longer necessary.

9.2.1 Screening (Days -28 to Day -1)

- Review of all Inclusion and Exclusion Criteria
- Complete medical/medication history including:
    - 2016 WHO criteria for ET (Appendix 16.2).
    - Disease history (i.e., past bleeding episodes and thromboembolic events)
    - History of all treatments for their current disease (including clinical course with hydroxyurea 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
- Calculate ECOG Performance Status (Appendix 16.4)
- MPN-SAF, to be completed as close to Day -7 as possible. Additionally, provide patient with copy of the MPN-SAF for completion prior to dosing on Day 1. (Appendix 16.6)
- Full PE, including Vital Signs – review of all body systems as indicated by signs/symptoms
- Height (without shoes)
- Full Local Laboratory Assessment
- Coagulation
- Urinalysis
- **Note:** In Italy, HIV, HAV, HBsAg, HBsAb, HBcAb and HCV testing must also be performed.

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[redacted]

9.2.2 Enrollment

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

- History of recent surgical procedures
- Recent use of investigational drugs
- Laboratory results, including historical laboratory values, will be assessed by the Principal Investigator (PI) before enrollment. Any deviation in laboratory values that are confirmed on re-examination to be clinically significant by the PI and that would jeopardize the safety of the patient or impact on the validity of the study results will result in exclusion of that patient.

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

If the patient screen fails during this time, document the reason(s) in the patient's source data and on the Screening & Enrollment log.

9.2.3 Last Day of Screening Period (Day -1)

On Day -1, contact the patient and remind them to:

- Report to the clinic the following day at the agreed time

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[redacted]

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[redacted]

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[redacted]

CCI

[redacted]

9.4 Additional Treatment Period (ATP)

Those patients deriving clinical benefit and safely tolerating IMG-7289; this definition applies throughout the document and will not be repeated with each reference to 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, 57, 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).

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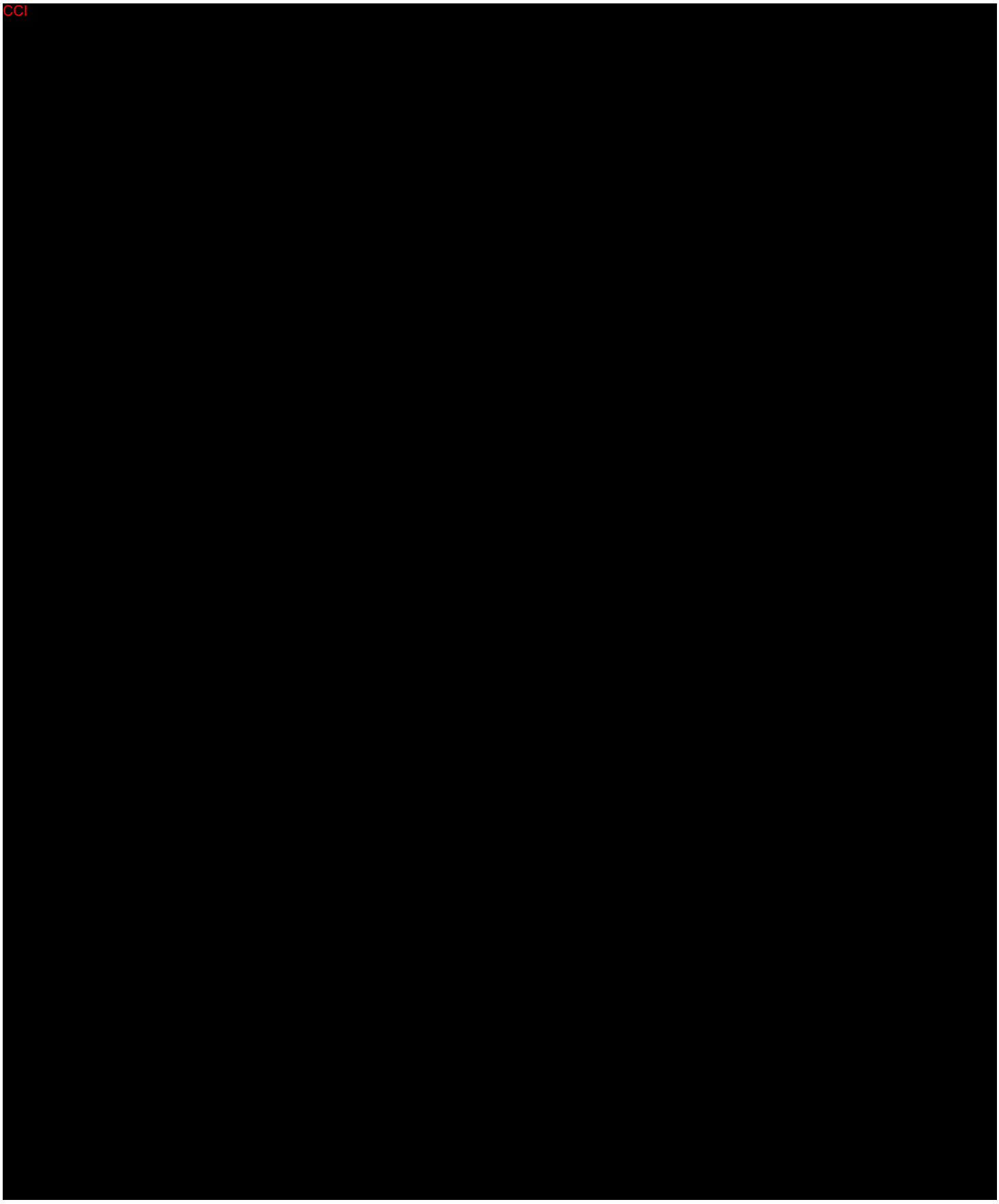

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[redacted]

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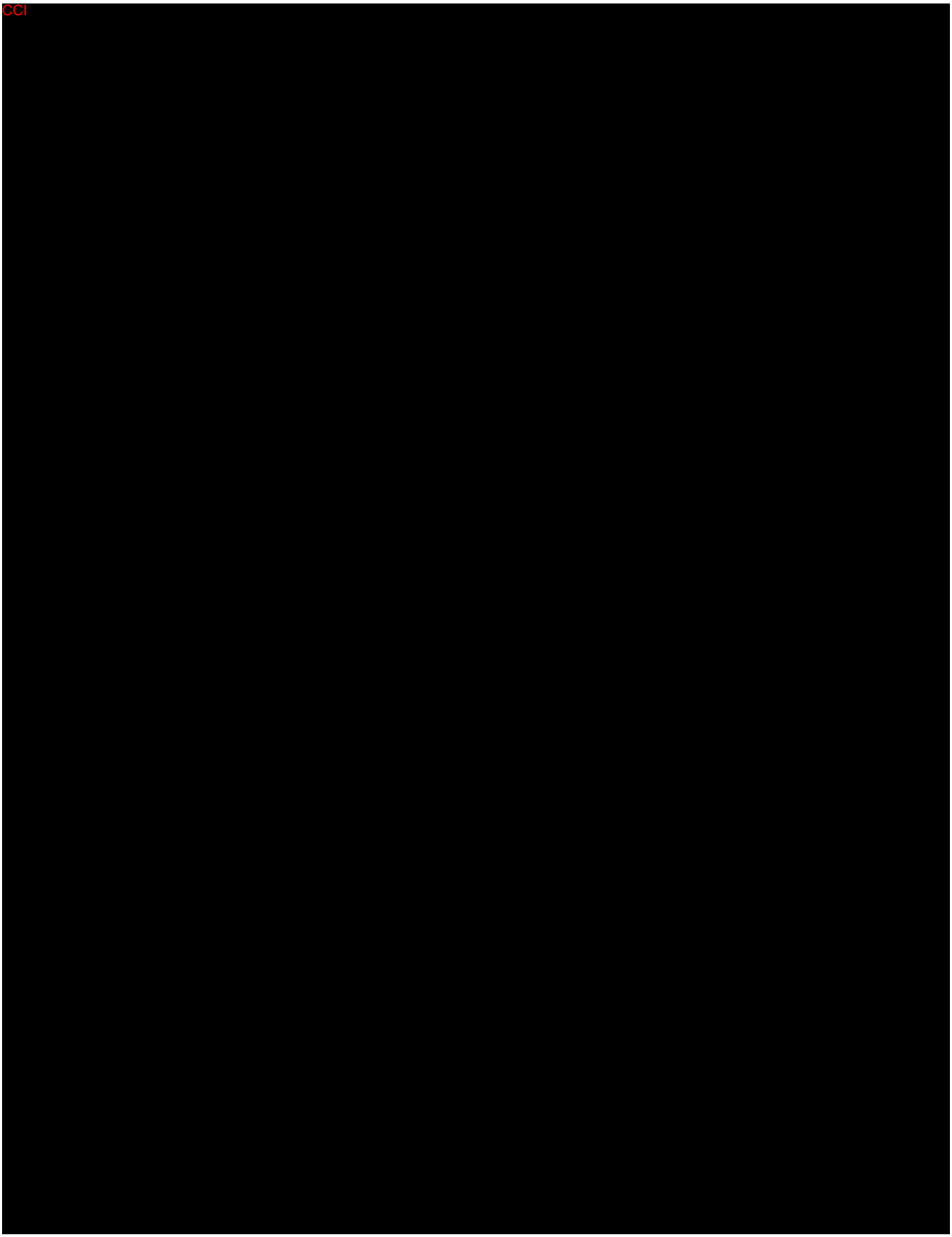

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[redacted]

Screening assessments and each study visit up to and including the EoS visit. Not included, however, [redacted] the particular analyte will only be analysed if the test is available at the particular institution.

10.1.1 Local Laboratory Measures

Biochemistry: Serum creatinine, uric acid, urea* or blood urea nitrogen (BUN)*, albumin, total bilirubin, gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), C-reactive protein (CRP) and serum ferritin.

Hematology: Hemoglobin, red blood cell count (RBC) (including nucleated RBC), hematocrit, platelets, white cell count and automated assessment of neutrophils, lymphocytes, monocytes, reticulocytes and blasts.

Coagulation: Prothrombin time (PT)*, activated partial thromboplastin time (aPTT) and International normalized ratio (INR).

Serum Pregnancy Test: For WOCBP, a serum pregnancy test will be utilized according to institution standard procedure. The result must be confirmed prior to next scheduled dose of IMG-7289.

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

[redacted]

Additional Tests for Italy: HIV test, HAV, HBsAg, HBsAb, HBcAb, HCV

[redacted]

10.1.2 Central Laboratory Measures

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[redacted]

11 SAFETY

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

Once an Investigator determines a patient is a treatment failure (see Section 6.8) or if the patient is withdrawn from treatment early due to a Dose Limiting Toxicity, the patient should discontinue study treatment and undergo follow-up period visits beginning with EoT (see Section 9.6.1).

11.1 Pregnancy

It is not known whether IMG-7289 can affect reproductive capacity, and the direct effects of IMG-7289 and the indirect effects of prior IMG-7289 exposure on fetal development are also unknown.

Every effort should be made to prevent pregnancy throughout the entire duration of participation in this study. All patients of reproductive potential involved in the study are required to use effective methods of contraception during the study and for 14 days after the last IMG-7289 dose. Female patients will be instructed to notify the Investigator immediately if they become pregnant; male patients will be instructed to notify the Investigator immediately if they discover that their sexual partner is pregnant. Pregnancy data during the study will be reported in an expedited manner using the Pregnancy Report Form and following the SAE reporting process (see Section 11.2.4). It will be necessary to collect detailed information on the course of any pregnancy occurring in a patient on study, including pregnancies in the partners of male patients, assuming consent to do so is provided. If the outcome and/or a complication of the pregnancy meets serious criteria (i.e., miscarriage or congenital anomaly/birth defect), then it should be reported as an SAE using the SAE Report Form.

Pregnant patients will discontinue study medication for the duration of the pregnancy. The pregnancy will be followed by the Investigator and the outcome of the pregnancy will be reported to the Pharmacovigilance group as per the Study Reference Manual (SRM).

All patients will be encouraged to discuss contraception and pregnancy concerns with their physician in advance of becoming pregnant. Full disclosure of a patient's participation in this study to their general practitioner is strongly recommended.

11.2 Adverse Events

The Investigator is responsible for monitoring the safety of patients who have enrolled in the study and for accurately documenting and reporting information as described in this section. Patients will be instructed to report to the Investigator any AE that they experience. Investigators will ask about the occurrence of AEs at each visit. Investigators are required to document all AEs occurring during the clinical study, commencing with the first dose of IMG-7289 through to the End of Study Visit (scheduled at 14 days post last IMG-7289 dose). Adverse event recording will continue for patients who discontinue study treatment early but remain in follow-up, until their End of Treatment, Pre-End of Study and End of Study Visits have been completed.

Note: Any medical event which occurs from the time of Informed Consent but prior to dosing with IMG-7289 must still be documented in the patient's medical notes and will be recorded on the appropriate medical history eCRF pages. **In the UK only**, serious AEs (SAEs) will be recorded from time of consent.

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

An AE is any undesirable physical, psychological or behavioral effect experienced by a patient during participation in an investigational study, in conjunction with the use of the drug or biologic, whether or not product-related. This includes any untoward signs or symptoms experienced by the patient from the time of first dose with IMG-7289 until completion of the study.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient and/or observed by the Investigator or medical staff
- Findings at physical examinations
- Laboratory abnormalities of clinical significance

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

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

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

11.2.1 Adverse Event Intensity

Adverse event intensity will be evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5, published 27 November 2017. For AEs not included in the NCI CTCAE, the Investigator will be required to assess the intensity of the adverse drug/biologic experience using the following categories and associated guidelines:

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

Note 1: A semi-colon indicates 'or' within the description of the grade.
Note 2: Activities of Daily Living (ADL)
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.2.2 Adverse Event Relatedness

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

- Unrelated: There was no relationship of the 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 SAB findings) or there is no other medical condition or intervention which would explain the occurrence of such an experience.
- Definite: The relationship of the use of the drug or biologic to the experience is considered definitively established.

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

11.2.3 Serious Adverse Events

Serious adverse events will be reportable from the time of first dose (time of consent for UK patients) through the End of Study Visit (scheduled for approximately 14 days post last IMG-7289 dose) **or** until the Investigator and Imago BioSciences determine that follow-up is no longer necessary. Serious adverse events that are suspected to be drug related will be reported even if they occur when the patient is no longer on the study.

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

Death

Life-threatening experience. Any adverse event that places the patient, in the view of the reporter, at immediate risk of death from the adverse event as it occurred, i.e., does not include an adverse event that had it occurred in a more severe form, might have caused death.

Required or prolonged inpatient hospitalization¥. The adverse event resulted in an initial

inpatient hospitalization or prolonged an existing hospitalization of the patient. If a patient is hospitalized as part of the clinical use of the product, a period of normal hospitalization will be outlined in the protocol or by the judgment of the Investigator. Hospitalizations longer than this period will be prolonged hospitalizations.

Persistent or significant disability/incapacity. An adverse event that resulted in a substantial disruption of a person's ability to conduct normal life functions.

Congenital Anomaly. The exposure of the patient to the drug or biologic during pregnancy that is judged to have resulted in the congenital anomaly/birth defect.

Important medical events. Adverse events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, may jeopardise the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Important medical events or interventions may be considered an SAE based upon medical judgment of the Investigator.

11.2.4 Reporting Serious Adverse Events

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

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

Important: For fatal and life-threatening events, the Sponsor's Medical Monitor should be contacted immediately. A death occurring during the study or information related to such occurrence that comes to the attention of the Investigator during the study must be reported immediately to the Sponsor. A detailed SAE reporting procedure and contact information will be included in the Study Reference Manual (SRM) and provided to the site before any patients are consented.

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

12 ANALYSIS AND STATISTICAL CONSIDERATIONS

12.1 General Considerations

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP). This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP.

12.2 Power

This study is designed to make an assessment of the safety, tolerability, and efficacy of IMG-7289 for the treatment of essential thrombocythemia. This is a single-arm trial with a primary endpoint that is a proportion variable (The proportion of subjects who achieve success defined as a reduction of platelet counts to ≤400k/μL (400 x 10^9/L) in the absence of new thromboembolic events). The test of significance is a one-sided test at the alpha=0.025 level of significance (equivalent to a two-sided test at the alpha=0.05 level of significance). CCI [redacted]

with a sample size of 21 subjects, there is an 80% probability that the study will be successful (where "success" is defined as rejecting the null hypothesis that the true rate is as low as 5%). If the sample size is increased to 30 subjects, the probability of study success is 90%. The primary objective of this CCI [redacted]

12.3 Treatment Assignment and Blinding

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

Effort will be made, as appropriate, to maintain continuity of study staff who administer/evaluate various assessments at each site [redacted]

12.4 Study Endpoints

12.4.1 Primary Endpoints

- The safety and tolerability of IMG-7289 will be assessed by the analysis of adverse events (AEs), as well as changes in physical examinations, vital signs and laboratory values as detailed below.
    - Monitoring of Adverse Events (AEs) including determination of thromboembolic events, dose limiting toxicities (DLTs), serious adverse events (SAEs), and AEs. AEs will be assessed [redacted], using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.
    - Changes in physical examinations, vital signs and laboratory values will also be evaluated [redacted]
- The reduction of platelet counts will be evaluated and assessed based on local laboratory measurements of platelet counts from Day 1 to each visit where platelets are measured.

[redacted]

CCI

[redacted]

Demographics will be tabulated and summarized. Medical and surgical history data at Screening will be listed, as will Physical Examination data CCI [redacted] at Screening, and at subsequent visits. All characteristics at baseline CCI [redacted] will be tabulated and summarized.

All patients receiving at least one dose of IMG-7289 will be included in the safety analysis.

Laboratory values outside the laboratory normal ranges will be summarized and assessed CCI [redacted]

Treatment-emergent adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized [redacted]

Concomitant medications will be listed by patient and coded using the WHO drug dictionary. Medical history will be listed by patient.

Descriptive statistics [redacted] will be calculated for quantitative safety data as well as for the differences to baseline, when appropriate. [redacted]

12.6 Pharmacodynamic Data

The primary efficacy objective for this study is to evaluate the reduction of platelet counts to ≤ 400 k/μL (400 x 10^9/L) in the absence of new thromboembolic events. The primary efficacy endpoint is the proportion of patients who achieve a reduction of platelet counts to ≤ 400 k/μL (400 x 10^9/L) in the absence of new thromboembolic events, which will be analyzed using an exact one-sample binomial test. [redacted] The proportions and corresponding 95% confidence intervals (CIs), [redacted], will be summarized and presented for each post baseline study visit. [redacted] Two-sided *p*-values will be calculated for Day 169 visit to test the null hypothesis, assuming the test statistic follows an exact binomial distribution. [redacted]

The durability of platelet count reduction is an exploratory efficacy objective. [redacted] The proportion of subjects who achieved a durable response will be summarized by treatment period. [redacted]

[redacted]

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[redacted]

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[redacted]

13 STUDY ADMINISTRATION

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

13.1 Ethical Considerations

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

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[redacted]

13.3 Institutional Review Board (IRB), Independent Ethics Committee (IEC) and Human Research Ethics Committee (HREC)

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

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

13.4 Study or Site Termination

The End-of-Trial date is considered to be the date of Database Lock.

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

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
2. Patient recruitment is unsatisfactory
3. Data recording is inaccurate or incomplete
4. Investigator(s) do not adhere to the protocol or applicable regulatory guidelines in conducting the study
5. GCP is not being maintained or adequately followed
6. Administrative reasons
7. Reasons unrelated to the study.

Study or site termination and follow-up will be performed in compliance with the conditions set forth in 21 Code of Federal Regulations (CFR) Section 312 and/or other national and local regulations, as applicable, and in compliance with the principles set forth in International Council on Harmonisation (ICH) Good Clinical Practices (GCPs), including ICH E6, and ethical principles established by the Declaration of Helsinki.

13.5 Study Monitoring Requirements

Monitoring and auditing procedures developed by Imago BioSciences will be followed in order to comply with ICH Good Clinical Practice (GCP) guidelines. On-site checking of the eCRFs for completeness and clarity, cross checking with source documents, and clarification of administrative matters will be performed, when possible. Additionally, off-site or 'remote' monitoring visits may be conducted as needed. Remote monitoring may consist of centralized monitoring or remote data

review. Centralized monitoring is the remote, cross-functional review and evaluation of accumulating in-house data conducted by data managers, central monitor associates, medical directors, the clinical team, and biostatisticians. The review of data within and across sites proactively identifies missing or inconsistent data, data trends, systematic or significant errors and enables site performance characteristics to be analyzed. Remote data review is intended to encompass as many activities performed in a routine on-site monitoring visit as is functionally possible, and as permitted by site policy and procedure. The remote review of data may be actioned *via* multiple pathways, often contingent on site's capabilities. Remote data review, specifically, has become critically important in the COVID-19 environment as a measure of safeguarding patient safety, while also minimizing risks to trial data integrity and facilitating GCP compliance. Note: Remove data review will only be implemented in Germany in times of increased safety measures such as the COVID-19 pandemic and only in special cases. Please see Section 16.9 for additional information pertaining to remote data review.

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

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

Imago BioSciences or its designee will monitor the study. Monitoring will be done by visits from representatives of Imago BioSciences (monitors) who will review the eCRFs and source documents. The monitors will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, email, telephone, and fax). The monitor/representative of Imago will perform an Investigator Site File review to confirm all documents required to reconstruct the conduct of the clinical trial are present. The ISF supports the validity of the research, as well as the conduct and integrity of the data collected, and needs to be maintained by the Investigator (or designee) and inspection ready at all times.

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

13.6 Quality Assurance

The study will be initiated and conducted under the sponsorship of Imago BioSciences. IMG-7289 and clinical supplies will be supplied by Imago BioSciences. Representatives of Imago BioSciences will monitor the study to verify study data, medical records, worksheets, and eCRFs are in accordance with current International Council on Harmonisation (ICH) GCPs and the respective local and national government regulations and guidelines.

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

13.7 Confidentiality

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

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

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

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

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

14 INVESTIGATOR REQUIREMENTS

14.1 Protocol Adherence

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

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

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

14.2 Source Documentation

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

14.3 Direct Access to Source Documentation

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

14.4 Case Report Forms

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

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

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

14.7 Training of Staff

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

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

staff involved.

14.8 Clinical Study Report

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

14.9 Retention of Records

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

15 REFERENCES

Adamo, A., Sese, B., Boue, S., Castano, J., Paramonov, I., Barrero, M.J., Izpisua Belmonte, J.C., 2011. LSD1 regulates the balance between self-renewal and differentiation in human embryonic stem cells. Nat Cell Biol **13**, 652-659.

Arber, A.A., Orazi, A., Hasserjian, R., Thiele, J., Borowitz, M.J., Le Beau, M.M., Bloomfield, C.D., Cazzola, M., Vardiman, J.W. 2016. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia Blood 127(20), 2391-2405

Bannister, A.J., Kouzarides, T., 2011. Regulation of chromatin by histone modifications. Cell Res **21**, 381-395.

Barbui T., Finazzi G., Carobbio A., *et al.,* Development and validation of an International Prognostic Score of thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis). Blood. 2012;120(26):5128-5133; quiz 5252.

Barosi G., Besses C., Birgegard G., *et al.* A unified definition of clinical resistance/intolerance to hydroxyurea in essential thrombocythemia: results of a consensus process by an international working group. Leukemia. 2007;21(2):277-280.

Barosi, G., Mesa, R., Finazzi, G., Harrison, C., Kiladjian J-J., Lengfelder, E., McMullin M.F, Passamonti, F., Vannucchi, A.M., Besses, C., Gisslinger, H., Samuelsson, J., Verstovsek, S., Hoffman, R.H., Pardanani, A., Cervantes, F., Tefferi, A. and Barbui, T. 2013 Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood 121, 4778-4781

Beisel, C., Paro, R., 2011. Silencing chromatin: comparing modes and mechanisms. Nat Rev Genet **12**, 123-135.

Bird, A. , 2002. DNA methylation patterns and epigentic memory. Genes Dev. 16, 6-21

Cerquozzi S, T.A., Blast transformation and fibrotic progression in polycythemia vera and essential thrombocythemia: a literature review of incidence and risk factors. Blood Cancer J, 2015. **5**(11): p. e366.

Chen, E. and Mullally, A. 2014. How does JAKV617F contribute to the pathogenesis of myeloproliferative neoplasms? Hematology (American Society of Hematology Education) 268-276

Foster, C.T., Dovey, O.M., Lezina, L., Luo, J.L., Gant, T.W., Barlev, N., Bradley, A., Cowley, S.M., 2010. Lysine-specific demethylase 1 regulates the embryonic transcriptome and CoREST stability. Mol Cell Biol **30**, 4851-4863.

Geyer, H., Scherber, R.M., Kosiorek, H., Unmet Needs for Symptom Control in Essential Thrombocythemia with Front Line Therapy. Blood, 2015. **126**(3): p. a408.

Goardon, N., Marchi, E., Atzberger, A., Quek, L., Schuh, A., Soneji, S., Woll, P., Mead, A., Alford, K.A., Rout, R., Chaudhury, S., Gilkes, A., Knapper, S., Beldjord, K., Begum, S., Rose, S., Geddes, N., Griffiths, M., Standen, G., Sternberg, A., Cavenagh, J., Hunter, H., Bowen, D., Killick, S., Robinson, L., Price, A., Macintyre, E., Virgo, P., Burnett, A., Craddock, C., Enver, T., Jacobsen, S.E., Porcher, C., Vyas, P. 2011. Coexistence of LMPP-like and GMP-like leukemia stem cells in acute myeloid leukemia. Cancer Cell **19**, 138-152.

Harris, W.J., Huang, X., Lynch, J.T., Spencer, G.J., Hitchin, J.R., Li, Y., Ciceri, F., Blaser, J.G., Greystoke, B.F., Jordan, A.M., Miller, C.J., Ogilvie, D.J., Somervaille, T.C., 2012. The histone demethylase KDM1A sustains the oncogenic potential of MLL-AF9 leukemia stem cells. Cancer Cell **21**, 473-487.

Jutzi, J.S., Kleppe, M., Dias, J., Staehle, H.F., Shank, K., Teruya-Feldstein, J., Gambheer, S.M.M., Dierks, C., Rienhoff, Jr., H.Y., Levine, R,L., Pahl, H.L. **2018** LSD1 inhibition prolongs survival

in mouse models of MPN by selectively targeting the disease clone *Hemasphere* 2, 3-16.

Kahl, P., Gullotti, L., Heukamp, L.C., Wolf, S., Friedrichs, N., Vorreuther, R., Solleder, G., Bastian, P.J., Ellinger, J., Metzger, E., Schule, R., Buettner, R., 2006. Androgen receptor coactivators lysine-specific histone demethylase 1 and four and a half LIM domain protein 2 predict risk of prostate cancer recurrence. Cancer Res **66**, 11341-11347.

Kerenyi, M.A., Shao, Z., Hsu, Y.J., Guo, G., Luc, S., O'Brien, K., Fujiwara, Y., Peng, C., Nguyen, M., Orkin, S.H., 2013. Histone demethylase Lsd1 represses hematopoietic stem and progenitor cell signatures during blood cell maturation. Elife **2**, e00633.

Kiladjian, J-J., Cassinat, B., Chevret, S., Turlure, P., Cambier, N., Roussel, M., Bellucci, S., Grandchamp, B., Chomienne, C., Fenaux, P. 2008. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. Blood 112(8), 3065-3072

Klose, R.J., Kallin, E.M., Zhang, Y., 2006. JmjC-domain-containing proteins and histone demethylation. Nat Rev Genet **7**, 715-727.

Kornberg, R. D., 1974. Chromatin structure: a repeating unit of histones and DNA. Science 184, 868–871

Kouzarides, T., 2007. Chromatin modifications and their function. Cell 128: 693 -705

Lara-Astiaso, D., Weiner, A., Lorenzo-Vivas, E., Zaretsky, I., Jaitin, D.A., David, E., Keren-Shaul, H., Mildner, A., Winter, D., Jung, S., Friedman, N., Amit, I., 2014. Immunogenetics. Chromatin state dynamics during blood formation. Science **345**, 943-949.

Lee, M.G., Wynder, C., Cooch, N., Shiekhattar, R., 2005. An essential role for CoREST in nucleosomal histone 3 lysine 4 demethylation. Nature **437**, 432-435.

Lim, S., Janzer, A., Becker, A., Zimmer, A., Schule, R., Buettner, R., Kirfel, J., 2010. Lysine-specific demethylase 1 (LSD1) is highly expressed in ER-negative breast cancers and a biomarker predicting aggressive biology. Carcinogenesis **31**, 512-520.

Lin, X.M., Zhong, W.T., Wang, C.L., Wang, S.Q., 2011. [Expression of histone demethylase lysine specific demethylase 1 in acute leukemia and its clinical significance]. Zhongguo Shi Yan Xue Ye Xue Za Zhi **19**, 1348-1352.

Lin, Y., Wu, Y., Li, J., Dong, C., Ye, X., Chi, Y.I., Evers, B.M., Zhou, B.P., 2010. The SNAG domain of Snail1 functions as a molecular hook for recruiting lysine-specific demethylase 1. EMBO J **29**, 1803-1816.

Metzger, E., Wissmann, M., Yin, N., Muller, J.M., Schneider, R., Peters, A.H., Gunther, T., Buettner, R., Schule, R., 2005. LSD1 demethylates repressive histone marks to promote androgen-receptor-dependent transcription. Nature **437**, 436-439.

Niebel, D., Kirfel, J., Janzen, V., Holler, T., Majores, M., Gutgemann, I. 2014. Lysine-sepcific demethylase 1 (LSD1) in haematopoietic and lympoid neoplasms Blood 124(1):151-152

Orkin, S.H., Hochedlinger, K., 2011. Chromatin connections to pluripotency and cellular reprogramming. Cell **145**, 835-850.

Rhodes, D.R., Kalyana-Sundaram, S., Mahavisno, V., Varambally, R., Yu, J., Briggs, B.B., Barrette, T.R., Anstet, M.J., Kincead-Beal, C., Kulkarni, P., Varambally, S., Ghosh, D., Chinnaiyan, A.M., 2007. Oncomine 3.0: genes, pathways, and networks in a collection of 18,000 cancer gene expression profiles. Neoplasia **9**, 166-180.

Rumi, E., Cazzola, M., Diagnosis, risk stratification, and response evaluation in classical myeloproliferative neoplasms. Blood, 2017. **129**: p. 680-692.

Saleque, S., Kim, J., Rooke, H.M., Orkin, S.H., 2007. Epigenetic regulation of hematopoietic differentiation by Gfi-1 and Gfi-1b is mediated by the cofactors CoREST and LSD1. Mol Cell

27, 562-572.

Schulte, J.H., Lim, S., Schramm, A., Friedrichs, N., Koster, J., Versteeg, R., Ora, I., Pajtler, K., Klein-Hitpass, L., Kuhfittig-Kulle, S., Metzger, E., Schule, R., Eggert, A., Buettner, R., Kirfel, J., 2009. Lysine-specific demethylase 1 is strongly expressed in poorly differentiated neuroblastoma: implications for therapy. Cancer Res **69**, 2065-2071.

Sever M., N.K.J., Verstovsek, S., Therapeutic options for patients with polycythemia vera and essential thrombocythemia refractory/resistant to hydroxyurea. Leuk Lymphoma, 2014. **55**(12): p. 2685-2690.

Shi, Y., Lan, F., Matson, C., Mulligan, P., Whetstine, J.R., Cole, P.A., Casero, R.A., Shi, Y., 2004. Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. Cell **119**, 941-953.

Shi, Y.J., Matson, C., Lan, F., Iwase, S., Baba, T., Shi, Y., 2005. Regulation of LSD1 histone demethylase activity by its associated factors. Mol Cell **19**, 857-864.

Somervaille, T.C., Cleary, M.L., 2006. Identification and characterization of leukemia stem cells in murine MLL-AF9 acute myeloid leukemia. Cancer Cell **10**, 257-268.

Somervaille, T.C., Matheny, C.J., Spencer, G.J., Iwasaki, M., Rinn, J.L., Witten, D.M., Chang, H.Y., Shurtleff, S.A., Downing, J.R., Cleary, M.L., 2009. Hierarchical maintenance of MLL myeloid leukemia stem cells employs a transcriptional program shared with embryonic rather than adult stem cells. Cell Stem Cell **4**, 129-140.

Spivak 2017 Myeloproliferative Neoplasms New Engl J Med 376(22), 2168-2181.

Sprussel, A., Schulte, J.H., Weber, S., Necke, M., Handschke, K., Thor, T., Pajtler, K.W., Schramm, A., Konig, K., Diehl, L., Mestdagh, P., Vandesompele, J., Speleman, F., Jastrow, H., Heukamp, L.C., Schule, R., Duhrsen, U., Buettner, R., Eggert, A., Gothert, J.R., 2012. Lysine-specific demethylase 1 restricts hematopoietic progenitor proliferation and is essential for terminal differentiation. Leukemia **26**, 2039-2051.

Thiele, J., Kvasnicka, H.M., Facchetti, F., Franco, V., van der Walt, J., Orazi, A. 2005. European consensus on grading bone marrow fibrosis and assessment of cellularity Haematologica 90(8), 1128-1132

Vannucchi, A.M., Guglielmelli, P., What are the current treatment approaches for patients with polycythemia vera and essential thrombocythemia? Hematology Am Soc Hemtol Educ Program, 2017. **17**(1): p. 480-488.

Wang, J., Hevi, S., Kurash, J.K., Lei, H., Gay, F., Bajko, J., Su, H., Sun, W., Chang, H., Xu, G., Gaudet, F., Li, E., Chen, T., 2009. The lysine demethylase LSD1 (KDM1) is required for maintenance of global DNA methylation. Nat Genet **41**, 125-129.

Wang, J., Scully, K., Zhu, X., Cai, L., Zhang, J., Prefontaine, G.G., Krones, A., Ohgi, K.A., Zhu, P., Garcia-Bassets, I., Liu, F., Taylor, H., Lozach, J., Jayes, F.L., Korach, K.S., Glass, C.K., Fu, X.D., Rosenfeld, M.G., 2007. Opposing LSD1 complexes function in developmental gene activation and repression programmes. Nature **446**, 882-887.

Whyte, W.A., Bilodeau, S., Orlando, D.A., Hoke, H.A., Frampton, G.M., Foster, C.T., Cowley, S.M., Young, R.A., 2012. Enhancer decommissioning by LSD1 during embryonic stem cell differentiation. Nature **482**, 221-225.

Whyte, W.A., Orlando, D.A., Hnisz, D., Abraham, B.J., Lin, C.Y., Kagey, M.H., Rahl, P.B., Lee, T.I., Young, R.A., 2013. Master transcription factors and mediator establish super-enhancers at key cell identity genes. Cell **153**, 307-319.

Wouters, B.J., Lowenberg, B., Erpelinck-Verschueren, C.A., van Putten, W.L., Valk, P.J., Delwel, R., 2009. Double CEBPA mutations, but not single CEBPA mutations, define a subgroup of acute myeloid leukemia with a distinctive gene expression profile that is uniquely associated with

a favorable outcome. Blood **113**, 3088-3091.

Yang. J., Huang, J., Dasgupta, M., Sears, N., Miyagi, M., Wang, B., Chance, M.R., Chen, X., Du, Y., Wang, Y., An, L., Wang, Q., Lu, T., Zhang, X., Wang, Z., Stark, G.R. 2010 Reversible methylation of promoter-bound STAT3 by histone-modifying enzymes Proc Nat Acad Sci 107(50), 21499-21504Zhang, W., Zecca, L., Wilson, B., Ren, H.W., Wang, Y.J., Wang, X.M., Hong, J.S., 2013. Human neuromelanin: an endogenous microglial activator for dopaminergic neuron death. Front Biosci (Elite Ed) **5**, 1-11.

Zhang, W., Zecca, L., Wilson, B., Ren, H.W., Wang, Y.J., Wang, X.M., Hong, J.S., 2013. Human neuromelanin: an endogenous microglial activator for dopaminergic neuron death. Front Biosci (Elite Ed) 5, 1-11

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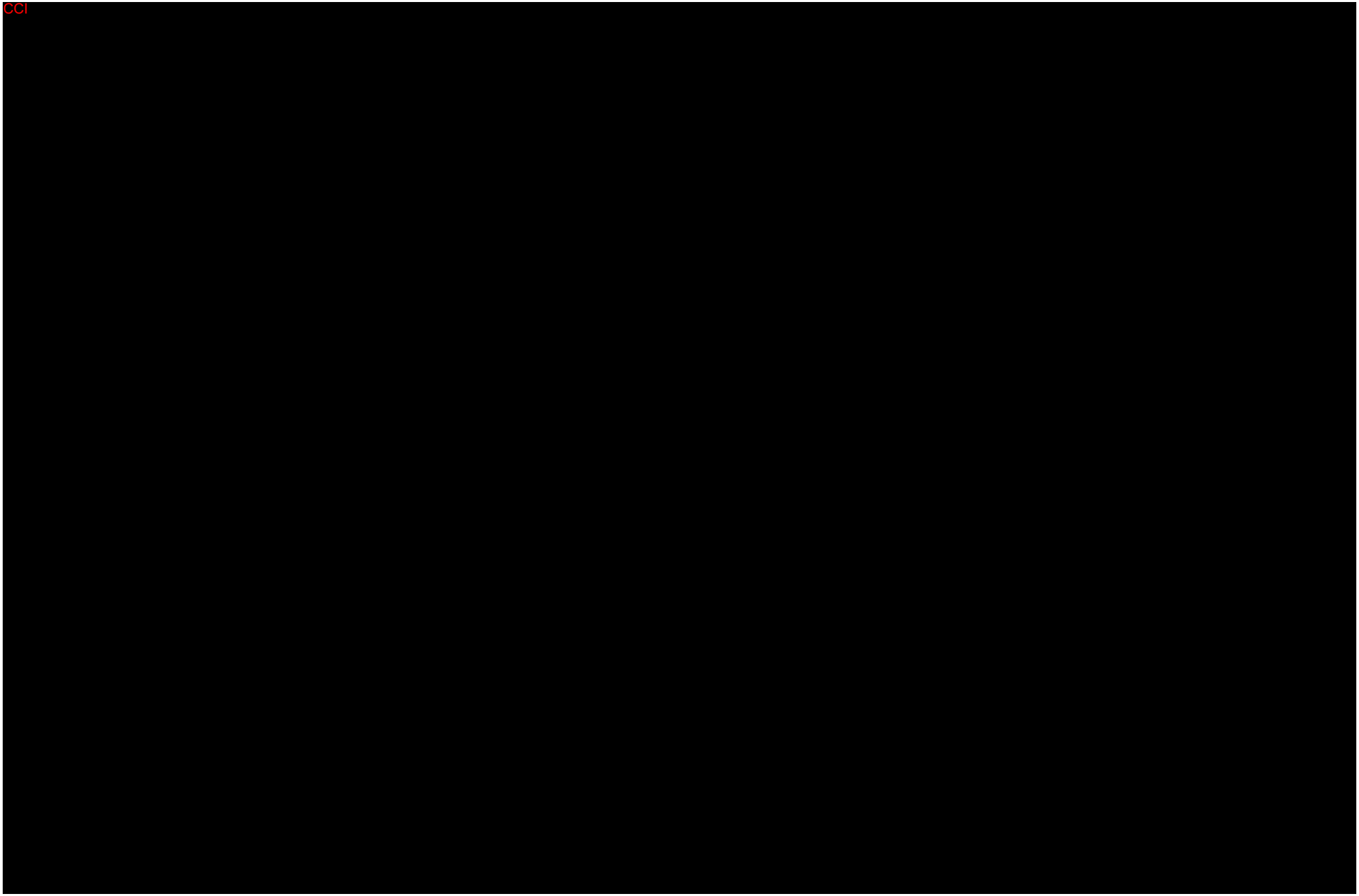

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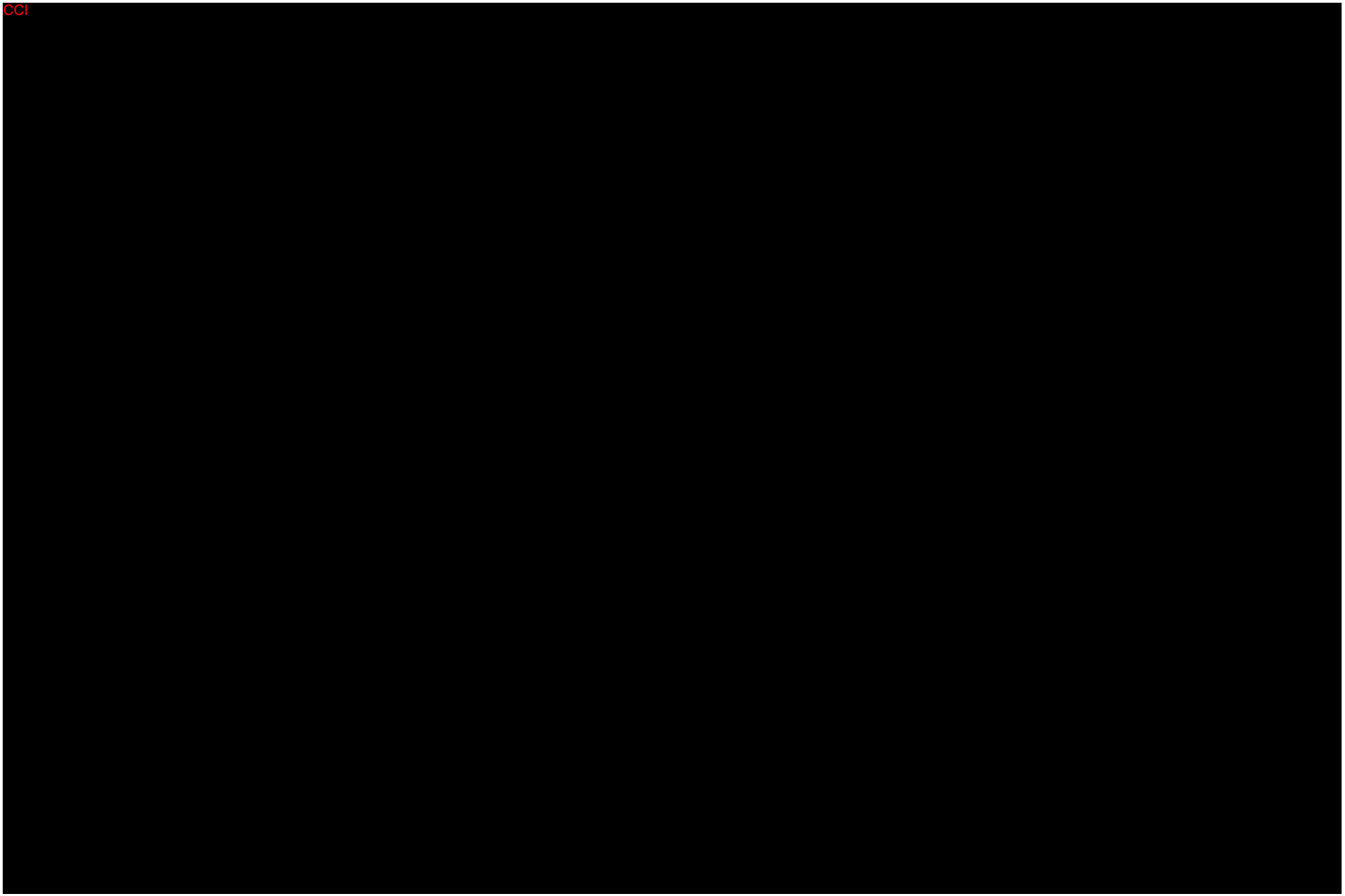

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16.2 ELN Criteria for Essential Thrombocythemia (Arber *et al.*, 2016)

Diagnostic Criteria for Essential Thrombocythemia† (WHO 2016)	
Major criteria:	1. Platelet count ≥450 × 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 criterion:	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)

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

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

*Slighly modified from the European Consensus Criteria as presented in Thiele *et al.*, 2005
Semiquantitative grading of BM fibrosis with minor modifications concerning collagen and osteosclerosis. Fiber density should be assessed only in hematopoietic areas.
[a]In grades MF-2 or MF-3 an additional trichrome stain is recommended.

16.4 Eastern Cooperative Group Performance Status

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

16.5 Revised Response Criteria for ET: IWG-MRT and ELN Consensus 2013 (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.

16.6 Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)

IMG-7289 -CTP-201
Patient Information: __ __ __ - __ __ __ (Site # Screen #) ___/___/___ (Initials) Completion Date: ____/_____/_____ (dd mmm yyyy)

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.

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)

Eighteen additional questions follow. Please be sure to complete all questions.

IMG-7289 -CTP-201
Patient Information: __ __ __ - __ __ __ (Site # Screen #) ___/___/___ (Initials) Completion Date: ____/_____/_____ (dd mmm yyyy)

Circle the one number that describes, 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 / 37°C)	(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)

16.7 Patient Global Impression of Change (PGIC)

IMG-7289 -CTP-201

Patient Information: __ __ __ - __ __ __ (Site # Screen #) ___/___/___ (Initials) Completion Date: ____/_____/_____ (dd mmm yyyy)

Patient Global Impression of Change (PGIC)

1. Compared to at the start of your treatment, how would you describe your **symptoms** due to essential thrombocythemia today?

- ☐ Much better [skip to 1a]
- ☐ Better [skip to 1a]
- ☐ A little better [skip to 1a]
- ☐ The same [exit]
- ☐ A little worse [skip to 1b]
- ☐ Worse [skip to 1b]
- ☐ Much worse [skip to 1b]

a. Was this improvement in your essential thrombocythemia symptoms an important change for you?
   - ☐ Yes
   - ☐ No

b. Was this worsening in your essential thrombocythemia symptoms an important change for you (by important we mean did it bother you)?
   - ☐ Yes
   - ☐ No

For use by participants in: IMG-7289-CTP-201; 08Nov2019

PGIC - United Kingdom/English - Version of 25 Jan 2018 - Mapi.
ID061053 / PGIC_TS25.0_eng-GB.doc

16.8 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 $\times 10^9$/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 $\times 10^9$/L and WBC < 2.5 $\times 10^9$/L at any dose of HU
- Platelet count > 400 $\times 10^9$/L and hemoglobin < 10 g/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.

16.9 Remote Data Review

16.9.1 Risk Assessment

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

16.9.2 Security Measures

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

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

16.9.3 Processes

As outlined in Section 13.5, remote data review is intended to encompass as many activities performed in a routine on-site monitoring visit as is functionally possible, and as permitted by site

policy and procedure. Remote data review has become critically important in the COVID-19 environment as a measure of safeguarding patient safety, while also minimizing risks to trial data integrity and facilitating GCP compliance. The source documents/source data to be made available for remote data review include those related to the primary endpoint and exploratory endpoints, safety, study drug dispensation and return and the reasons for exclusion of a subject from the trial.

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

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

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

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

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

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

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

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

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

- Usage must comply with applicable local regulations/regulatory guidance.
- During remote data review by video call/conferencing care will be taken to avoid inadvertent viewing of individuals who should not be part of the interaction.

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

Note: In Germany, the sending of redacted source data is generally not permissible as a method for the remote review of data; however, single redacted documents may be used at times to confirm an individual data-point.

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

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

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

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

- The prepared source document package, including transmittal form, will be provided by one of the following methods:
    - Overnight Courier
    - Secure Fax Transmission
    - Scanned images via secure email (encrypted email or password protected email attachment. If the latter, the password will be provided to Monitor via telephone)
    - A secure platform for document exchange
- A set of the prepared source document package, including transmittal form, will be retained in the Investigator's Site File. Note: These documents will not be retained in Germany.