Official Protocol Title:	A Multi-Center, Open Label Study to Assess the Safety, Steady-State Pharmacokinetics and Pharmacodynamics of IMG-7289 in Patients with Myelofibrosis
NCT number:	NCT03136185
Document Date:	23-June-2020

Protocol Title:	A Multi-Center, Open Label Study to Assess the Safety, Steady-State Pharmacokinetics and Pharmacodynamics of IMG-7289 in Patients with Myelofibrosis
Protocol No.:	IMG-7289-CTP-102
Investigational Product:	IMG-7289 (Bomedemstat)
Indication:	Myelofibrosis
Study Phase:	Phase 1/2a **Phase 2b – expansion component**
EudraCT Number:	2018-003811-23
IND Number:	130,789
Sponsor:	Imago BioSciences, Inc. 2729 Debbie Court San Carlos, CA 94070 - USA

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Original Protocol: 01 November 2016
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UK only - Addendum 3: 19 February 2019
Italy only - Addendum 4: 04 July 2019
Amendment 5: 02 September 2019
Amendment 6: 23 June 2020

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

PPD

Signature

23 June 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 Conference on Harmonization document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance"; and the Declaration of Helsinki.

_____ _____

Investigator Signature Date

_____ _____

Investigator Name (Print)

Table of Contents

1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

1.1 List of Abbreviations

Abbreviation	Definition
<, ≤, >, ≥	less than, less than or equal to, greater than, greater than or equal to
±	plus
Ac	acetylation
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
BCR-ABL	breakpoint cluster region-Abelson
BUN	blood urea nitrogen
°C	degrees Centigrade
CALR	calreticulin
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CI	Clinical Improvement
CL/F	apparent total clearance of drug after oral administration
Clinical Benefit	not meeting progressive disease criteria as per Section 16.7 and safely tolerating IMG-7289
C_{min}	minimum observed plasma concentration at 24 hours from last dose
CoREST	Co-repressor for RE1-silencing transcription factor
CR	complete remission or response
CXCL	chemokine (C-X-C Motif) ligand
CXCR4	chemokine (C-X-C motif) receptor 4
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	co-efficient of variation
D	Day
DIC	Disseminated Intravascular Coagulation
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DNMT	DNA-methyltransferase

Abbreviation	Definition
D_{pi}	pharmacodynamic dose; the estimated dose of IMG-7289 needed in humans that provides sufficient exposure to inhibit normal haematopoiesis safely during a fraction of the 24-hour dosing cycle
D_s	starting dose
DSMC	Data Safety Monitoring Committee
DSMP	Data Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event free survival
ELN	European Leukaemia Network
EMH	extramedullary haematopoiesis
EOS	end of study
EOT	end of treatment
EPO	Erythropoietin
ESC	embryonic stem cell
ET	essential thrombocythaemia
FAD	flavine adenine dinucleotide
FPFV	first patient first visit
Free base of IMG-7289	*N*-[(2*S*)-5-{[(1*R*,2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, **free base**
FSH	follicle stimulating hormone
g or gm	Gram
g/dL	gram per deciliter
GCP	good clinical practice
G-CSF	gram colony stimulating factor
GFI1	growth factor independent 1 transcription factor
GFP	green fluorescent protein
GFR	glomerular filtration rate
GGT	gamma glutamyltransferase
GI	Gastrointestinal
GLP	good laboratory practice
GM-CSF	granulocyte-macrophage colony stimulating factor
GMP	Good Manufacturing Practices
H	Histone
HbF	foetal haemoglobin
HDAC	histone deacetylase
HED	human equivalent dose
HIV	human immunodeficiency virus

Abbreviation	Definition
HREC	Human Research Ethics Committee
HSC	haematopoietic stem cell
HSCT	haematopoietic stem cell transplant
IC	inhibitory concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL	Interleukin
IMG-7289	*N*-[(2*S*)-5-{[(1*R*,2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1*H*-1,2,3-triazol-1-yl)benzamide, **bis-tosylate salt**; bomedemstat
indels	insertions and deletions
INR	International normalized ratio
IPF	immature platelet fraction
IRB	Institutional Review Board
IUD	intrauterine device
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
JAK	Janus Kinases
K	Lysine
KD	knockdown
KDM1A	lysine-specific demethylase 1
Kg	Kilogram
L	litre
LDH	lactate dehydrogenase
LIC	leukaemia initiating cell
LPLV	last patient last visit
LSD1	lysine-specific demethylase 1
LSDi	LSD1 inhibition or inhibitors
MAO; MAOI	monoamine oxidase(s); monoamine oxidase inhibitor(s)
MCH	mean cell haemoglobin
MCHC	mean cell haemoglobin concentration
MCV	mean cell volume
me; Me	methyl; methylation
Mg	Milligram
mg/kg	milligram per kilogram
mg/kg/d	milligram per kilogram per day
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis

Abbreviation	Definition
mL	millilitre
mL/min	millilitres/minute
MPL	myeloproliferative leukaemia virus oncogene, thrombopoietin receptor
MPN	myeloproliferative neoplasias or neoplasms
MPP	multipotent progenitor
MPN-SAF TSS	Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score
MPV	mean platelet volume
MRI	magnetic resonance imaging
mRNA	messenger RNA
Ms	milliseconds
MTD	maximally tolerated dose
MYB	V-Myb Avian Myeloblastosis Viral Oncogene Homolog
NCI	National Cancer Institute
ng·hr/mL	nanogram an hour per milliliter
nM	Nanomolar
NOAEL	no-observed-adverse-effect-level
NURD	nuclear remodeling and histone deacetylase
OCT4	octamer-binding transcription factor 4
OS	overall survival
PD	Pharmacodynamics
PE	physical examination
PET-MF	post-essential thrombocythaemia myelofibrosis
PFS	progression free survival
Ph	phosphorylation
PI	Principal Investigator (at each site responsible for patient care)
PISCF	Participant Information Sheet/Consent Form
PK	Pharmacokinetics
PKAP	Pharmacokinetic Analysis Plan
PMF	primary myelofibrosis
PPV-MF	post-polycythaemia vera myelofibrosis
PR	partial remission or response
PT	prothrombin time
PV	polycythaemia vera
QD	once daily
RBC	red blood cell
RDW	red cell distribution width
REST	RE-1 silencing transcription factor

Abbreviation	Definition
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
Sh	short hairpin
SOA	schedule of assessments
SOC	standard-of-care
SOX2	see SRY
SRM	Study Reference Manual
SRY	(sex determining region Y)-box 2; also known as SOX2
STAT	Signal Transducer and Activator of Transcription
T_{max}	time to maximum concentration
TCP	Tranylcypromine
TF	transcription factor
TNF	tumour necrosis factor
TPO	Thrombopoietin
µL	Microliter
µM	Micromolar
Ub	ubiquitination
VAF	variant allele frequency
V_z/F	apparent volume of distribution during terminal phase after oral administration
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of child-bearing potential

2 PROTOCOL SYNOPSIS

Protocol Title: A Multi-Center, Open Label Study to Assess the Safety, Steady-State Pharmacokinetics and Pharmacodynamics of IMG-7289 in Patients with Myelofibrosis

Protocol No: IMG-7289-CTP-102

Investigator/Study Centers: Approximately 25 sites in Australia, Germany, Italy, UK and US with additional sites and countries as needed.

Study Objectives:

Hypothesis: IMG-7289 (bomedemstat) is a safe and tolerable orally available agent when administered to patients with myelofibrosis including primary myelofibrosis (PMF), post-polycythaemia vera myelofibrosis (PPV-MF), and post-essential thrombocythaemia myelofibrosis (PET-MF) (collectively referred to as 'MF'); inhibition of lysine-specific demethylase 1 (LSD1) by IMG-7289 will reduce spleen size in those with splenomegaly, improve haematopoiesis and reduce constitutional symptoms associated with these disorders.

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

- Safety and tolerability
- Pharmacokinetics (Phase 1/2a only)
- Reduction in spleen volume

Exploratory Objectives$^{\phi}$: To evaluate in MF patients treated with IMG-7289:

- The adequacy of the treatment regimen in producing a pharmacodynamic effect
- Haematologic response*
- Improvement in constitutional symptoms assessed using the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF; Phase 1/2a only) and the MPN-SAF TSS (Total Symptom Score; Phase 2b)
- Reduction in bone marrow fibrosis score
- Relationship between dose and plasma trough concentrations over time (Phase 1/2a only)
- The impact of therapy on disease burden as measured by malignant-cell specific nucleic markers (DNA or RNA)**
- The effect of treatment on cytokine profiles***
- The relationship between genetic aberrations in malignant cells and pharmacodynamic response
- To correlate conventional clinical responses with exploratory assessments of response

*Haematologic parameters, all of which may be assessed during treatment or after drug has been discontinued for a specified interval, may comprise: complete blood count (CBC) including platelets, red and white blood cell (RBC and WBC) and circulating blast cell counts; cellular composition of the bone marrow (% blasts); and, the induction of foetal haemoglobin.
**Nucleic markers include RNA and/or DNA mutations detected by sequencing or other nucleic assay methods.
***Cytokine quantification.
$^{\phi}$Some or all may be analysed time and cost permitting.

Investigational Drug: The active drug substance is identified as IMG-7289 (bomedemstat). IMG-7289 is an irreversible inhibitor of LSD1. CCI [redacted]

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: CCI [redacted] 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 seventy-five (75) patients eighteen years of age or older with intermediate-1, -2 or high risk PMF, PPV-MF, PET-MF (referred to collectively as 'MF') will be treated.

Methodology: This is a multi-center, open-label study evaluating the safety, tolerability, steady-state pharmacokinetics and pharmacodynamics of IMG-7289 administered orally once daily in patients with myelofibrosis (MF).

The therapeutic goal for the treatment of MF is to inhibit the activity of LSD1 in haematopoietic cells, particularly megakaryocytes, for only a fraction of the 24-hour dosing cycle, sufficient to reduce platelets to a safe level while inhibiting to the greatest extent possible the production, by megakaryocytes, of cytokines and growth factors that drive bone marrow fibrogenesis and symptoms. Considerations for a safe and therapeutic starting dose included chronic toxicology studies, in conjunction with the clinical experience of the patients who have received IMG-7289 to date in both IMG-7289-CTP-101 and -102. In the CTP-101 study, IMG-7289 was administered to patients with high-risk AML and MDS; the therapeutic thesis was to completely inhibit LSD1 in all haematopoietic cells, targeting both leukaemic stem cells and blasts, recognizing that patients would need clinical support for cytopenias. The starting dose was 0.75 mg/kg/d and the effective dose, at which no safety signals were observed, was deemed 6.0 mg/kg/d. Though the great majority of the patients entered the study with Grade 3/4 thrombocytopenia, patients at all dose levels of IMG-7289 required platelet transfusions. This sensitivity of thrombopoiesis to LSD1 inhibition in high-risk AML/MDS patients reflects the generally compromised nature of the bone marrow, including the reduction of megakaryocytes, in that disease.

Taking this observation into account in association with the therapeutic goal for the treatment of myeloproliferative neoplasms - inhibiting LSD1 activity in haematopoietic cells for only a *fraction* of the 24-hour dosing cycle - and PK modeling, a starting dose (D_s) of 0.25 mg/kg/d was selected for the Phase 1/2a portion of this study. CCI [redacted] A dose-response curve was subsequently generated that provided a titration algorithm to adjust dose to achieve the modified target platelet count of between 50-75 k/µL (50-75 x 10^9/L), devised with a view to minimizing the probability of severe thrombocytopenia. CCI [redacted] Accordingly, to enable patients to more quickly reach the optimum dose while still maintaining an adequate safety margin, a new IMG-7289 starting dose of 0.5 mg/kg QD was selected with protocol Amendment 4. With continued observation of additional patients treated, the estimated optimal dose for most patients ranges between 0.6 and 0.8 mg/kg/d. Thus, a new starting dose of 0.6 mg/kg/d has been chosen, CCI [redacted] Starting therapy at a dose closer to the optimal dose should accelerate the process of symptom and spleen volume reduction. Additional detail for the rationale on the dose and dose schedule can be found in Section 3.6.

CCI [redacted]

Study Conduct

This study initiated as a Phase 1/2a study assessing the safety of the starting dose, an 85 day duration of treatment, and the pharmacokinetic and pharmacodynamic effects of IMG-7289, with transition to a Phase 2b study incorporating changes supported by the Phase 1/2a data. This study consists of two treatment periods: the Initial Treatment Period (ITP), followed by the Additional Treatment Period (ATP). Patients are now enrolling in the Phase 2b portion of the study, in which patients are treated daily for 169 days in the ITP. The ATP offers treatment to qualifying patients for an additional 169 days.

During the ITP, patients will return for study assessments weekly for 8 weeks CCI [redacted] For the exceptional patient whose dose has not stabilized, weekly visits may continue at the PI's discretion (note: bi-weekly visits may also continue post Day 112). CCI [redacted] Such patients qualify for entry into the ATP, a transition which should occur without interruption in dosing. Patients not deriving clinical benefit, or who achieve complete response (CR), partial response (PR) or clinical improvement (CI) and subsequently relapse (Section 16.7) the equivalent of treatment failures, will discontinue IMG-7289 and undergo End of Treatment (EoT), pre-End of Study (pre-EoS) and End of Study (EoS) visits.

In the ATP, treatment may continue for an additional 169 days in those patients deriving clinical benefit, as determined by the Principal Investigator. Qualifying patients will return for study assessments monthly CCI [redacted] It is anticipated that patients continuing in the ATP will have already achieved a stable dose, with bi-weekly visits no longer necessary. For the exceptional patient whose dose has not stabilized, bi-weekly visits may continue at the PI's discretion. On Day 168, patients will undergo the same procedures and assessments as in the ITP, including MRI or CT (if the patient is not a candidate for MRI), and bone marrow sampling. Prior to or at the CCI [redacted] 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.

Note: In Germany, use of computerised tomography (CT) is not permitted for patients unable to undergo magnetic resonance imaging (MRI). Only MRI is permitted for study purposes.

All patients will undergo follow-up period visits, including an EoT visit on the day of last dose or as soon as possible thereafter, a pre-EOS visit approximately 14 days post last dose, and an EoS visit approximately 28 days post last dose. Patients that do not enter the ATP, or discontinue early, will enter the follow-up period beginning with an EoT.

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 and by peripheral blood and urine analyses. Pharmacodynamic effects will be closely monitored by frequent haematology 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, all patients will be dosed to the estimated dose of IMG-7289 needed in humans that provides sufficient exposure to inhibit normal haematopoiesis safely for a fraction of the 24-hour dosing cycle (designated the D_{pi}).

Initial Treatment Period (ITP):

Note: Please refer to Section 7.2.3.1 for patients currently being treated under Amendment 5

For patients commencing treatment under Amendment 6, treatment will begin on Day 0 at the new D_s of 0.6 mg/kg QD. In association with this increased starting dose, the first up-titration is not permitted until Day 28. Extending the time to first up-titration from Day 14 to Day 28 is supported by the observation that the time needed to reach a stable platelet count is between 3 and 4 weeks; additionally, this approach minimizes the risk of severe thrombocytopenia for the few patients who may require less than 0.6 mg/kg/d. CCI [redacted]

The platelet titration target expected to be associated with a clinically significant therapeutic effect is:

- A platelet count of ≥ 50 to ≤ 75 k/µL (50-75 x 10^9/L).

Please refer to Section 7.2.3.2 for additional information on the dosing of Amendment 6 patients.

Additional Treatment Period (ATP): Qualifying patients will 're-start' IMG-7289 on ATP Day 0, with dose titration continuing as *per* the Titration Rules in **Table 3**; there should be no interruption in dosing (i.e., Day 168 = Day 0 of new ATP). Additional dose-titration may occur in consultation with the Medical Monitor.

Study Duration: CCI [redacted] the anticipated duration of participation in the study is expected to be at least 32 weeks from first patient-first visit (FPFV) to last patient-last visit (LPLV). Additional treatment may be given, contingent on an assessment of patient benefit.

Study Assessments: The assessments outlined below are presented in detail by study visit in Section 9, and in the Schedule of Assessments Sections 16.1).

The Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) will be used. The 24-HOUR RECALL tool (Appendix 16.8) will be completed daily for the 7 days preceding first dose (Days -6 to pre-dose Day 0) during Baseline. The 7-DAY RECALL tool will be completed weekly from Day 7 through the EoS Visit (Appendix 16.9). Multiple questionnaires will need to be provided to patient for completion between visits as visit schedule decreases over time.

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

> **Note:** In the UK, serious AEs (SAEs) will be recorded from time of consent through the EoS **or** until the Investigator and Imago BioSciences determine follow-up is no longer necessary.

Physical Examinations (PE), including vital signs: a **Full Physical Exam** will be performed at Screening. **Limited Physical Exams (LPE)** will be performed at all other clinic visits throughout the study. LPEs include weight, a review of body systems to assess change from previous PE, and spleen measurement. The edge of the spleen shall be determined by palpation, measured in centimeters, using a soft ruler/tape, from the costal margin to the point of greatest splenic protrusion. The spleen should be measured in the same manner at all visits.

Urine or serum pregnancy testing will be performed for women of child-bearing potential (WOCBP; defined in Section 6.1) at Screening, Baseline (if separate from Screening visit), pre-dose Day 0, monthly (i.e., Days 28, 56, 84, 112, 140 and 168) 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 Baseline (no more than 21 days prior to the first IMG-7289 dose).
- At Day 168 (±7 days).
- Approximately every 6 months thereafter, at Day 168 (±7 days) of the ATP, for as long as the patient continues to qualify.
- At EoT and ET (unless performed within the prior 5 weeks), and upon suspicion of relapse (unless performed in the last 21 days or is scheduled in the next 7 days).

*Aspirate from the first pull whenever possible, but no later than the second pull, is required.
**The total number of bone marrow evaluations required during the ITP is 2 in ~32 weeks. Additional marrow evaluation is required only if the patient qualifies for the ATP, demonstrates response followed by suspected relapse, or evidence of progressive disease.

MRI or CT (if the patient is not a candidate for MRI) of the abdomen will be performed.

- Pre-dose Day 0 (±2 days)
- At the Day 84 and Day 168 visits (±7 days)
- Approximately every 6 months thereafter, at Day 168 (±7 days) of the ATP, for as long as the patient continues to qualify

- At EoT, ET, and upon suspicion of relapse (unless performed within the prior 5 weeks)

Note: In Germany, use of computerised tomography (CT) is not permitted for patients unable to undergo magnetic resonance imaging (MRI). Only MRI is permitted for study purposes.

Clinical laboratory measures: The following laboratory measures will be performed at Screening, Baseline (if separate from Screening visit), pre-dose Day 0, upon suspicion of relapse, at the EoT, pre-EoS, and EoS/ET visits, and in accordance with the below:

- Biochemistry – monthly (i.e., Days 28, 56, 84, 112, 140 and 168) throughout the study
- Haematology – every clinic visit throughout the study
- Coagulation – monthly (i.e., Days 28, 56, 84, 112, 140 and 168) throughout the study
- Urinalysis – Day 84 and Day 168 throughout the study

CCI Sample collection time-points are below.

- Pre-dose Day 0, Days 14, 28, 84 and 168, and each Day 168 visit 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)

Red Cell Haemoglobin F (HbF) and %F cells (Selected sites only/ITP only):

- Pre-dose Day 0, Day 84 and Day 168
- At EoT and ET (both required only if the patient discontinues during the ITP)

CCI

*Any bone marrow aspirate samples will undergo genomic analysis as per the bone marrow sampling schedule.

CCI

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

Eligibility Criteria:

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

Inclusion Criteria:

1. Willing and able to sign the approved informed consent.

2. Age: 18+ years old at Screening.
3. Diagnosis of either PMF per World Health Organization (WHO) diagnostic criteria for myeloproliferative neoplasms (Section 16.2), PPV-MF per the IWG-MRT (Section 16.3), or PET-MF per the IWG-MRT (Section 16.4) and meet the following additional subtype specific criteria:
   a. Classified as high risk (3 prognostic factors), intermediate risk-2 (2 prognostic factors) or intermediate risk-1 (1 prognostic factor). The prognostic factors, defined by the International Working Group (Cervantes, *et al*., 2009):
      i. Age > 65 years;
      ii. Presence of constitutional symptoms (weight loss, fever, night sweats);
      iii. Marked anaemia (Hgb < 10g/dL)*;
      iv. **History** of leukocytosis [WBC > 25 x10^9/L (25,000/µL)];
      v. Circulating blasts ≥ 1%.

   *A haemoglobin value < 10 g/dL must be demonstrated during Screening for patients who are not transfusion dependent. Patients receiving regular transfusions of packed red blood cells will be considered to have haemoglobin < 10 g/dL for the purpose of evaluation of risk factors.
4. Be refractory or resistant to, inadequately controlled by or intolerant of available approved therapy, or in the Investigator's judgment, are not candidates for available approved therapy (note: approved therapy includes ruxolitinib and, in the US, fedratinib).
5. Eastern Cooperative Oncology Group (ECOG) performance status score ≤2.
6. Peripheral blast count ≤10% prior to dosing on Day 0.
7. Absolute neutrophil count ≥ 0.5 x 10^9/L (500/µL) prior to dosing on Day 0.
8. Platelet count ≥ 100 x 10^9/L (100 k/µL) prior to dosing on Day 0.
9. Life expectancy >36 weeks.
10. Have discontinued all previous therapies for MPNs including ruxolitinib, any chemotherapeutic agents, immunosuppressive therapy (e.g., corticosteroids > 10 mg/day with the noted exception: use of corticosteroids for management of gout is allowed; maintenance supplemental corticosteroid therapy such as prednisone ≤ 10 mg/day or corticosteroid equivalent is allowed), immune modulators (e.g., thalidomide), radiotherapy for at least 2 weeks prior, and interferon for 4 weeks prior to study Day 0. Low dose acetylsalicyclic acid is permitted. Palliative radiation treatment to non-index or bone lesions performed < 2 weeks before treatment may be considered with Medical Monitor approval.
11. Amenable to bone marrow evaluation, peripheral blood and urine sampling during the study.
12. Able to swallow capsules.
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 28 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 as refraining from heterosexual intercourse). Patients practicing abstinence must agree to use an approved method of contraception should they become sexually active during the study.

Note: In the UK, males with a pregnant partner must agree to use a condom to avoid exposure to the developing child.

*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. Has undergone major surgery ≤4 weeks prior to starting study drug or has not recovered from side effects of such surgery.
2. Has undergone any surgical procedure within 2 weeks, excluding minor procedures (e.g., skin biopsy or central venous catheter placement/removal) prior to starting study drug.
3. History of splenectomy.
4. History of or scheduled haematopoietic stem-cell transplant within 24 weeks of screening.
5. Unresolved treatment related toxicities from prior therapies (unless resolved to ≤ Grade 1).
6. Current use of a prohibited medication (e.g., romiplostim) or expected to require any of these medications during treatment with the investigational drug.
7. 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.
8. Current use of monoamine oxidase A and B inhibitors (MAOIs).
9. Uncontrolled active infection.
10. 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).
11. Evidence at the time of Screening of risk of bleeding, including any of the following:
    a. Activated partial thromboplastin time (aPTT) ≥ 1.3 x the local upper limit of normal
    b. International normalized ratio (INR) ≥ 1.3 x the local upper limit of normal
    c. History of severe thrombocytopenia or platelet dysfunction unrelated to a myeloproliferative disorder or its treatment
    d. Known bleeding disorder (e.g., dysfibrinogenaemia, factor IX deficiency, haemophilia, Von Willebrand's disease, Disseminated Intravascular Coagulation [DIC], fibrinogen deficiency, or other clotting factor deficiency)
12. Evidence at the time of Screening of significant renal or hepatic insufficiency (unless due to haemolysis, or leukaemic infiltration) as defined by any of the following local lab parameters:
    a. 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
    b. Aspartate transaminase (AST) or alanine aminotransferase (ALT) ≥2 x the local upper limit of normal
13. Known human immunodeficiency virus (HIV) infection or known active Hepatitis B or Hepatitis C virus infection (testing will not be conducted as part of Screening procedures).

    For Italy ONLY, Exclusion 13 reads: Active infection with hepatitis 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).

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 study Day 0.
16. Pregnant or lactating females; females intending to become pregnant at any time during the study.

GUIDELINES: These guidelines are for use by the Investigator, study staff and patient to safeguard patient safety while maintaining data integrity. Please contact the Medical Monitor with questions.

1. In general, supportive care (transfusions, administration of anti-fungals, etc.) should be maintained in accordance with institutional policy. Additionally:
   a. It is advised that patients with a platelet count ≤ 10 x 10^9/L (10 k/μL) be transfused.
2. Hydroxyurea may be used during the study in case of proliferation as follows:
   a. At the PIs discretion, initiate hydroxyurea treatment for white cell count ≥ 30 x 10^9/L (30,000/μL) and majority of cells appear to be immature cells (myelocytes/promyelocytes)
   b. Discontinue hydroxyurea treatment when white cell count is < 10 x 10^9/L (10,000/μL)
3. Patients taking medications that have 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.
4. Cessation of IMG-7289 is invariably associated with a rebound in thrombopoiesis and platelet counts may easily exceed the baseline in any given patient. When IMG-7289 is discontinued, the platelet count should be monitored closely and the timing of the start of an alternative therapy should take this into account.

PROHIBITED MEDICATIONS/TREATMENTS: Please consult the Medical Monitor with any questions pertaining to prohibited medications.

1. All cytotoxic agents, with the exception of hydroxyurea
2. All haematopoietic growth factors: romiplostim, eltrombopag, granulocyte and granulocyte-macrophage colony stimulating factor (G-CSF and GM-CSF) and erythropoietin (EPO)
3. Prednisone or prednisolone > 10 mg/day (noted exception: use of corticosteroids for management of gout is allowed) and dexamethasone > 4 mg/day. Maintenance supplemental corticosteroid therapy such as prednisone ≤ 10 mg/day or corticosteroid equivalent is allowed.
4. Monoamine oxidase A and B inhibitors
5. Anticoagulant and nonsteroidal anti-inflammatory drug (NSAID; including aspirin) use are prohibited in patients when their platelet count is < 50 x 10^9/L (50 k/μL)

Management of Study Toxicities: Adverse event intensity will be evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, published 14 June 2010. Please refer to Section 8.2 for additional detail on management of study toxicities, including reduction of the starting dose based on DLT.

Definitions:

Haematologic Toxicity: Haematologic 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 haematopoiesis observed in non-clinical and clinical studies are expected in humans; these are pharmacodynamic effects of LSD1 inhibition by IMG-7289, thus 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 <u>related to IMG-7289</u>:

- Thrombocytopenia leading to clinically significant sequelae (i.e., a clinically significant bleeding event* or the need for prophylactic transfusions);
- A clinically significant bleeding event* in a patient with a platelet count >50 x 10^9/L (50 k/μL);
- Any Grade 4 or 5 <u>non-haematologic</u> adverse event;

- Any Grade 3 non-haematologic adverse event with failure to recover to Grade 2 within 7 days of drug cessation, with the following exceptions:
  - ≥ Grade 3 nausea, vomiting or diarrhea that responds to standard medical care
  - ≥ Grade 3 aesthenia lasting less than 14 days
- Any Grade 3 electrolyte abnormality unrelated to the underlying malignancy and persisting greater than 24 hours.

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

Patients who experience a DLT may have their dose adjusted downward if the Medical Monitor and Principal Investigator deem it safe for the patient to continue on IMG-7289.

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

Expected toxicities with IMG-7289 are reported in the latest edition of the Investigator's Brochure.

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.

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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 polycythaemia vera (PV), essential thrombocythaemia (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 haematopoietic stem/progenitor cell resulting in abnormalities in red cell, granulocyte and platelet production often in association with marrow fibrosis and extramedullary haematopoiesis and, in some cases evolution to acute myeloid leukaemia (AML).

Myelofibrosis is, *per se*, a clinical feature of many benign and malignant disorders (Popat *et al*., 2006). MF in the context of MPNs, variably termed primary or secondary myelofibrosis, myelofibrosis with myeloid metaplasia, agnogenic myeloid metaplasia, or primary myelosclerosis, is a chronic inflammatory process in which excess collagen is deposited in bone marrow, impairing haematopoiesis.

The chronic MPNs are disorders of haematopoiesis which share mutations that constitutively activate the physiologic signal transduction pathways responsible for myeloid haematopoiesis. The common pathogenic mechanism is activation of the Janus Kinase (JAK) and signal transducer and activators of transcription (STAT); the JAK-STAT pathway is the signaling transduction pathway for the lineage-specific growth factors including thrombopoietin (TPO) and erythropoietin (EPO) (Abdel-Wahab and Levine, 2009; Stark and Darnell, 2012). MF patients have gain-of-function missense mutations in *JAK2* (65%) and/or the myeloproliferative leukaemia virus oncogene, *MPL* (4%). The more common alleles, $JAK2^{V617F}$ and MPL^{W515L}, result from G-to-T transversion mutations, the most common cause of which is oxidative damage to DNA. Insertion and deletion (indels) mutations found in *CALR* (23%) are similarly gain-of-function mutations that result in activation of the JAK-STAT pathway (Rumi *et al.*, 2014; Nangalia *et al*., 2013).

Many chromosomal and genetic abnormalities have also been identified in the MPNs. Some, like deletions of chromosome 20q, may be antecedent cytogenetic abnormalities that predispose to mutations in *JAK2* or are epistatic, that together determine the subsequent clinical course. The underlying mechanisms that generate the common pathogenic mutations, and the antecedent and subsequent mutations necessary to cause clinical disease and to shape the natural history remain a mystery. In light of the unfruitful search for additional highly recurrent mutations with whole genome sequencing, these influences may be specific to the cell of origin in which the mutations arose, epigenetic and even physiologic, considering the reportedly worse natural history of polycythaemia in women compared to men (Spivak *et al*., 2014).

Some MPN patients are asymptomatic at the time of diagnosis, and PV, ET and MF can be difficult to clinically distinguish. Common presenting manifestations can include stroke, fatigue, weight loss, night sweats, fever, dyspnea, and abdominal discomfort owing to splenomegaly. Leukocytosis, thrombocytosis and splenomegaly can be present. Major complications arise from cytopenias secondary to bone marrow failure, extramedullary haematopoiesis (principally in the spleen and liver), and evolution to AML. Splenomegaly is for many patients the most distressing complication of

myelofibrosis leading to discomfort, inanition, splenic infarction, portal and pulmonary hypertension, and blood cell sequestration, while thrombosis is the dreaded complication of elevated red blood cell mass.

Myelofibrosis associated with somatic mutations in haematopoietic stem/progenitor cells is a progressive neoplastic disorder with a median lifespan of 5.5 years from the time of diagnosis, a shorter mean survival time compared to PV and ET (Hultcrantz *et al.,* 2015). Death most often results from the consequences of thrombocytopenia or neutropenia, haemorrhage or infection (Malak *et al.,* 2012). Complications exacerbating morbidity secondary to anaemia and extramedullary haematopoiesis include portal hypertension and heart failure.

There are no specific treatments for the MPNs. The JAK1/2 inhibitor ruxolitinib is approved for the treatment of disease-related symptoms and splenomegaly in adult myelofibrosis (including PMF, PPV-MF and PET-MF) patients. It is effective at alleviating constitutional symptoms, normalizing blood counts and reducing spleen size in many patients. Ruxolitinib does not appear to significantly alter the natural history of the disease but mortality in a three year period is reduced 50% in the high-risk patients. Ruxolitinib is effective only during administration; symptoms recur soon after treatment is stopped. Fibrosis in the marrow is largely unaffected by treatment with ruxolitinib; there is no short-term clinical impact on *JAK2*^{V617F} allele frequencies, but treatment for more than three years may reduce the allele burden (Deininger *et al*., 2015).

Other treatments principally manage symptoms. Anaemia associated with an erythropoietin (EPO) level <100 mU/mL may respond to EPO therapy but is associated with an increase in hepatosplenomegaly. Prednisone can be effective for patients with evidence of active inflammation or autoimmune disease. Allopurinol is used to treat hyperuricaemia. Thalidomide at doses up to 100 mg/day in combination with prednisone improves anaemia and thrombocytopenia in approximately 60% of PMF patients and reduces spleen size in approximately 20% but is not approved for this indication in many countries. 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 but is not approved for this indication in many countries (Kiladjian *et al*., 2008). Hydroxycarbamide has a low incidence of acute toxicity but also causes myeloid suppression. Low-dose alkylating agents can reduce organomegaly, reverse marrow fibrosis and improve blood counts but only occasionally has durable effects.

No chemotherapeutic agent has averted MPN disease progression, myelofibrosis or thrombosis. The only potentially curative treatment, haematopoietic stem cell transplantation (HSCT), has been employed more sparingly in the era of ruxolitinib though this trend is reversing as it becomes more widely appreciated that ruxolitinib is not curative nor does it decrease the risk of leukaemic transformation. The use of reduced intensity conditioning has reduced treatment-related mortality and enhanced overall survival at five-years from 47% with earlier regimens to 67% with one-year non-relapse mortality at 15-20%. (Guardiola *et al.,* 1999; Kroger *et al*., 2009; Gupta, Hari and Hoffman, 2012).

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 a collection 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 a 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 changes in 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 come from restoring the pattern of gene expression characteristic of differentiating myeloid progenitor cells.

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 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 haematopoietic stem cells (HSCs) and progenitor cells (Sprussel *et al.*, 2012). An inducible *LSD1* KD resulted in profound but reversible thrombocytopenia, neutropenia and anaemia; monocyte numbers were increased. *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 ESC is phenomenologically similar to the essential role LSD1 plays during myeloid haematopoiesis, 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 Myelofibrosis

Over-expression of *LSD1* messenger RNA (mRNA) and excess LSD1 protein have been observed in many tumour types, including poorly-differentiated neuroblastoma, squamous cell carcinoma, Ewing's sarcoma, AML, neuroendocrine carcinomas and epithelial tumours 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 MPN, 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 tumour types in culture with LSD1 inhibitors (LSDi) has been reported to inhibit tumour 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 leukaemia, treatment with LSD1 inhibitors induced monocytic markers of differentiation, reduced clonogenic potential of leukaemia 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 substrates for LSD1 (Yang *et al*., 2010).

Proof-of-concept studies were performed in well established, pre-clinical mouse models of PMF. Compared to mice treated with vehicle, LSD1 inhibition (LSDi) in transplanted 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 haematopoiesis (EMH). Most notably, there was near-complete resolution of reticulin fibrosis in the bone marrow in the LSDi treatment arm. This effect is not observed in this model when treating with ruxolitinib. LSD1 inhibition had a significant impact on serum inflammatory cytokine concentrations. The anti-cytokine effects of JAK1/2 inhibition by ruxolitinib was more modest compared to what was achieved with LSDi, as exemplified by a very marked reduction in the plasma concentration of the Chemokine (C-X-C Motif) Ligand 5 (CXCL5), a key participant in the pathologic inflammatory state of MPN.

LSD1 inhibition also reduced the mutant allele burden to a degree not seen with JAK1/2 inhibitor therapy. 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. This effect is not observed in this model when treating with ruxolitinib. 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.

3.4 Background on IMG-7289

IMG-7289 is an orally available, irreversible inhibitor of LSD1, active against LSD1 and human AML cells at concentrations of <5 nM. Irreversible inhibitors of LSD1 include tranylcypromine (TCP) which has been used for the treatment of depression for decades. The targets of TCP therapy, however, include all FAD-dependent monoamine oxidases (MAOs) in addition to LSD1. TCP inactivates LSD1 in a manner identical to its action on MAO-A and MAO-B because these three enzymes share a similar oxidative chemistry. CCI

[redacted]

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

The treatment effects with an LSD1 inhibitor (LSDi) are anticipated to be distinct from treatment with standard cytotoxic agents or with Janus Kinase (JAK) inhibitors. LSD1 inhibition has specific effects on all myeloid lineages. LSD1 activity is needed for the differentiation of progenitors to red cells, platelets and granulocytes. [redacted]. Hence, LSD1 inhibition changes the composition in the marrow and the periphery of cells from these four lineages, [redacted]

The morphologic and clinical pathology changes may not be familiar to clinicians and haematopathologists. As such, there is potential for confusion in the interpretation of peripheral haematologic parameters and the morphology of bone marrow cells. Outlined below are some of the anticipated clinical scenarios that might be observed in MF 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:

[redacted]

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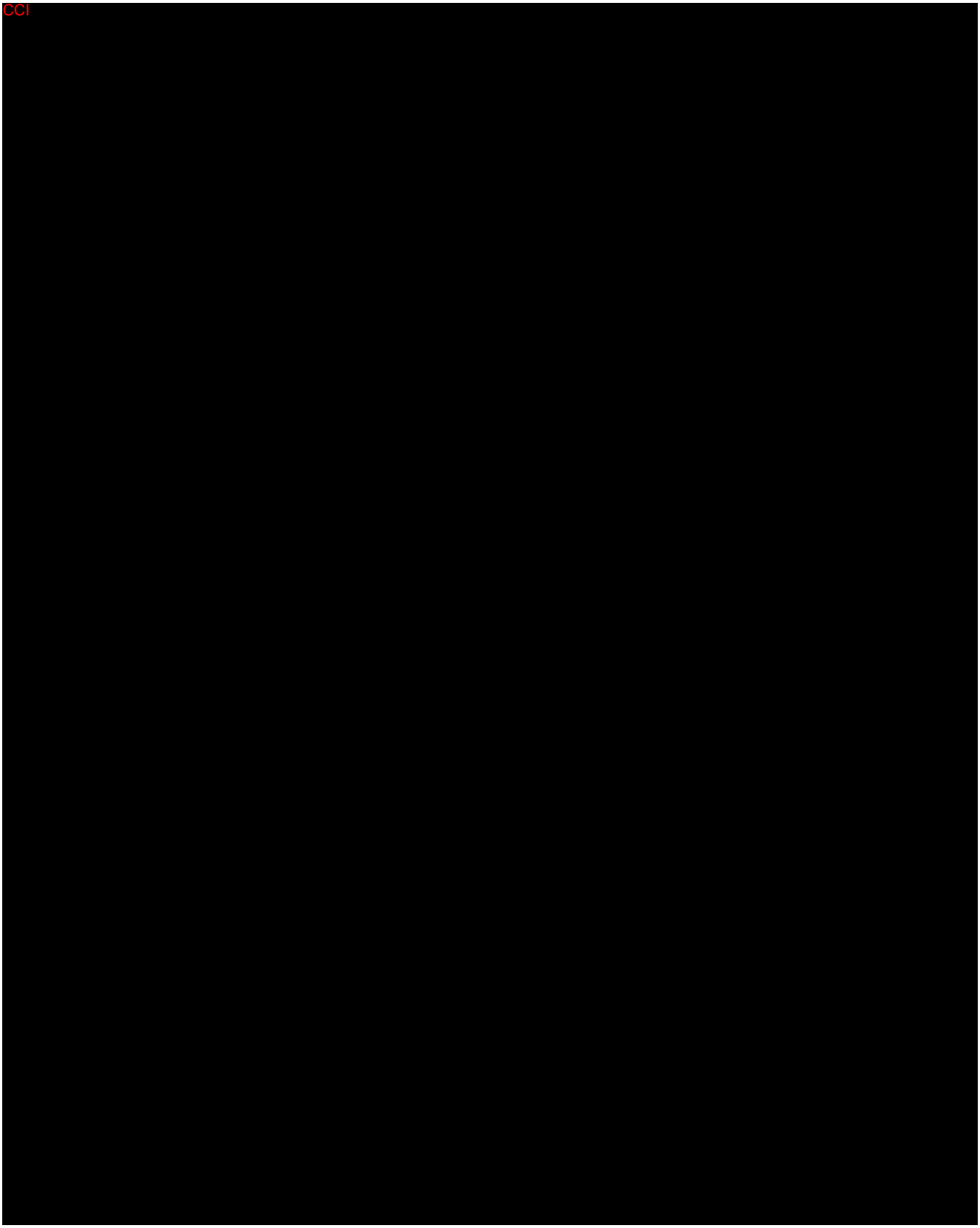

Please refer to the Investigator's Brochure, Section 6.3 for Reference Safety Information.

3.6 IMG-7289 Dose Justification

A summary of the starting dose and dosing schedule are provided below. Further information, including additional relevant data, can be found in the Investigator's Brochure.

3.6.1 Rationale for and Safety of the Proposed IMG-7289 Starting Dose

The initial scientific goals of the study were to determine the pharmacokinetic parameters of IMG-7289 in MF patients, and to establish the safety of dose-titration based on a weekly haematology evaluation and the impact of inhibiting LSD1 for a fraction of the dosing cycle (24 hours). Inhibition of LSD1 *in vitro* and in non-clinical models of AML (Harris *et al.*, 2012) induces monocytic differentiation of malignant myeloid cells, reduces their self-renewal potential, inhibits their growth and induces cell death. In mouse models of MF, the percentage of mutant cells is also reduced following treatment with IMG-7289.

LSD1 activity is essential for normal myeloid maturation; loss of >90% LSD1 activity in mice is associated with an arrest in the differentiation of myeloid progenitors and hence maturation of megakaryocytes, erythrocytes and granulocytes (Sprussel *et al.*, 2012). The production of monocytes, however, does not require LSD1 activity. Consistent with the respective lifespan of platelets, granulocytes and red cells, complete LSD1 inhibition leads to thrombocytopenia, neutropenia and anaemia with the reduced number of platelets being the first evident effect. Independent of lifespan, for a given exposure, production of platelets appears more sensitive to the inhibition of LSD1 than is production of granulocytes or red cells.

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The starting dose was 0.75 mg/kg/d and the effective dose, at which no safety signals have been observed, was deemed to be 6.0 mg/kg/d. Though the great majority of the patients entered the study with Grade 3/4 thrombocytopenia, patients at all dose levels of IMG-7289 required platelet transfusions. This sensitivity of thrombopoiesis to LSD1 inhibition in high-risk AML/MDS patients reflects the generally compromised nature of the bone marrow, including the reduction of megakaryocytes in that disease.

The therapeutic goal for the treatment of myeloproliferative neoplasms is to inhibit the activity of LSD1 in haematopoietic cells, particularly megakaryocytes, for only a *fraction* of the 24-hour dosing

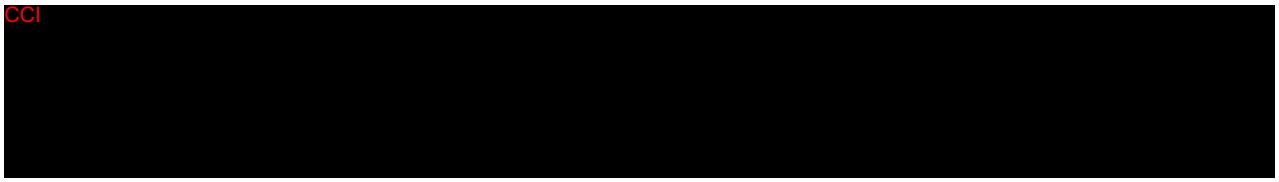
cycle, sufficient to reduce platelets to a safe level while inhibiting to the greatest extent possible the production, by megakaryocytes, of cytokines and growth factors that drive bone marrow fibrogenesis and symptoms. Taking this thesis, the toxicology observations, and the PK studies into account, a starting dose (D_s) of 0.25 mg/kg/d was selected for the Phase 1/2a portion of this study. This dose was expected to be safe, but sub-therapeutic, that is, a dose insufficient to reduce the platelet count to the target range (NB: range was 100-200 thousand (k) platelets per microliter (k/μL; 100 x 10^9/L) in original protocol). A dose-response curve was subsequently generated that provided a titration algorithm to adjust dose to achieve the modified target platelet count of between 50-75 k/μL (50-75 x 10^9/L), devised with a view to minimizing the probability of severe thrombocytopenia. Based on the patients treated up to that time, the dose sufficient to achieve a platelet count in the target range of 50-75 k/μL (50-75 x 10^9/L) CCI [redacted] a new IMG-7289 starting dose of 0.5 mg/kg QD was selected with Protocol Amendment 4. With the continued observation of additional patients treated, the estimated optimal dose for most ranges between 0.6 and 0.8 mg/kg/d. Thus, a new starting dose of 0.6 mg/kg/d has been chosen, one that is at least 75% of the estimated optimal dose for the majority of patients. Starting therapy at a dose closer to the optimal dose should accelerate the process of symptom and spleen volume reduction.

Dose escalation or de-escalation may occur as per the rules detailed in Section 7.2.3, contingent on study Day and based on the impact of LSDi on platelet, ANC and Hgb counts. Observations regarding dose-response have led to modifications of the titration schedule. As additional patients have been treated, it has been noted that for a given daily dose, the time needed to reach a stable platelet count is between 3 and 4 weeks. CCI [redacted], following the first dose, no up-titrations may be made until ITP Day 28, and thereafter, no more frequently than every three weeks. Prolonging the time to first up-titration from ITP Day 14 to ITP Day 28 also minimizes the risk of severe thrombocytopenia for the few patients who may require less than 0.6 mg/kg/d. In conjunction with the increased starting dose and the longer intervals between up-titrations, the incremental dose titrations have been decreased. By allowing 21 days for equilibration of the platelet count to a *new* dose, combined with smaller dose titrations, it is expected patients will be subject to fewer fluctuations in both dose and platelet counts. This is also expected to provide more consistent exposure to drug with the effect of enhancing the clinical benefits.

In summary, *per* the dosing changes undertaken with this amendment, in association with the increased starting dose of 0.6 mg/kg/d, CCI [redacted] while **down-titrations** can be made at any time in the best interests of the patient. Titration and re-challenge rules specific to ITP Days 7, 14 and 21 have been generated to instruct whether patient doses should be maintained or down-titrated (**Table 2**), with a second set of rules specific to ITP Day 28 and onward (**Table 3**).

3.6.2 Rationale for the IMG-7289 Dosing Schedule

The phenotypic effects of LSD1 inhibition are mediated through changes in the gene expression patterns that are a consequence of transcriptional reprogramming that occurs in the absence of LSD1 activity (Harris *et al*., 2012). The phenotypic consequences are cell-specific, include differentiation and, ultimately, cell death. In the primary pharmacology studies with IMG-7289, these changes take place over a period of days to weeks; in the assay for self-renewal potential (clonogenicity), these changes take days or weeks to observe. Complete and sustained inhibition of LSD1 may be the best strategy to rapidly reduce the leukaemic stem cell burden in the case of AML; however, in a less aggressive myeloid neoplasm such as myelofibrosis, that has characteristics more similar to a paraneoplastic condition, chronic treatment at doses that do not completely inhibit LSD1 is anticipated to be well tolerated while having a significant impact on disease. At these doses in mouse MF models, the gradual loss of cells bearing the MPN mutation (*Jak2* or *Mpl*) is observed over the course of LSD1 inhibition. What emerges from these mouse studies is a strategy that balances safety with clinical efficacy: inhibit the enzyme for only a fraction of the 24-hour dosing cycle to allow some normal haematopoiesis to occur, thus preventing profound thrombocytopenia. This therapeutic dose must be identified in each patient because variations in the severity of disease will dictate the starting platelet count and sensitivity to drug.



At the doses proposed in this study, the concentration of IMG-7289 is sufficient to inhibit haematopoiesis for a fraction of the 24-hour dosing period allowing LSD1 activity to return and resume its function in normal haematopoiesis. Chronic daily administration of IMG-7289 in rat, dog and humans has been well tolerated. No safety signals have been observed in either the AML/MDS or myelofibrosis studies with IMG-7289 at doses up to CCI

4 HYPOTHESIS AND OBJECTIVES

4.1 Hypothesis

IMG-7289 is a safe and tolerable orally available agent when administered to patients with myelofibrosis including primary myelofibrosis (PMF), post-polycythaemia vera-myelofibrosis (PPV-MF), and post-essential thrombocythaemia-myelofibrosis (PET-MF) (collectively referred to as 'MF'); inhibition of lysine-specific demethylase 1 (LSD1) by IMG-7289 will reduce spleen size in those with splenomegaly, improve haematopoiesis and reduce constitutional symptoms associated with these disorders.

4.2 Objectives

The following primary and exploratory objectives will be evaluated in patients with myelofibrosis including primary myelofibrosis (PMF), post-polycythaemia vera-myelofibrosis (PPV-MF), and post-essential thrombocythaemia-myelofibrosis (PET-MF) (collectively referred to as 'MF').

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*Haematologic parameters, all of which may be assessed during treatment or after drug has been discontinued

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5 INVESTIGATIONAL PLAN

5.1 Overview

This is a multi-center, open-label study evaluating the safety, tolerability, steady-state pharmacokinetics and pharmacodynamics of IMG-7289 administered orally once daily in patients with myelofibrosis (MF).

The therapeutic goal for the treatment of MF is to inhibit the activity of LSD1 in haematopoietic cells for only a *fraction* of the 24-hour dosing cycle, sufficient to reduce platelets to a safe level while inhibiting to the greatest extent possible the production, by megakaryocytes, of cytokines and growth factors that drive bone marrow fibrogenesis and symptoms. Considerations for a safe and therapeutic starting dose included chronic toxicology studies, in conjunction with the clinical experience of the patients who have received IMG-7289 to date in both IMG-7289-CTP-101 and -102. In the CTP-101 study, IMG-7289 was administered to patients with high-risk AML and MDS; the therapeutic thesis was to completely inhibit LSD1 in all haematopoietic cells, targeting both leukaemic stem cells and blasts, recognizing that patients would need clinical support for

cytopenias. The starting dose was 0.75 mg/kg/d and the effective dose, at which no safety signals have been observed, was deemed 6.0 mg/kg/d. Though the great majority of the patients entered the study with Grade 3/4 thrombocytopenia, patients at all dose levels of IMG-7289 required platelet transfusions. This sensitivity of thrombopoiesis to LSD1 inhibition in high-risk AML/MDS patients reflects the generally compromised nature of the bone marrow including the reduction of megakaryocytes, in that disease.

Taking this observation into account in association with the therapeutic goal for the treatment of myeloproliferative neoplasms – inhibiting LSD1 activity in haematopoietic cells for only a fraction of the 24-hour dosing cycle – and PK modeling, a starting dose (D_s) of 0.25 mg/kg/d was selected for the Phase 1/2a portion of this study. This dose was expected to be safe, but sub-therapeutic, that is, a dose insufficient to reduce the platelet count to the target range (NB: range was 100-200 thousand platelets per microliter (k/µL; 100-200 x 10^9/L) in original protocol). A dose-response curve was subsequently generated that provided a titration algorithm to adjust dose to achieve the modified target platelet count of between 50-75 k/µL (50-75 x 10^9/L), devised with a view to minimizing the probability of severe thrombocytopenia. CCI [redacted] Based on the patients treated up to that time, the dose sufficient to achieve a platelet count in the target range of 50-75 k/µL (50-75 x 10^9/L) was expected to range from between 0.5 to 2.0 mg/kg. The mean efficacious dose, that dose needed to achieve the target platelet count, was 0.81 mg/kg (range 0.5 to 1.9 mg/kg); the mean maximum dose administered was 0.86 mg/kg. Accordingly, to enable patients to more quickly reach the optimum dose while still maintaining an adequate safety margin, a new IMG-7289 starting dose of 0.5 mg/kg QD was selected for protocol Amendment 4. With the continued observation of additional patients treated, the estimated optimal dose for most ranges between 0.6 and 0.8 mg/kg/d. Thus, a new starting dose of 0.6 mg/kg/d has been chosen, one that is at least 75% of the estimated optimal dose for the majority of patients. Starting therapy at a dose closer to the optimal dose should accelerate the process of symptom and spleen volume reduction. Additional detail for the rationale on the dose and dose schedule can be found in Section 3.6.

To ensure patient safety, a Data Safety Monitoring Committee (DSMC)/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. Two sentinel patients were dosed sequentially at the original D_s of 0.25 mg/kg/d for 7 days and monitored twice-weekly before any additional patients were treated. The DSMC/SAB convened within 4 days post-completion of 7 days of treatment for each of the sentinel patients and determined it was safe for:

1. Each sentinel patient to continue dosing, and
2. Additional patients to begin treatment with IMG-7289.

Additionally, the DSMC/SAB convened post-completion of 7 days of treatment of the required three patients at the new D_s and determined:

1. The safety of the new D_s, and
2. The ITP Day 3 (mid-week) visit could be removed from the visit schedule.

This study initiated as a Phase 1/2a study, assessing the safety of the starting dose, an 85 day duration of treatment, and the pharmacokinetic and pharmacodynamic effects of IMG-7289, with transition to a Phase 2b study including implementation of changes supported by the Phase 1/2a data. This study consists of two treatment periods: The Initial Treatment Period (ITP), followed by the Additional Treatment Period (ATP). Patients are now enrolling in the Phase 2b portion of the study, in which patients are treated daily for 169 days in the ITP. 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 Section 16.7 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 14 days post last dose, and an End-of-Study (EoS) visit approximately 28 days post last dose. Patients that do not enter the ATP, or discontinue early, will undergo follow-up, beginning with an EoT visit.

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 and by peripheral blood and urine analyses. Pharmacodynamic effects will be closely monitored by frequent haematology 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 (ITP)

Through the use of dose titration, all patients will be dosed to the D_{pi} of IMG-7289. The D_{pi} is anticipated to be ≤ 2 mg/kg QD; however, this is not the upper limit for titration purposes as the dose needed to achieve a therapeutic effect will vary among patients and may change over time. The platelet titration target expected to be associated with a clinically significant therapeutic effect is:

- A platelet count of ≥ 50 to ≤ 75 k/µL (50-75 x 10^9/L)

Additional details pertaining to dosing are located in Section 7.2.3.

During the ITP, patients will return to the clinic for study assessments weekly for 8 weeks (ITP Days 7, 14, 21, 28, 35, 42, 49 and 56), at least bi-weekly for 8 weeks (ITP Days 70, 84, 98 and 112) and then monthly for 8 weeks (ITP Days 140 and 168). It is anticipated that by Week 8 (Day 56) patients will have achieved a stable dose, with weekly visits no longer necessary. For the exceptional patient whose dose has not stabilized, weekly visits may continue at the PI's discretion (note: bi-weekly visits may also continue post Day 112). On Days 84 and 168, patients will undergo abdominal MRI or CT (if the patient is not a candidate for MRI). On Day 168, bone marrow sampling is also required. Prior to or at the Day 168 visit, but ideally at the Day 140 visit for logistical purposes, a 'qualification' assessment will be made to determine whether the patient is deriving clinical benefit. Such patients qualify for entry into the ATP, a transition which should occur without interruption in dosing. Patients not deriving clinical benefit, or who achieve CR, PR or CI and subsequently relapse (Section 16.7), the equivalent of treatment failures, will discontinue IMG-7289 and undergo all necessary follow up visits.

Note: In Germany, use of computerised tomography (CT) is not permitted for patients unable to undergo magnetic resonance imaging (MRI). Only MRI is permitted for study purposes.

5.1.2 Additional Treatment Period (ATP) for Qualifying Patients Only

For the purposes of clarity and efficiency, rather than continuing to present chronological days/ weeks, visits are presented as 'ATP Day 0', followed by, 'ATP Days 28, 56, 84', etc. Qualifying patients will 're-start' IMG-7289 on ATP Day 0, with dose titration continuing as per the Titration Rules table (Section 7.2.3.2); there should be no interruption in dosing (Day 168 = Day 0 of the next ATP). Additional dose-titration may occur in consultation with the Medical Monitor.

During the ATP, qualifying patients will return to the clinic monthly for study assessments (ATP Days 0, 28, 56, 84, 112, 140 and 168). It is anticipated that patients continuing in the ATP will have already achieved a stable dose, with bi-weekly visits no longer necessary. For the exceptional patient whose dose has not stabilized, bi-weekly visits may continue at the PI's discretion. On Day 168, patients will undergo the same procedures and assessments as per ITP Day 168, including MRI or CT (if patient is not a candidate for MRI), and bone marrow sampling. Prior to or at the Day 168 visit, but ideally at the Day 140 visit for logistical purposes, a 'qualification' assessment will again be made to determine whether the patient is continuing to derive clinical benefit, thereby re-qualifying for continued treatment in the ATP. The ATP is iterative and may repeat (ATP1, ATP2, etc.), without interruption in dosing, as long as the patient continues to qualify.

Note: In Germany, use of computerised tomography (CT) is not permitted for patients unable to undergo magnetic resonance imaging (MRI). Only MRI is permitted for study purposes.

Patients not deriving clinical benefit, or who achieve CR, PR or CI and subsequently relapse (Section 16.7), the equivalent of treatment failures, 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 IMP, and withdrawal are not acceptable methods of contraception.

6.1.1 Inclusion Criteria

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

1. Willing and able to sign the approved informed consent.
2. Age: 18+ years old at Screening.
3. Diagnosis of either PMF per World Health Organization (WHO) diagnostic criteria for myeloproliferative neoplasms (Section 16.2), PPV-MF per the IWG-MRT (Section 16.3), or PET-MF per the IWG-MRT (Section 16.4) and meet the following additional subtype specific criteria:
    a. Classified as high risk (3 prognostic factors), intermediate risk-2 (2 prognostic factors) or intermediate risk-1 (1 prognostic factor). The prognostic factors, defined by the International Working Group (Cervantes, *et al*., 2009):
        i. Age > 65 years;
        ii. Presence of constitutional symptoms (weight loss, fever, night sweats);
        iii. Marked anaemia (Hgb < 10g/dL)*;
        iv. **History** of leukocytosis [WBC > 25 x10^9/L (25,000/µL)];
        v. Circulating blasts ≥ 1%.

    *A haemoglobin value < 10 g/dL must be demonstrated during Screening for patients who are not transfusion dependent. Patients receiving regular transfusions of packed red blood cells will be considered to have haemoglobin < 10 g/dL for the purpose of evaluation of risk factors.
4. Be refractory or resistant to, inadequately controlled by or intolerant of available approved therapy, or in the Investigator's judgment, are not candidates for available approved therapy (note: approved therapy includes ruxolitinib and, in the US, fedratinib).
5. Eastern Cooperative Oncology Group (ECOG) performance status score ≤2.
6. Peripheral blast count ≤10% prior to dosing on Day 0.
7. Absolute neutrophil count ≥ 0.5 x 10^9/L (500/µL) prior to dosing on Day 0.
8. Platelet count ≥ 100 x 10^9/L (100 k/µL) prior to dosing on Day 0.
9. Life expectancy >36 weeks.
10. Have discontinued all previous therapies for MPNs including ruxolitinib, any chemotherapeutic agents, immunosuppressive therapy (e.g., corticosteroids > 10 mg/day with the noted exception: use of corticosteroids for management of gout is allowed; maintenance supplemental corticosteroid therapy such as prednisone ≤ 10 mg/day or corticosteroid equivalent is allowed), immune modulators (e.g., thalidomide), radiotherapy for at least 2 weeks prior, and interferon for 4 weeks prior to study Day 0. Low dose acetylsalicyclic acid is permitted. Palliative radiation treatment to non-index or bone lesions performed < 2 weeks before treatment may be considered with Medical Monitor approval.
11. Amenable to bone marrow evaluation, peripheral blood and urine sampling during the study.
12. Able to swallow capsules.

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 28 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 as refraining from heterosexual intercourse). Patients practicing abstinence must agree to use an approved method of contraception should they become sexually active during the study.

Note: In the UK, males with a pregnant partner must agree to use a condom to avoid exposure to the developing child.

* 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 any of the following criteria:

1. Has undergone major surgery ≤4 weeks prior to starting study drug or has not recovered from side effects of such surgery.
2. Has undergone any surgical procedure within 2 weeks, excluding minor procedures (e.g., skin biopsy or central venous catheter placement/removal) prior to starting study drug.
3. History of splenectomy.
4. History of or scheduled haematopoietic stem-cell transplant within 24 weeks of screening.
5. Unresolved treatment related toxicities from prior therapies (unless resolved to ≤ Grade 1).
6. Current use of a prohibited medication (e.g., romiplostim) or expected to require any of these medications during treatment with the investigational drug.
7. 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.
8. Current use of monoamine oxidase A and B inhibitors (MAOIs).
9. Uncontrolled active infection.
10. 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).
11. Evidence at the time of Screening of risk of bleeding, including any of the following:
    a. Activated partial thromboplastin time (aPTT) ≥ 1.3 x the local upper limit of normal
    b. International normalized ratio (INR) ≥ 1.3 x the local upper limit of normal
    c. History of severe thrombocytopenia or platelet dysfunction unrelated to a myeloproliferative disorder or its treatment
    d. Known bleeding disorder (e.g., dysfibrinogenaemia, factor IX deficiency, haemophilia, Von Willebrand's disease, Disseminated Intravascular Coagulation [DIC], fibrinogen deficiency, or other clotting factor deficiency)

12. Evidence at the time of Screening of significant renal or hepatic insufficiency (unless due to haemolysis, or leukaemic infiltration) as defined by any of the following local lab parameters:
    a. 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
    b. Aspartate transaminase (AST) or alanine aminotransferase (ALT) ≥2 x the local upper limit of normal
13. Known human immunodeficiency virus (HIV) infection or known active Hepatitis B or Hepatitis C virus infection (testing will not be conducted as part of Screening procedures).

> **For** Italy ONLY, Exclusion 13 reads: Active infection with hepatitis 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).

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 0.
16. Females who are pregnant or breastfeeding or plan to become pregnant or breastfeed at any time during the study.

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 75 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 Conference 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. The reason for withdrawal, if given, will be provided to the Sponsor and documented in the eCRF. 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
- 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.

6.4 Replacement of Dropouts

A minimum of [redacted] patients are required to complete the entirety of the Initial Treatment Period (including MRI/CT). Non-completers may or may not be replaced as determined by the DSMC/SAB.

Note: In Germany, use of computerised tomography (CT) is not permitted for patients unable to undergo magnetic resonance imaging (MRI). Only MRI is permitted for study purposes.

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. Additionally:
   a. It is advised that patients with a platelet count ≤ 10 x 10^9/L (10 k/µL) be transfused.
2. Hydroxyurea may be used during the study in case of proliferation as follows:
   a. At the PI's discretion, initiate hydroxyurea treatment for white cell count ≥ 30 x 10^9/L (30,000/µL) and majority of cells appear to be immature cells (myelocytes/ promyelocytes)
   b. Discontinue hydroxyurea treatment when white cell count is < 10 x 10^9/L (10,000/µL)
3. Patients taking medications that have 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.
4. Cessation of IMG-7289 is invariably associated with a rebound in thrombopoiesis and the platelet count can easily exceed the baseline value in any given patient. When IMG-7289 is discontinued, the platelet count should be monitored closely and the timing of the start of an alternative therapy should take this into account.

6.6 Prohibited Medications

Please consult the Medical Monitor with any questions pertaining to prohibited medications.

1. All cytotoxic agents, with the exception of hydroxyurea
2. All haematopoietic growth factors: romiplostim, eltrombopag, granulocyte and granulocyte-macrophage colony stimulating factor (G-CSF and GM-CSF) and erythropoietin (EPO)
3. Prednisone and prednisolone > 10 mg/day (noted exception: use of corticosteroids for management of gout is allowed) and dexamethasone > 4 mg/day. Maintenance supplemental corticosteroid therapy such as prednisone ≤ 10 mg/day or corticosteroid equivalent is allowed.
4. Monoamine oxidase A and B inhibitors
5. Anticoagulant and nonsteroidal anti-inflammatory drug (NSAID; including aspirin) use are prohibited in patients when their platelet count is < 50 x 10^9/L (50 k/µL)

6.7 Patients Who Terminate Early or Discontinue Study Medication

All patients who terminate the study early, or who discontinue IMG-7289 will be requested to return for follow-up visits, beginning with an End of Treatment visit as detailed in Section 9.6.1. If a patient refuses to enter follow-up, then an Early Termination visit should be performed as detailed in Section

9.6.3. Patients who discontinue IMG-7289 due to a DLT will be asked to undergo the EoT, Pre-EoS and EoS visits.

6.8 Treatment Failure

MF patients not deriving clinical benefit (defined as not meeting progressive disease criteria as per Section 16.7 and safely tolerating IMG-7289), or who achieve complete response (CR), partial response (PR) or clinical improvement (CI) and subsequently relapse (Section 16.7), the equivalent of treatment failures, will discontinue IMG-7289 and undergo the EoT, pre-EoS and EoS visits.

7 STUDY TREATMENT

7.1 Formulation, Labeling, Packaging and Storage

7.1.1 Formulation

The drug product is IMG-7289, CCI [redacted] Details on capsules, including strengths, colours and sizes, can be found in the Pharmacy Manual.

The capsules will be manufactured in accordance with Annex 13 and principles of cGMP at:

Xcelience LLC
4910 Savarese Circle
Tampa, FL 33634 USA

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

7.1.2 Packaging and Labeling

IMG-7289 will be supplied to the site pharmacy department by Imago BioSciences (or designee) in bottles containing capsules in accordance with all applicable regulatory requirements.

Labels will also be in accordance with all applicable regulatory requirements for the labeling of active pharmaceutical ingredients and with Annex 13 of GMP. Labels will contain the drug name, protocol number, lot number, expiry date, storage conditions, name of the local Sponsor and a caution that the drug is for clinical trials use only.

7.1.3 Storage

The recommended long-term storage conditions for IMG-7289 is for the storage temperature not to exceed 25°C. IMG-7289 must be stored in a secure area with access limited to the Investigator and authorized staff and under the physical conditions that are consistent with IMG-7289-specific requirements. IMG-7289 supplies will be stored securely under the appropriate conditions according to the country, state and regional laws. Procedures for IMG-7289 storage and accountability will be detailed in a pharmacy manual.

7.2 Dispensing, Administration, Dosage and Missed Doses

7.2.1 Dispensing

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

The Investigator is responsible for IMG-7289 accountability, reconciliation and record maintenance (Section 14.5). The Investigator must provide a prescription form every time drug is dispensed, including (but not limited to) the identification of the patient to whom drug is to be dispensed, the patient's weight, the requested dose in mg and the Investigator (or designee's) signature.

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 0, it is not required that IMG-7289 be taken in the clinic; this will be determined based on the patient's regular daily dosing time. When applicable, the date and time of each administration in the clinic will be recorded in the source notes.

IMG-7289 dosing will be based on the patient's ITP Day 0 weight. If during the study the patient's weight differs from ITP Day 0 by more than 10%, the amount of IMG-7289 dispensed should be corrected per the dose chart provided. In cases where using the ITP Day 0 weight is impractical for dispensing, a weight taken as close to ITP Day 0 as possible (e.g., Screening/Baseline) may be used; weight at a current visit may also occasionally need to be used. The source data must clearly document the weight used.

Patients should be instructed to:

- Take their IMG-7289 once daily, CCI [redacted]
- Swallow their IMG-7289 capsules whole, with a glass of water
- Take IMG-7289 on an empty stomach (fast for 1 hour prior to and 30 minutes after dose)

Patients may have clear liquids prior to their dose, and following study drug administration.

7.2.3 Dosage: Initial Treatment Period

In the ITP, all patients will be treated daily, for 169 days. Dosing will begin on Day 0 at a starting dose of IMG-7289 free base contingent on the protocol version the patient enrolled under. 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, all patients will be dosed to the IMG-7289 D_{pi}; the dose needed to safely inhibit normal haematopoiesis for a *fraction* of the dosing cycle. At every visit, a haematology assessment will be performed for use in association with the Titration and Re-challenge Rules which are based on an evaluation of platelet, absolute neutrophil (ANC) and haemoglobin (Hgb) counts in comparison with results from the prior visit. Please refer to Section 7.2.3.1 for patients currently being treated under Amendment 5, and Section 7.2.3.2 for Amendment 6 details.

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

- A platelet count of ≥ 50 to ≤ 75 k/μL (50-75 x 10^9/L)

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 haematologic parameters.

CCI

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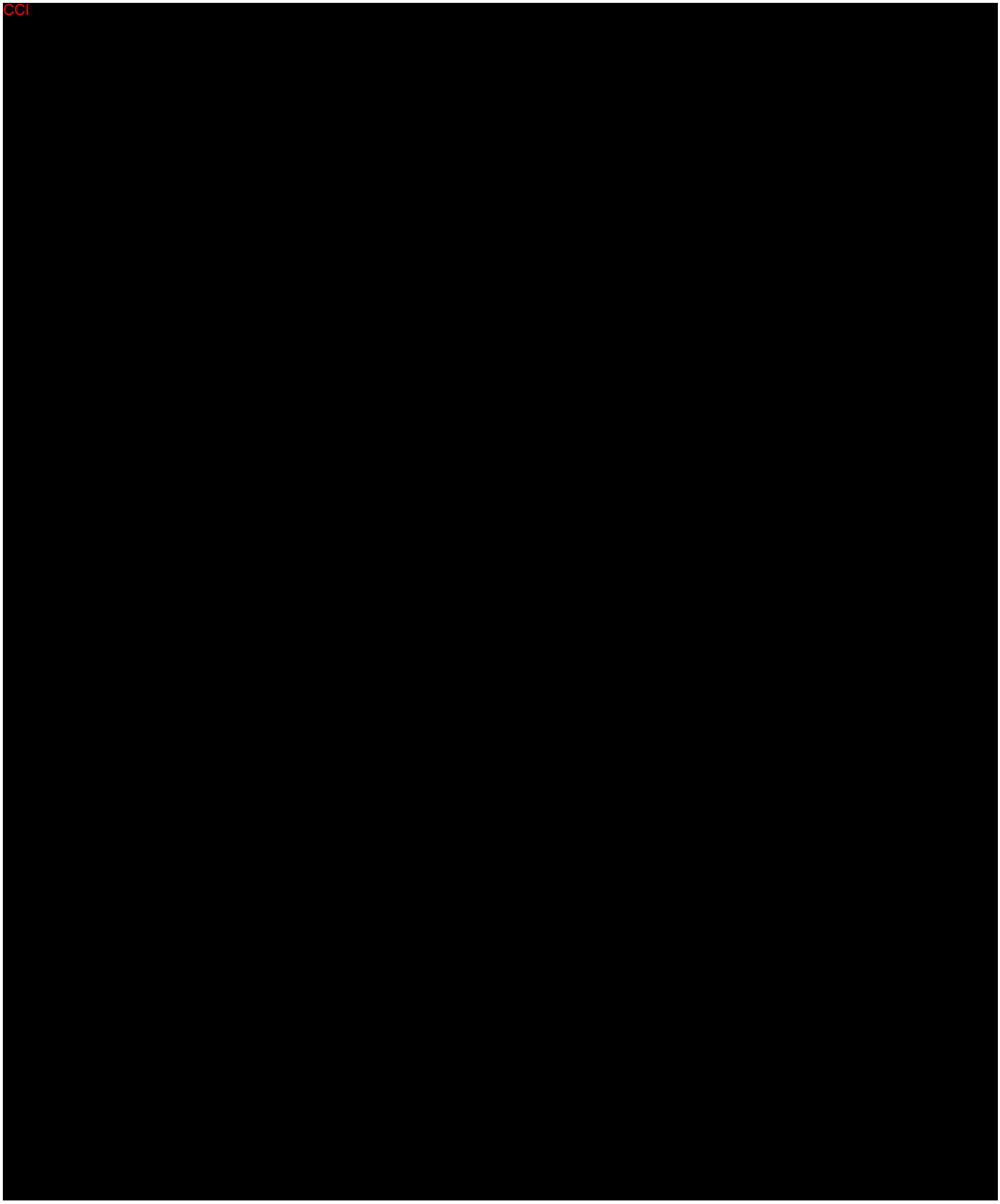

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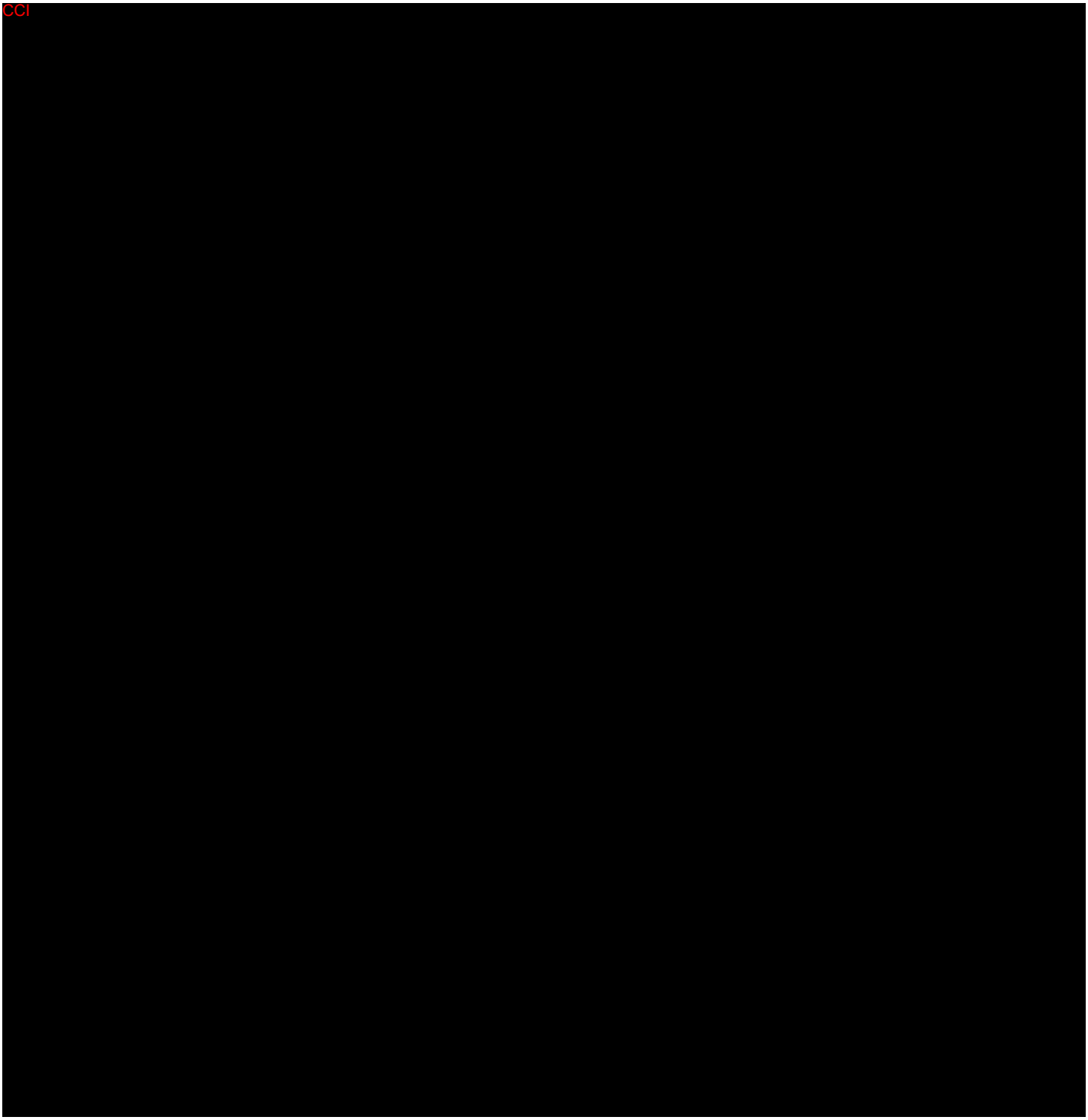

CCI purposes and to enable re-challenge to commence as soon as counts return to the required level, if safe to do so.

CCI

7.2.4 Dosage: Additional Treatment Period

For all patients entering a new Additional Treatment Period, dose titration will be per the Titration Rules in **Table 3**. Additional dose-titration may occur in consultation with the Medical Monitor.

7.2.5 Missed Doses

Patients who do not take their IMG-7289 dose at the usual required time should take it immediately upon noting that it was not taken; the patient should not take the dose more than 12 hours after the usual dosing time. If a patient misses a dose, they should not take two doses the following day, but should notify their study coordinator and continue with their normal daily dose the following day. For a dosing hiatus due to an SAE, please consult the Medical Monitor for guidance on re-start of dosing. Patients who miss an extended duration of IMG-7289 doses or exhibit serial non-compliance with treatment may be removed from the study at the discretion of the Sponsor.

7.2.6 Interruption of Dosing

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

8 DATA SAFETY MONITORING COMMITTEE (DSMC)/SAFETY ADVISORY BOARD (SAB) REVIEWS AND MANAGEMENT OF STUDY TOXICITIES, INCLUDING STOPPING RULES

8.1 Data Safety Monitoring Committee (DSMC)/Safety Advisory Board Reviews

Safety will be monitored throughout the study in accordance with a Data Safety Monitoring Plan (DSMP)/Safety Advisory Board Plan (SABP) by a DSMC/SAB constituted by, at a minimum: the Imago BioSciences Principal Medical Monitor, the Coordinating/Lead Principal Investigator and an Independent designee, an AML clinical trials specialist with extensive clinical experience. The DSMC/SAB will provide recommendations regarding the conduct of the study and guidance to Investigators to ensure the safety and well-being of all participating patients. To do so, the DSMC/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. DSMC responsibilities will remain in effect until the study has ended.

The DSMC/SAB will also review patient dose titrations and may recommend adjustments. At the original D_s, data from the first sentinel patient was reviewed by the DSMC/SAB prior to dosing the next sentinel patient. The DSMC/SAB convened within 4 days post-completion of 7 days of treatment for each of the sentinel patients at the original D_s and determined it was safe for:

1. Each sentinel patient to continue dosing, and
2. Additional patients to begin treatment with IMG-7289.

Additionally, the DSMC/SAB convened post-completion of 7 days of treatment of the required three patients at the new D_s and determined:

1. The safety of the new D_s, and
2. The ITP Day 3 (mid-week) visit could be removed from the visit schedule.

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 4.03, published 14 June 2010.

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 studies are reported in the latest available edition of the Investigator's Brochure.

8.2.1 Haematologic Toxicity

Haematologic values outside of the normal reference range are inherent features of MPNs, and are expected effects of many therapeutic attempts to manage these diseases.

Both genetic knockdown (KD) of LSD1 mRNA and pharmacologic inhibition of LSD1 show that the loss of LSD1 activity arrests the production of mature red cells, platelets and granulocytes while over-producing monocytes (Sprussel *et al.*, 2012; Kerenyi *et al.*, 2013). Production of cells of lymphoid lineage, B and T cells is unimpaired indicating that LSD1 has very cell-specific functions and its inhibition also has very specific effects. LSD1 inhibition in malignant myeloid cells causes the induction of monocytic differentiation markers, as well as a reduction of self-renewal potential of neoplastic cells, all of which eventually result in apoptosis of treated cells. Thus, the anaemia, thrombocytopenia, neutropenia and monocytosis attending LSD1 inhibition, as observed in animals treated with IMG-7289, reflect primary pharmacodynamic effects. The kinetics of anaemia, thrombocytopenia, and neutropenia following complete LSD1 inhibition are a function of the lifespan of the individually affected cell types. Over the course of LSD1 inhibition, platelet and neutrophil counts are the most affected, reflecting their short mean lifespans of approximately seven and twelve days, respectively. Recovery of peripheral counts is reversible, rapid, and temporarily overshoots baseline haematologic values. At lower doses, the effects on haematopoiesis are much less pronounced suggesting that a modicum of residual LSD1 activity is sufficient to support blood cell formation. Thus, both the duration of LSD1 inhibition as well as the degree of inhibition are critical to the pharmacodynamic effects on myeloid lineages.

The intended dosing plan for MF patients is predicated on the observation that inhibition of LSD1 has a therapeutic effect when LSD1 is inhibited for a *fraction* of the 24 hour dosing cycle, sufficient to reduce platelets to a safe level while inhibiting to the greatest extent possible the production, by megakaryocytes, of cytokines and growth factors that drive bone marrow fibrogenesis and symptoms. The concentrations of IMG-7289 needed to achieve maximal effects on growth, differentiation and apoptosis *in vitro* with primary patient-derived malignant myeloid cells as well as *JAK2*^{V617F} cell lines are similar to concentrations that *in vivo* inhibit red cell, platelet and granulocyte production. It is therefore expected that MF patients will require treatment at doses sufficient to reduce platelet counts and, to a lesser degree, absolute neutrophil counts. These reversible cytopenias can be managed clinically as needed with transfusions as well as broad-spectrum antibiotics in the case of febrile neutropenia, as are already standard practices in the routine management of malignant myeloid diseases.

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

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8.2.3 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 25 x 10^9/L (25 k/µL), the patient's platelet counts don't return to > 50 x 10^9/L (50 k/µL) within 21 days.

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

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9 STUDY ASSESSMENTS

This section provides comprehensive detail on the visits and assessments required; this section should serve as the main guidance for use during study visits. The Schedule of Assessments (Section 16.1) contains these details in schematic form, and is provided for use in a supportive/reference capacity only. In an effort to maintain clarity while facilitating a modicum of brevity, the 'Terms' in **Table 4** below will be utilized in this section to encompass the broader 'Protocol Meaning' as stated.

Table 4: List of Protocol Terms and Meanings

Term	Protocol Meaning

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

Full Local Lab Assessment	Assessment consisting of the following test panels to be performed locally (see Section 10.1.1 for specific analytes required): • Haematology with manual differential • Coagulation • Biochemistry • Urine or serum pregnancy test for women of child bearing potential (WOCBP); results to be reviewed prior to dosing, if applicable
Collect MPN-SAF TSS	MPN-SAF TSS is to be completed by the patient in their native language and in the format provided. The 24-HOUR RECALL tool will be completed daily for the 7 days preceding first dose (Days -6 to pre-dose Day 0) during Baseline. The 7-DAY RECALL tool will be completed weekly from Day 7 through the EoS Visit. Ideally, the 7-DAY RECALL version will be completed on the same time and day each week for consistency. On visit days, the MPN-SAF TSS should be completed prior to the study visit, and if the patient arrives without a completed MPN-SAF TSS, then it will be completed during the visit and collected prior to the patient departing. Importantly, multiple MPN-SAF TSS forms will need to be provided to the patient for completion between visits as visit frequency decreases to less than weekly. Date of completion should be documented on each MPN-SAF TSS completed.

Term	Protocol Meaning
Bone Marrow Sampling	• Aspirate (sample taken from first pull, whenever possible, and no later than the second) and biopsy collected as per site standard procedure. • A central laboratory will perform morphology review, myelofibrosis grading and genomic analysis (See Section 10.1.2). • **Note:** Any results available from site routine work-up, including morphology, cytogenetics, other genetic interrogations will be collected for study purposes either *via* the eCRF or through collection of local reports.
Dosing Instructions	• Instruct patients to refer to their Dosing Card every day, for details on 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 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 Baseline and Enrollment

The Screening period is comprised by Screening and Baseline visits which may be performed on the same day; in this circumstance, the visit must be completed within 21 days before Day 0. If the patient screen fails, document the reason(s) in the source data and on the Screening & Enrollment log.

Adverse events (AEs) will be assessed at every visit. 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.

Note: In the UK, serious AEs (SAEs) will be recorded from time of consent through the EoS **or** until the Investigator and Imago BioSciences 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 PMF (Section 16.2), or IWG-MRT recommended criteria for PPV-MF (Section 16.3) or PET-MF (Section 16.4).
    - Risk determination, using the IWG prognostic factors
    - Calculate ECOG performance status (Section 16.6)
    - History of all treatments for their current disease (including clinical course with ruxolitinib and/or other MF therapy) or any previous oncologic conditions; including chemical, surgical and/or radiotherapeutic
    - All concomitant medication, in addition to any used in the 15 days prior to Screening
    - Transfusion history, including: each RBC transfusion received with approximate volume and total units transfused over the 6 month period prior to Screening

    Note: while on-study, any blood product transfusion received (RBC, platelets, etc.), with approximate volumes, and total units transfused will also be documented.
- Full PE, including Vital Signs – review of all body systems as indicated by signs/symptoms
- Height (without shoes)
- Full Local Laboratory Assessment

Note: In Italy, HIV, HBsAg, HBsAb, HBcAb and HCV testing must also be performed.

- Urinalysis

Note: If Screening/Baseline **are not** occurring on the same day, then please refer to Section 9.2.2. If Screening/Baseline **are** occurring on the same day, then the following are required at Screening:

- Germline sample(s) for Central Laboratory genomic analysis
- Blood samples for Central Laboratory genomic analysis*
- Bone Marrow Sampling*
- Schedule MRI or CT (if patient is not a candidate for MRI) for pre-dose Day 0 ± 2 days
- Provide patient with multiple copies of the MPN-SAF TSS **24-HOUR RECALL** tool and instruct patient to complete the questionnaire daily for 7 consecutive days beginning on Day -6 and ending pre-dose Day 0.

*If possible, bone marrow and blood sampling for genomic analysis should be performed on the same day.

9.2.2 Baseline Period (Days -21 to Day -1) and Enrollment

If Screening and Baseline visits are conducted on separate days, then the following are required at the Baseline visit:

- Limited PE, including vital signs
- Full Local Laboratory Assessment
- Urinalysis

- Germline sample(s) for Central Laboratory genomic analysis
- Blood samples for Central Laboratory genomic analysis*
- Provide patient with multiple copies of the MPN-SAF TSS **24-HOUR RECALL** tool and instruct patient to complete the questionnaire daily for 7 consecutive days beginning on Day -6 and ending pre-dose Day 0
- Bone Marrow Sampling*
- Schedule MRI or CT (if patient is not a candidate for MRI) for pre-dose Day 0 (± 2 days)

Note: In Germany, use of computerised tomography (CT) is not permitted for patients unable to undergo magnetic resonance imaging (MRI). Only MRI is permitted for study purposes.

*If possible, bone marrow and blood sampling for genomic analysis should be performed on the same day.

9.2.3 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/Baseline 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.

9.2.4 Last Day of Screening Period (Day -1)

On Day -1 the study coordinator will contact the patient and remind them to:

- Report to the clinic the following day at the agreed time
- Not eat for at least 1 hour prior to dosing as IMG-7289 is to be taken on an empty stomach

9.3 Initial Treatment Period (ITP)

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

9.3.1 ITP Day 0 – Treatment Start

9.3.1.1 ITP Pre-Dose Day 0

- Update medical/medication history with any changes since Screening
- Limited PE, including Vital Signs

- Collect the completed copies of the MPN-SAF TSS, and provide patient with the MPN-SAF TSS **7-DAY RECALL** tool for completion prior to arriving for, or at their Day 7 visit
- Full Local Laboratory Assessment
- Urinalysis

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- Perform abdominal MRI (or CT if the patient is not a candidate for MRI) within a ±2 day window
- Dispense doses sufficient until the next visit and provide Dosing Instructions
- Ensure patient continues to meet eligibility criteria prior to dosing

Note: In Germany, use of computerised tomography (CT) is not permitted for patients unable to undergo magnetic resonance imaging (MRI). Only MRI is permitted for study purposes.

9.3.1.2 ITP Dosing Day 0

- Administer Study Drug

9.3.1.3 ITP Post-Dose Day 0

- Patients should remain in clinic for at least 2 hours post first dose
- Query for Adverse Events, using non-directive questions (i.e., "How are you feeling")
- Schedule Day 7 clinic visit

9.3.2 ITP Weekly Visits - Days 7, 14, 21, 28, 35, 42, 49 and 56 (± 2 days)

- Limited PE, including Vital Signs
- Adverse Events and Concomitant Medications
- Collect MPN-SAF TSS and provide the MPN-SAF TSS **7-DAY RECALL** tool to patient for completion prior to arriving for, or at the next visit
- Pre-dose: Perform haematology assessment and determine if dose titration is required in accordance with:
  - **Amendment 6 patients:** Refer to Section 7.2.3.2, and utilize:
    - **Table 2** for Days 7, 14 and 21
    - **Table 3** for Day 28 and onward
  - **Continuing Amendment 5* patients:** Refer to Section 7.2.3.1, and utilize:
    - **Table 1**
- Pre-dose: Perform drug accountability and collect study medication
- Dispense doses sufficient until the next visit and provide Dosing Instructions
- Schedule next clinic visit

*Amendment 5 patients must complete the Initial Treatment Period and transition to Amendment 6 titration and re-challenge rules upon commencing the Additional Treatment Period.

9.3.2.1 ITP Days 7, 21, 35, 42 and 49 only

- Pre-dose: Blood sample for haematology

9.3.2.2 ITP Day 14 only

- Pre-dose: Blood sample for haematology
- Pre-dose: Blood sample for Central Laboratory cytokine analysis

9.3.2.3 ITP Day 28 only

- Pre-dose: Full Local Laboratory Assessment
- Pre-dose: Blood sample for Central Laboratory cytokine analysis

9.3.2.4 ITP Day 56 only

- Pre-dose: Full Local Laboratory Assessment
- Provide extra copies of the MPN-SAF TSS **7-DAY RECALL** tool to patient sufficient until the next visit (for completion during the 'off' week, Day 63 and prior to arriving for, or at the Day 70 visit)

9.3.3 ITP Bi-Weekly Visits - Days 70, 84, 98 and 112 (± 2 days)

Note: It is anticipated that by Week 8 patients will have achieved a stable dose, with weekly visits no longer necessary. For the exceptional patient whose dose has not stabilized, weekly visits may continue at the PI's discretion. For such patients, the following is required at each weekly visit:

- Pre-dose: Blood sample for haematology
- Pre-dose: Perform haematology assessment and determine if dose titration is required in accordance with:
  - **Amendment 6 patients:** Refer to Section 7.2.3.2, and utilize:
    - **Table 3**
  - **Continuing Amendment 5* patients:** Refer to Section 7.2.3.1, and utilize:
    - **Table 1**

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

- Limited PE, including Vital Signs
- Adverse Events and Concomitant Medications
- Collect MPN-SAF TSS and provide extra copies of the MPN-SAF TSS **7-DAY RECALL** tool to patient sufficient until the next visit (for completion during each 'off' week, i.e., Days 77, 91 and 105 and prior to arriving for, or at the next visit)
- Pre-dose: Perform haematology assessment and determine if dose titration is required in accordance with:
  - **Amendment 6 patients:** Refer to Section 7.2.3.2, and utilize:
    - **Table 3**
  - **Continuing Amendment 5* patients:** Refer to Section 7.2.3.1, and utilize:
    - **Table 1**

- Perform drug accountability and collect study medication
- Dispense doses sufficient until the next visit and provide Dosing Instructions
- Schedule next clinic visit

*Amendment 5 patients must complete the Initial Treatment Period and transition to Amendment 6 titration and re-challenge rules upon commencing the Additional Treatment Period.

9.3.3.1 ITP Days 70 and 98 only

- Pre-dose: Blood sample for haematology

9.3.3.2 ITP Day 84 only

- Pre-dose: Full Local Laboratory Assessment
- Pre-dose: Urinalysis
- Pre-dose: Blood sample for Central Laboratory genomics (all sites), cytokine (all sites), HbF and %F cell (US sites only) analysis
- Perform abdominal MRI (or CT if patient is not a candidate for MRI (±7 days))

Note: In Germany, use of computerised tomography (CT) is not permitted for patients unable to undergo magnetic resonance imaging (MRI). Only MRI is permitted for study purposes.

9.3.3.3 ITP Day 112 only

- Pre-dose: Full Local Laboratory Assessment
- Provide extra copies of the MPN-SAF TSS **7-DAY RECALL** tool to patient sufficient until the next visit (for completion during each 'off' week, i.e., Days 119, 126 and 133 and prior to arriving for, or at the next visit).

9.3.4 ITP Monthly Visits - Days 140 and 168 (± 3 days)

Note: It is anticipated that by Week 20 patients will have achieved a stable dose, with bi-weekly visits no longer necessary. For the exceptional patient whose dose has not stabilized, bi-weekly visits may continue at the PI's discretion. For such patients, the following is required at each bi-weekly visit:

- Pre-dose: Blood sample for haematology
- Pre-dose: Perform haematology assessment and determine if dose titration is required in accordance with:
  - **Amendment 6 patients:** Refer to Section 7.2.3.2, and utilize:
    - **Table 3**
  - **Continuing Amendment 5* patients:** Refer to Section 7.2.3.1, and utilize:
    - **Table 1**

All other patients will undergo the following at monthly visits:

- Limited PE, including Vital Signs
- Adverse Events and Concomitant Medications
- Collect MPN-SAF TSS and provide extra copies of the MPN-SAF TSS **7-DAY RECALL** tool to patient sufficient until the next visit (for completion during each "off" week, i.e., Days 147, 154 and 161 and prior to arriving for, or at the next visit)
- Pre-dose: Full Local Laboratory Assessment
- Pre-dose: Perform haematology assessment and determine if dose titration is required (necessary at Day 168 only if patient is continuing to ATP) in accordance with:
  - **Amendment 6 patients:** Refer to Section 7.2.3.2, and utilize:
    - **Table 3**
  - **Continuing Amendment 5* patients:** Refer to Section 7.2.3.1, and utilize:
    - **Table 1**
- Perform drug accountability and collect study medication
- Dispense doses sufficient until the next visit and provide Dosing Instructions (necessary at Day 168 only if patient is continuing to ATP)
- Schedule next clinic visit

*Amendment 5 patients must complete the Initial Treatment Period and transition to Amendment 6 titration and re-challenge rules upon commencing the Additional Treatment Period.

9.3.4.1 ITP Day 140 only

- Provide extra copies of the MPN-SAF TSS **7-DAY RECALL** tool to patient to patient sufficient until the next visit (for completion during each 'off' week, i.e., Days 147, 154 and 161 and prior to arriving for, or at the next visit)
- **Qualification:** Assess whether the patient is eligible for the ATP. If it is determined that the patient is deriving clinical benefit (defined as not meeting progressive disease criteria as per Section 16.7 and safely tolerating IMG-7289), then the patient qualifies for and may enter the ATP upon completion of the Day 168 visit . This qualification assessment is initiated at Day 140 for logistical purposes and may be reversed at the Day 168 visit in consideration of patient status at the time.

9.3.4.2 ITP Day 168 only

- Urinalysis
- Pre-dose: Blood sample for Central Laboratory genomics (all sites), cytokine (all sites), HbF and %F cell (US sites only) analysis
- Perform abdominal MRI (or CT if patient is not a candidate for MRI (±7 days))

Note: In Germany, use of computerised tomography (CT) is not permitted for patients unable to undergo magnetic resonance imaging (MRI). Only MRI is permitted for study purposes.

- Bone Marrow Sampling (±7 days to ensure availability of results for qualification assessment if required by the Investigator)
- **Qualification:** Confirm applicability of earlier determination regarding patient eligibility for continued treatment in the ATP, contingent on whether the patient is deriving clinical benefit. If the patient is entering the ATP, please proceed to Section 9.4 below. If the patient is not entering the Additional Treatment Period, please proceed to Section 9.6 below.

9.4 Additional Treatment Period (ATP)

Those patients deriving clinical benefit (defined as not meeting progressive disease criteria as per Section 16.7 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 0', followed by, 'ATP Days 28, 56, 84,' 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 0 assessments may be performed on the same day as Day 168 of the prior treatment period.

For patients enrolled under Amendment 5 that have re-consented to Amendment 6, please note that when commencing their next ATP the Amendment 6 dose titration rules (**Table 3**) will be followed; until such transition, the Amendment 5 dose titration rules (**Table 1**) will be followed.

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

9.4.1 ATP Day 0 - Treatment 'Re-start'

9.4.1.1 Day 0

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

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

- Verify patient meets the criteria for additional treatment
- Limited PE, including Vital Signs
- Adverse Events and Concomitant Medication
- Collect MPN-SAF TSS and provide extra copies of the MPN-SAF TSS **7-DAY RECALL** tool to patient sufficient until the next visit (for completion during each 'off' week, i.e., Days 7, 14 and 21 and prior to arriving for, or at the next visit)
- Pre-dose: Full Local Laboratory Assessment
- Urinalysis
- Pre-dose: Perform haematology assessment and determine if dose titration is required according to **Table 3** in Section 7.2.3.2*

- Dispense doses sufficient until the next visit and provide Dosing Instructions
- Administer Study Drug, if appropriate, based on patient's routine dosing time
- Schedule next clinic visit

*Amendment 5 patients starting a new ATP Day 0 after re-consenting to Protocol Amendment 6 will be treated under Amendment 6 titration and re-challenge rules.

9.4.2 ATP Days 28, 56, 84, 112, 140 and 168 (±4 days)

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

- Pre-dose: Blood sample for haematology
- Pre-dose: Perform haematology assessment and determine if dose titration is required in accordance with:
  - **Amendment 6 patients:** Refer to Section 7.2.3.2, and utilize:
    - **Table 3**
  - **Continuing Amendment 5* patients:** Refer to Section 7.2.3.1, and utilize:
    - **Table 1**

All other patients will undergo the following at monthly visits.

- Limited PE, including Vital Signs
- Adverse Events and Concomitant Medications
- Collect MPN-SAF TSS and provide extra copies of the MPN-SAF TSS **7-DAY RECALL** tool to patient sufficient until the next visit (for completion during each 'off' week, i.e., Days 35, 42, 49, etc. and prior to arriving for, or at the next visit)
- Pre-dose: Full Local Laboratory Assessment
- Pre-dose: Perform haematology assessment and determine if dose titration is required (necessary at Day 168 only if patient is continuing in ATP) in accordance with:
  - **Amendment 6 patients:** Refer to Section 7.2.3.2, and utilize:
    - **Table 3**
  - **Continuing Amendment 5* patients:** Refer to Section 7.2.3.1, and utilize:
    - **Table 1**
- Perform drug accountability and collect study medication
- Dispense doses sufficient until the next visit and provide Dosing Instructions (necessary at Day 168 only if patient is continuing in ATP)
- Schedule next clinic visit

*Amendment 5 patients must complete the Treatment Period they are currently being treated under in accordance with the Amendment 5 titration and re-challenge rules and will transition to the Amendment 6 rules upon commencing a new Additional Treatment Period.

9.4.2.1 ATP Day 84 only

- Urinalysis

9.4.2.2 ATP Day 140 only

- Assess whether the patient continues to be eligible for the ATP. If it is determined that the patient is deriving clinical benefit (defined as not meeting progressive disease criteria as per Section 16.7 and safely tolerating IMG-7289), then the patient qualifies for and may re-enter the ATP upon completion of the Day 168 visit. This qualification assessment is initiated at Day 140 for logistical purposes and may be reversed at the Day 168 visit in consideration of patient status at that time.

9.4.2.3 ATP Day 168 only

- Urinalysis
- Blood sample for Central Laboratory genomics and cytokine analysis
- Perform abdominal MRI (or CT if patient is not a candidate for MRI (±7 days)).

Note: In Germany, use of computerised tomography (CT) is not permitted for patients unable to undergo magnetic resonance imaging (MRI). Only MRI is permitted for study purposes.

- Bone Marrow Sampling (±7 days to ensure availability of results for qualification assessment if required by the Investigator) unless performed in the prior 5 weeks
- **Qualification:** Confirm applicability of earlier determination regarding patient eligibility for continued treatment in the ATP, contingent on whether the patient is deriving clinical benefit. If the patient is re-entering the ATP, please revert back to Section 9.4 for the ATP visit schedule and associated procedures and assessments; otherwise, please proceed to Section 9.6 below for follow-up visits.

9.5 Suspected Relapse

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

- Limited PE, including Vital Signs
- Adverse Events and Concomitant Medications
- Collect MPN-SAF TSS **7-DAY RECALL** tool
- Full Local Laboratory Assessment
- Urinalysis
- Blood samples for Central Laboratory genomic analysis*
- Perform abdominal MRI or CT (if patient is not a candidate for MRI) within ±7 days of visit, unless performed in the prior 5 weeks

Note: In Germany, use of computerised tomography (CT) is not permitted for patients unable to undergo magnetic resonance imaging (MRI). Only MRI is permitted for study purposes.

- Bone Marrow Sampling* (unless performed in the last 21 days or is scheduled in next 7 days)

*If possible, bone marrow and blood sampling for genomic analysis should be performed on the same day.

9.6 Follow-Up Period Visits

9.6.1 End of Treatment

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

Patients should return to the clinic for the following assessments:

- Limited PE, including Vital Signs
- Adverse Events and Concomitant Medications
- Collect MPN-SAF TSS and provide copies of the **7-DAY RECALL** tool to patient for completion each week prior to Pre-EoS Visit
- Full Local Laboratory Assessment

Note: In Italy, HIV, HBsAg, HBsAb, HBcAb and HCV testing must also be performed.

- Urinalysis
- Collect blood sample for Central Laboratory genomics (all sites)*, cytokine (all sites), HbF** and %F cell** (US sites only) analysis
- Bone Marrow Sampling* (only if not performed in the previous 5 weeks)
- Perform abdominal MRI or CT (if patient is not a candidate for MRI) within ±7 days of visit, unless performed in the prior 5 weeks

Note: In Germany, use of computerised tomography (CT) is not permitted for patients unable to undergo magnetic resonance imaging (MRI). Only MRI is permitted for study purposes.

- Ensure all study medication has been returned and accounted for (if applicable)
- Schedule the pre-End of Study visit 14 days post last dose

*If possible, bone marrow and blood sampling for genomic analysis should be performed on the same day.
**Only required if End of Treatment occurs during ITP.

9.6.2 Pre-End of Study Visit

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

Patients should return to the clinic for the following assessments:

- Limited PE, including Vital Signs
- Adverse Events and Concomitant Medications
- Collect MPN-SAF TSS and provide copies of the MPN-SAF TSS **7-DAY RECALL** tool to patient for completion each week prior to EoS visit
- Full Local Laboratory Assessment
- Urinalysis
- Ensure all study medication has been returned and accounted for (if applicable)

- Schedule the End of Study visit in 14 days' time

9.6.3 End of Study/Early Termination Visit

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

End of Study: patients should be seen in clinic 28 days (± 2 days) after the last dose of study drug.

The following assessments are required at End of Study/Early Termination visit:

- Limited PE, including Vital Signs
- Adverse Events and Concomitant Medications
- Collect MPN-SAF TSS **7-DAY RECALL** tool
- Full Local Laboratory Assessment
- Urinalysis
- Blood samples for Central Laboratory genomic analysis*
- Ensure all study medication has been returned and accounted for (if applicable)

At Early Termination only:

- Collect blood sample for Central Laboratory cytokine (all sites)**, HbF** and %F cell** (US sites only) analysis
- Bone Marrow Sampling* (only if not performed in the previous 5 weeks)
- Perform abdominal MRI or CT (if patient is not a candidate for MRI) within ±7 days of visit, unless performed in the prior 5 weeks

Note: In Germany, use of computerised tomography (CT) is not permitted for patients unable to undergo magnetic resonance imaging (MRI). Only MRI is permitted for study purposes.

*If possible, bone marrow and blood sampling for genomic analysis should be performed on the same day.
**Only required if Early Termination occurs during ITP.

10 LABORATORY SAMPLING FOR SAFETY, PK AND PD ANALYSIS

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

The amount of blood collected from each patient will vary based on collection of drug concentration samples contingent on upward dose titrations determined by platelet count evaluation. The average of the blood volumes, which varies by institution, is provided below for each cohort.

Initial Treatment Period: Approximately 425-455 mL blood contingent on whether HbF and %F cells are to be analyzed, over 32 weeks. Approximately 4-6 mL of bone marrow aspirate fluid and 2-4 cm of trephine bone marrow biopsy will be collected over ~32 weeks.

Note: The above blood volume, and bone marrow sampling time-points and volume, includes all Screening assessments and each study visit up to and including the EoS visit. Not included, however, are any additional procedures required if a patient qualifies for the Additional Treatment Period.

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

10.1 Laboratory Measures

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

10.1.1 Local Laboratory Measures

Biochemistry: C-reactive protein, calculated creatinine clearance* (by Cockcroft-Gault method) and/or serum creatinine*, uric acid, urea* or blood urea nitrogen (BUN)*, albumin, protein, total bilirubin, conjugated (direct) bilirubin*, unconjugated (indirect) bilirubin*, gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH).

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Note: In Italy, ***Additional Tests:*** HIV test, HBsAg, HBsAb, HBcAb, HCV are required at Screening and End of Treatment. Test results will not be entered into the clinical database; eligibility will be confirmed for patients *via* the question "Does the patient satisfy all inclusion and exclusion criteria?" on the Inclusion/ Exclusion (IE) eCRF. Individual inclusion/exclusion criteria will be source document verified.

Urine or Serum Pregnancy Test: For WOCBP, either a urine or serum pregnancy test will be utilized according to institution standard procedure. For either method, 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.

Bone marrow sampling: At each sample time-point both an aspirate and biopsy sample is required, to be obtained as per site standard procedure. Evaluation will be performed centrally (see Section 10.1.2); however, any locally available cytogenetic or genetic interrogations performed on samples obtained at the same time-point as study samples, will also be reported in the eCRF or collected *via* local lab reports.

Sample Processing: Imago BioSciences will not provide either a laboratory manual or study supplies for the collection and handling of samples to be analysed locally. Local laboratory standard procedures should be followed at each site.

Blood sample volume: the volume of blood needed to perform all local lab measurements varies by institution but is approximately 15 mL.

10.1.2 Central Laboratory Measures

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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 Section9.6.1).

11.1 Pregnancy

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 28 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).

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.

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 28 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.

Note: In the UK, serious AEs (SAEs) will be recorded from time of consent through the EoS **or** until the Investigator and Imago BioSciences determine that follow-up is no longer necessary.

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

Progression of underlying malignancy is not reported as an AE if it is consistent with the suspected progression of the underlying cancer. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. If there is any uncertainty about an AE being due to only the disease under study, it should be reported as an AE.

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 4.03, published 14 June 2010. 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 DSMC findings) or there is no other medical condition or intervention which would explain the occurrence of such an experience.
- Definite: The relationship of the use of the drug or biologic to the experience is considered definitively established.

If a causal relationship is considered probable, possible, or definite by the Investigator 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 the time of first dose through the End of Study Visit (scheduled for approximately 28 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.

> **Note:** In the UK, serious AEs (SAEs) will be recorded from time of consent through the EoS **or** until the Investigator and Imago BioSciences determine that follow-up is no longer necessary.

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 hospitalisation¥. The adverse event resulted in an initial inpatient hospitalisation or prolonged an existing hospitalisation of the patient. If a patient is hospitalised as part of the clinical use of the product, a period of normal hospitalisation will be

outlined in the protocol or by the judgment of the Investigator. Hospitalisations longer than this period will be prolonged hospitalisations.

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 hospitalisation 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.

¥**Note:** Hospitalization consistent with progression of underlying malignancy should NOT be reported as an SAE. An SAE with an outcome of death solely due to progression of the underlying malignancy does not need to be reported as an SAE.

11.2.4 Reporting Serious Adverse Events

SAEs will be reported promptly, using the SAE Report Form, once the Investigator determines that the event meets the protocol definition of an SAE. The Investigator or designee will report the SAE **within 24 hours of 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 Responsible Person 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. Contact numbers will be provided to the site, with a detailed SAE reporting procedure to be included in the Study Reference Manual (SRM), before any patients are consented.

Table 5: Serious Adverse Event Reporting Contact Details

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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). Additionally, a Pharmacokinetic Analysis Plan (PKAP) will be prepared. These documents 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/PKAP.

12.2 Power

This study is designed to make an assessment of the safety, tolerability, and pharmacokinetics of the capsule formulation of IMG-7289. The number of patients is sufficiently powered to determine mean pharmacokinetic parameters. Given that all pharmacodynamic (PD) metrics are exploratory in nature, the study is not powered to make statements about the statistical significance of any changes observed.

12.3 Treatment Assignment and Blinding

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

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

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 CCI

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CCI [redacted]

Note: In the UK, serious AEs (SAEs) will be recorded from time of consent through the EoS **or** until the Investigator and Imago BioSciences determine that follow-up is no longer necessary.

- Changes in physical examinations, vital signs and laboratory values will also be evaluated and assessed from Screening/Baseline until EoS/ET. Information on the timing of these assessments is presented in the schedule of assessment. CCI [redacted]

CCI [redacted]

- Pharmacokinetic (PK) parameters will be determined in accordance with earlier protocol versions and the PKAP associated with the study (Phase 1/2a only).
- Reduction in spleen volume will be assessed based on spleen volume measured by MRI (or CT scan where applicable) from Day 0, and spleen size measured by palpation from Baseline, to each visit where the variables are measured.

Note: In Germany, use of computerised tomography (CT) is not permitted for patients unable to undergo magnetic resonance imaging (MRI). Only MRI is permitted for study purposes.

CCI [redacted]

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[redacted]

12.5 Safety and Tolerability Data

Demographics will be tabulated and summarized. Medical and surgical history data at Screening will be listed, as will Physical Examination data (including height and weight) at Screening, and at subsequent visits. All characteristics at baseline such as age, weight, height and vital signs (resting heart rate, semi-supine systolic/diastolic blood pressure, respiratory rate and temperature) parameters 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 for change from Day 0 and trends indicating a safety signal.

Treatment-emergent adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized for the number of patients reporting the AE and the number of AEs reported. A by-patient AE data listing including (but not limited to) verbatim term, coded term, severity, and relationship to treatment will be provided.

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

Descriptive statistics (arithmetic mean, standard deviation (SD), sample size, CV (coefficient of variation), median, minimum, maximum, and number) will be calculated for quantitative safety data as well as for the differences to baseline, when appropriate. In addition, a shift table describing out of normal range shifts will be provided for clinical laboratory results and physical examination results. For safety and tolerability, missing data including those not obtained because of death will be the last value carried forward.

12.6 Pharmacokinetics Data

Pharmacokinetics data will be handled as outlined in earlier protocol versions and analysed in accordance with the PKAP associated with this study (Phase 1/2a only).

12.7 Pharmacodynamic Data

Measuring the activity IMG-7289 has in producing a pharmacodynamics response (PD) is an exploratory objective. There are four PD responses of interest. The effect of the drug(s) on normal myeloid haematopoiesis, which will be measured by standard peripheral blood counts with on therapy. The PD effect on inflammatory cytokines and growth factors which will measured regularly before and during the treatment period. The PD effect on the mutant allele burden of the patients-specific mutations identified at the time of enrollment and assessed in bone marrow cells (when accessible) and in peripheral blood at the end of the treatment period. The PD effect on the change in spleen volume by MRI and palpation. The PD effect on the change in bone marrow fibrosis score.

Chi-square (χ^2), Fisher exact, and Kruskal-Wallis tests may be used to assess the significance of differences in haematologic and pharmacodynamics markers among the patients and differing doses of IMG-7289. If applicable, progression free survival (PFS), event free survival (EFS), and overall survival (OS) will be calculated using the Kaplan-Meier method.

13 STUDY ADMINISTRATION

The names, titles, and addresses of the Investigators and study personnel are listed in the Site Contacts list in a Study Reference Manual for Protocol IMG-7289-CTP-102 and 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).

13.2 Participation Information Sheet/Consent Form (PISCF)

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

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

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

13.3 Institutional Review Board (IRB), 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 Conference 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 whenever 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. Any implementation of remote data review will be performed in accordance with the applicable local regulations/regulatory guidance. Please see Section 16.10 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).

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 Conference 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.

14.5 Study Drug Accountability

Accountability for study drug at the trial site is the responsibility of the Investigator. The Investigator will ensure that study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the drugs' delivery date to the

site, inventory at the site, use by each patient, and return to Imago BioSciences (or disposal of the drug, if approved by Imago BioSciences) will be maintained by the clinical site. These records will adequately document that the patients were provided the drugs and doses as specified in the protocol and should reconcile all study drugs received from Imago BioSciences. Accountability records will include dates, quantities, batch/serial numbers, expiry dates (if applicable), and patient numbers. Imago BioSciences or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

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

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

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

14.6 Disposal of Study Drug

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

14.7 Training of Staff

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

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

14.8 Clinical Study Report

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

14.9 Retention of Records

Records and documents pertaining to the conduct of this study, including eCRFs, source documents, consent forms, laboratory test results, and medication inventory records, 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.

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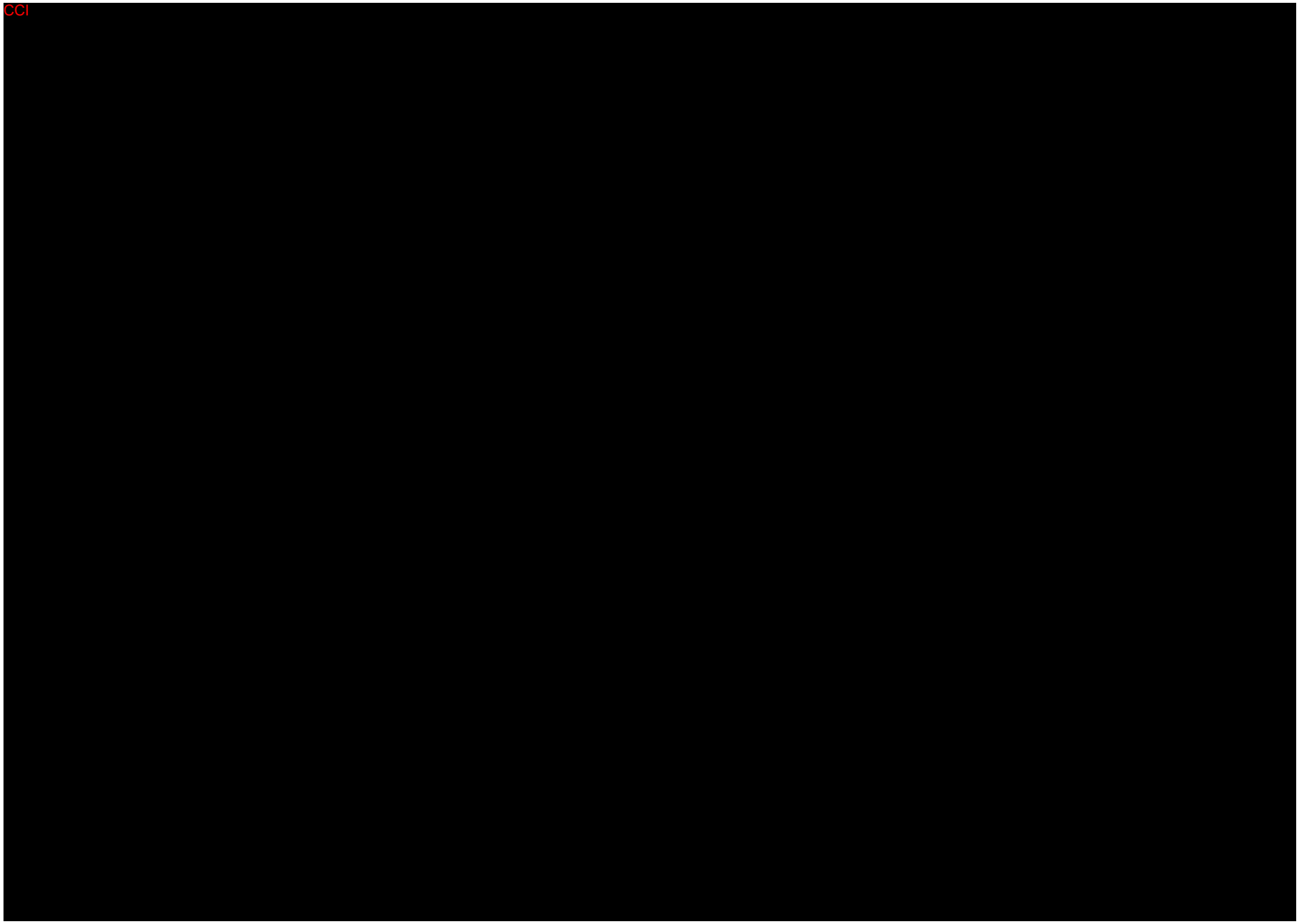
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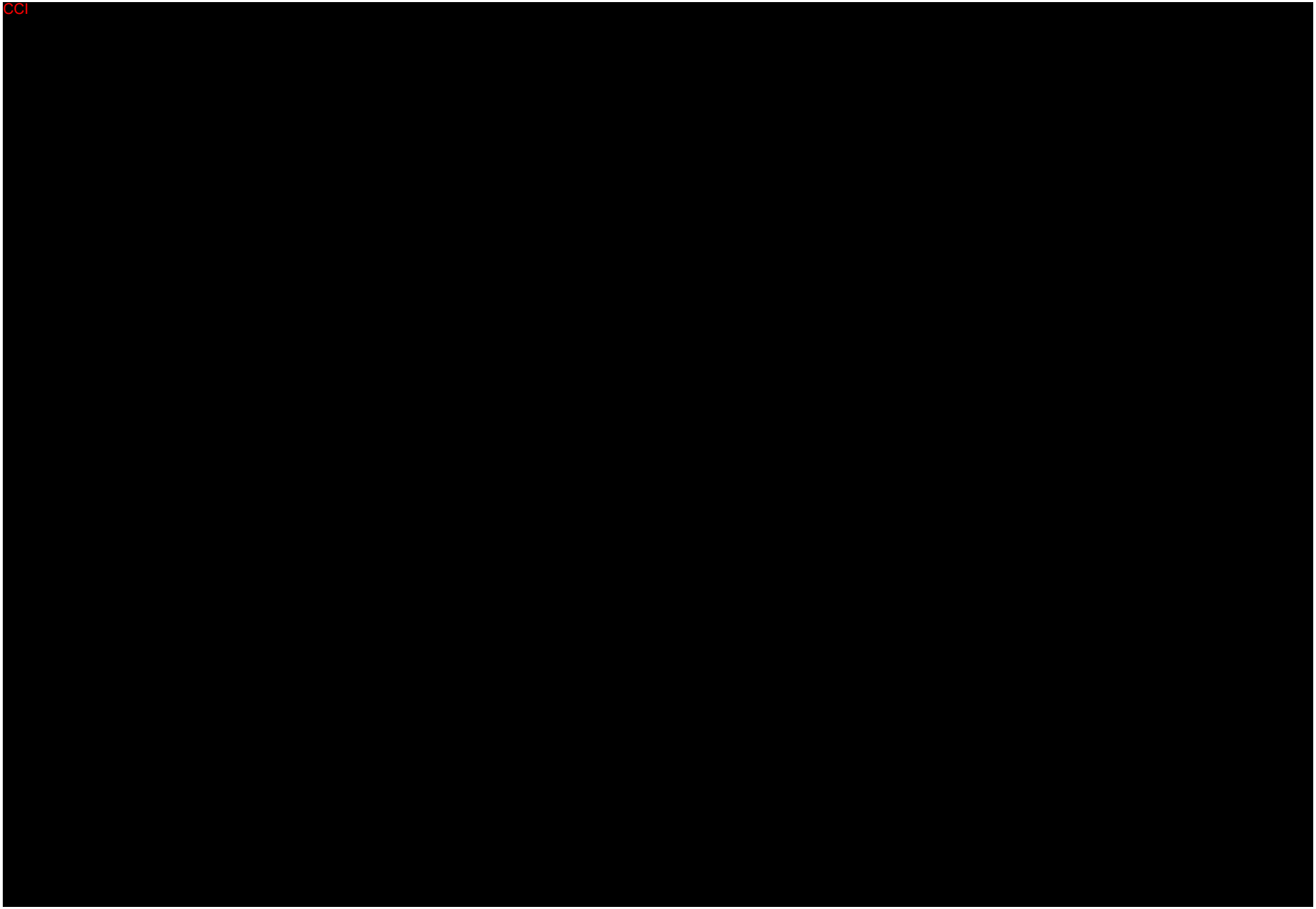
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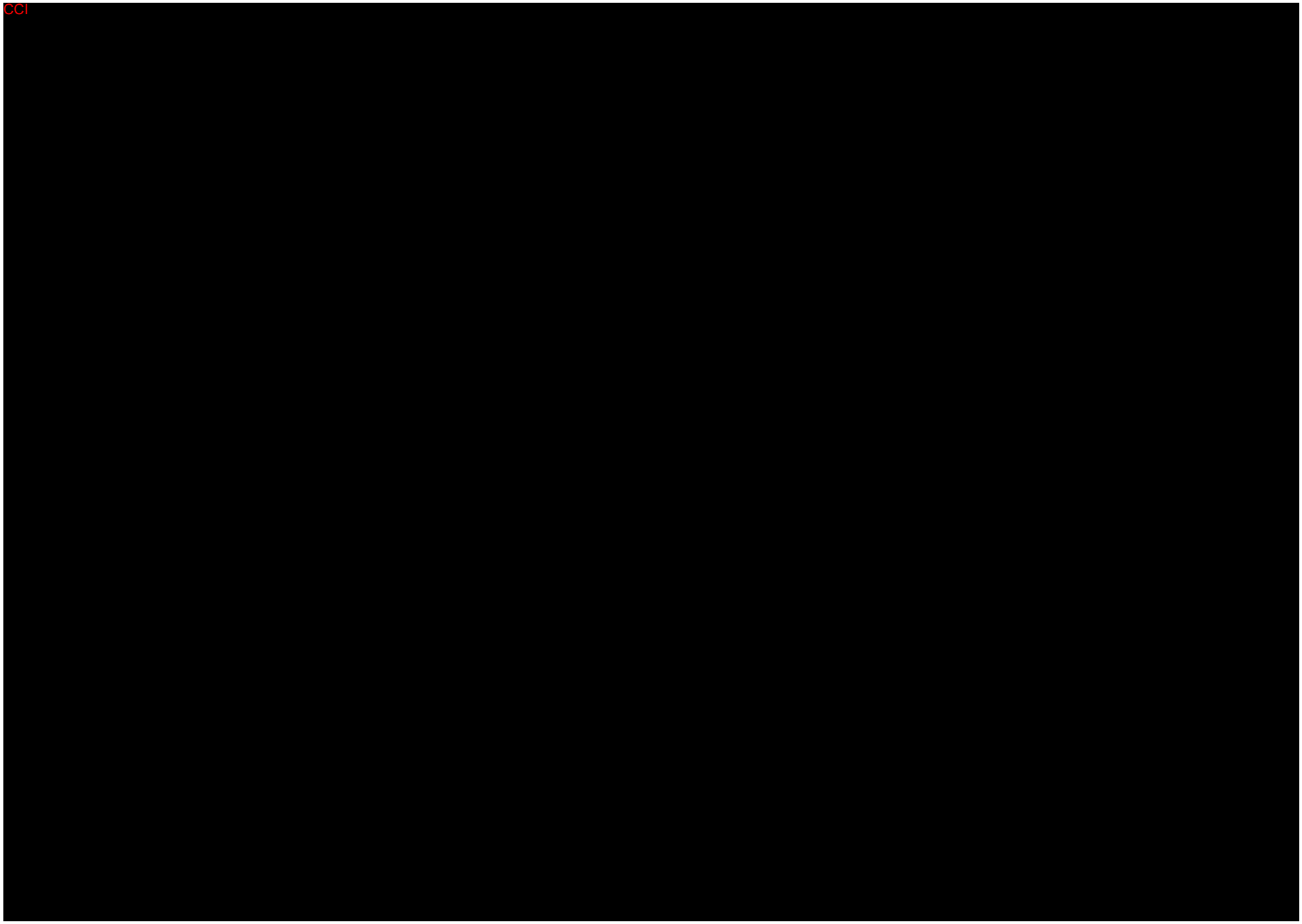
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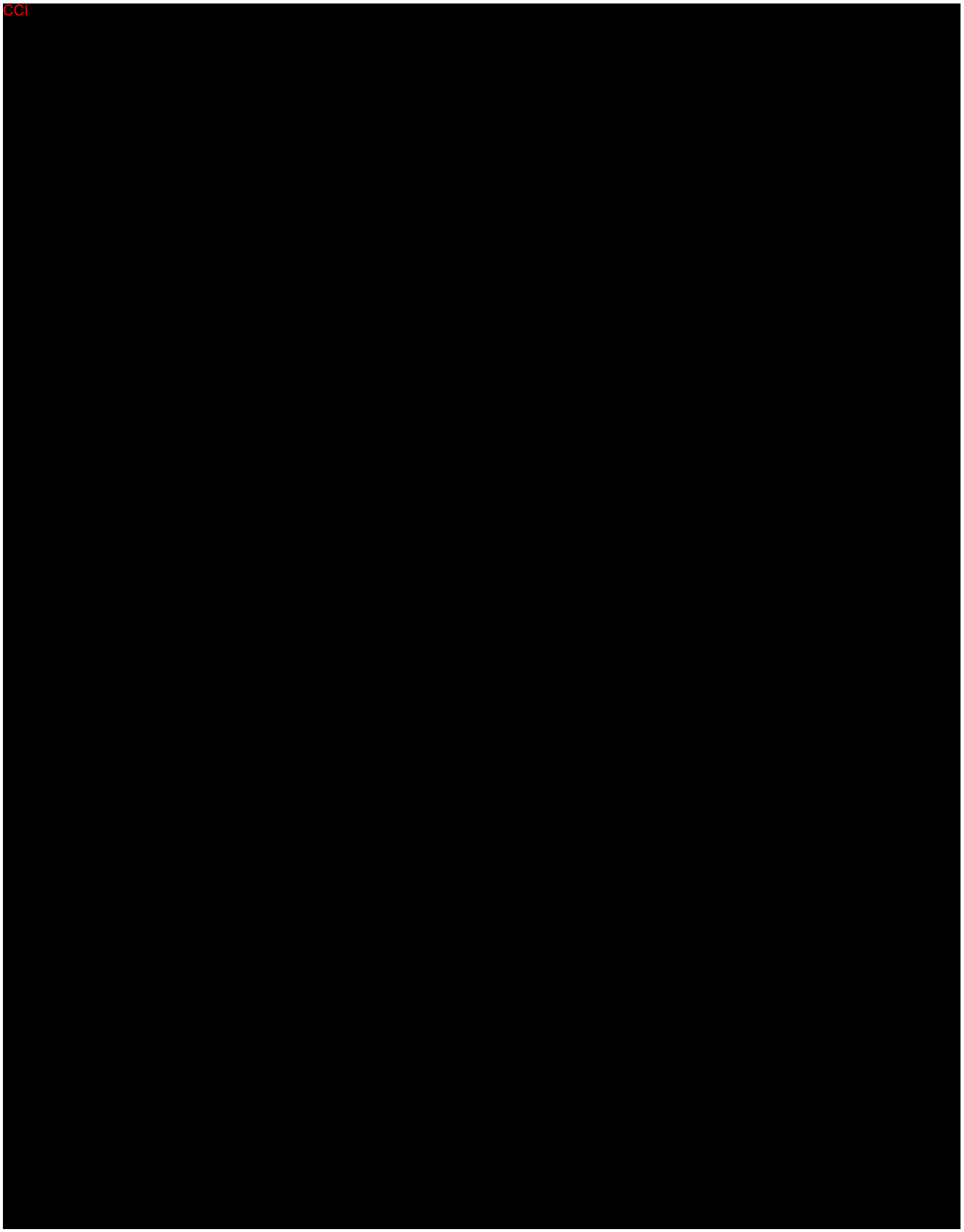

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16.2 The 2016 WHO Diagnostic Criteria for Primary Myelofibrosis (PMF)

		Primary Myelofibrosis (PMF)¥
Major criteria	1	Presence of megakaryocytic proliferation and atypia accompanied by either reticulin and/or collagen fibrosis grades 2 or 3 (see Table 16.5)
	2	Not meeting WHO criteria for ET, PV, *BCR-ABL1+* CML, MDS, or other myeloid neoplasm
	3	Demonstration of *JAK2*, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker,† or absence of reactive bone marrow fibrosis‡
Minor criteria	1	Anaemia not attributed to no comorbid condition
	2	Leukocytosis ≥11 x 10^9/L
	3	Palpable splenomegaly
	4	LDH increased to above upper normal limit of institutional reference range
	5	Leukoerythroblastosis

WHO indicates World Health Organization; PMF, primary myelofibrosis; Hgb, haemoglobin; CML, chronic myelogenous leukaemia; MDS, myelodysplastic syndrome; BM, bone marrow; Epo, erythropoietin; LDH, lactate dehydrogenase; EEC, endogenous erythroid colony.5

¥ The diagnosis of PMF requires meeting all 3 major criteria and 2 minor criteria.

† In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (e.g., *ASXL1*, *EZH2*, *TET2*, *IDH1*/*IDH2*, *SRSF2*, *SF3B1*) are of help in determining the clonal nature of the disease.

‡ BM fibrosis secondary to infection, autoimmune disorder, or other chronic inflammatory conditions, hairy cell leukaemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

16.3 IWG-MRT Recommended Diagnostic Criteria for Post-Polycythaemia Vera Myelofibrosis (PPV-MF)

Diagnostic Criteria for Post-Polycythaemia Vera Myelofibrosis (PPV-MF)	
Required criteria:	1 Documentation of a previous diagnosis of polycythaemia vera as defined by the WHO criteria
	2 Bone marrow fibrosis grade 2–3 (on 0–3 scale) or grade 3–4 (on 0–4 scale)*
Additional criteria: (two are required)	1 Anaemia or sustained loss of requirement for phlebotomy in the absence of cytoreductive therapy
	2 A leukoerythroblastic peripheral blood picture
	3 Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
	4 Development of ≥1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

16.4 IWG-MRT Recommended Diagnostic Criteria for Post-Essential Thrombocythaemia Myelofibrosis (PET-MF)

Diagnostic Criteria for Post-Essential Thrombocythaemia Myelofibrosis	
Required criteria:	1 Documentation of a previous diagnosis of essential thrombocythaemia as defined by the WHO criteria
	2 Bone marrow fibrosis grade 2–3 (on 0–3 scale) or grade 3–4 (on 0–4 scale)*
Additional criteria: (two are required)	1 Anaemia and a ≥2 g/dL decrease from baseline haemoglobin level
	2 A leukoerythroblastic peripheral blood picture
	3 Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
	4 Increased lactate dehydrogenase
	5 Development of ≥1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

*Grade 2–3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grade 3–4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

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

16.6 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

16.7 Revised IWG-MRT and ELN Response Criteria for MF

Response categories	Required criteria (for all response categories, benefit must last for ≥12 weeks to qualify as a response)
CR	Bone marrow:* Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF† and
	Peripheral blood: Haemoglobin ≥100 g/L and <UNL; neutrophil count ≥ 1 x 10^9/L and <UNL; Platelet count ≥100 x 10^9/L and <UNL; <2% immature myeloid cells‡ and
	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
PR	Peripheral blood: Haemoglobin ≥100 g/L and <UNL; neutrophil count ≥1 x 10^9/L and <UNL; platelet count ≥100 x 10^9/L and <UNL; <2% immature myeloid cells‡ and
	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH or
	Bone marrow:* Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF†, and peripheral blood: Haemoglobin ≥85 but <100 g/L and <UNL; neutrophil count ≥1 x 10^9/L and <UNL; platelet count ≥50, but <100 x 10^9/L and <UNL; <2% immature myeloid cells‡ and
	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Clinical improvement (CI)	The achievement of anaemia, spleen or symptoms response without progressive disease or increase in severity of anaemia, thrombocytopenia, or neutropenia§
Anaemia response	Transfusion-independent patients: a ≥20 g/L increase in haemoglobin level¶ Transfusion-dependent patients: becoming transfusion-independent‹

Response categories	Required criteria (for all response categories, benefit must last for ≥12 weeks to qualify as a response)
Spleen response	A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable** or
	A baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≥50%**
	A baseline splenomegaly that is palpable at <5 cm, below the LCM, is not eligible for spleen response
	A spleen response requires confirmation by MRI or computed tomography showing ≥35% spleen volume reduction
Symptoms response	A ≥50% reduction in the MPN-SAF TSS††
Progressive disease‡‡	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or
	A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or
	A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm or
	Leukaemic transformation confirmed by a bone marrow blast count of ≥20% or
	A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 x 10^9/L that lasts for at least 2 weeks
Stable disease	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI, or
	Loss of anaemia response persisting for at least 1 month or
	Loss of spleen response persisting for at least 1 month

EMH, extramedullary haematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven non-hepatosplenic EMH); LCM, left costal margin; UNL, upper normal limit.

*Baseline and post-treatment bone marrow slides are to be interpreted at one sitting by a central review process.

†Grading of MF is according to the European classification Thiele *et al*. European consensus on grading bone marrow fibrosis and assessment of cellularity. It is underscored that the consensus definition of a CR bone marrow is to be used only in those patients in which all other criteria are met, including resolution of leukoerythroblastosis.

‡Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, <5% immature myeloid cells are allowed.

§See above for definitions of anaemia response, spleen response, and progressive disease. Increase in severity of anaemia constitutes the occurrence of new transfusion dependency or a ≥20 g/L decrease in haemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet or absolute neutrophil count, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In addition, assignment to CI requires a minimum platelet count of ≥25000 x 10^9/L and absolute neutrophil count of ≥0.5 x 10^9/L.

¶Applicable only to patients with baseline haemoglobin of <100 g/L.

ŧTransfusion dependency before study enrollment is defined as transfusions of at least 6 units of packed red blood cells (PRBC), in the 12 weeks prior to study enrollment, for a haemoglobin level of < 85 g/L, in the absence of bleeding or treatment-induced anaemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent patients requires absence of any PRBC transfusions during any consecutive "rolling" 12-week interval during the treatment phase, capped by a haemoglobin level of ≥ 85 g/L.

**Spleen response must be confirmed by imaging studies where a ≥35% reduction in spleen volume, as assessed by MRI or CT, is required. Furthermore, a ≥35% volume reduction in the spleen, by MRI or CT, constitutes a response regardless of what is reported with physical examination.

††Symptoms are evaluated by the MPN-SAF TSS. The MPN-SAF TSS is assessed by the patients themselves and includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0-100 scale). Symptoms response requires ≥50% reduction in the MPN-SAF TSS.

‡‡Progressive disease assignment for splenomegaly requires confirmation by MRI or computed tomography showing a ≥25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to post-treatment measurements.

16.8 Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) – 24-Hour Recall

IMG-7289 -CTP-102
Patient Information: __ __ __ - 1 __ __ (Site # Screen #) ___/___/___ (Initials) Completion Date: ____/_____/_____ (dd mmm yyyy)

24-HOUR RECALL

Myeloproliferative Neoplasm Symptom Assessment Form
Total Symptom Score (MPN-SAF TSS)

Instruction: Completion of this version of the MPN-SAF TSS is required prior to dosing in the IMG-7289-CTP-102 study. It is required *daily* from Day -6 until pre-dose Day 0.

Symptom	1 to 10 (0 if absent) ranking (1 is most favorable and 10 least favorable)
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past **24 hours**	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes, during the PAST 24 HOURS, 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 discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with Concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
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)

For use by participants in: IMG-7289-CTP-102; V2, 28Aug2019 **24-HOUR RECALL**

16.9 Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) – 7-Day Recall

IMG-7289 -CTP-102
Patient Information: __ __ __ - 1 __ __ (Site # Screen #) ___/___/___ (Initials) Completion Date: ____/_____/_____ (dd mmm yyyy)

7-DAY RECALL

Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

Instruction: Completion of this version of the MPN-SAF TSS begins on study Day 7 and is then required *weekly* during your participation in the IMG-7289-CTP-102 study.

Symptom	1 to 10 (0 if absent) ranking (1 is most favorable and 10 least favorable)
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past **7 DAYS**	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes, during the PAST 7 DAYS, 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 discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with Concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
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)

For use by participants in: IMG-7289-CTP-102; V1, 28Aug2019 7-DAY RECALL

16.10 Remote Data Review

16.10.1 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.

16.10.2 Security Measures

Monitors are only permitted to undertake remote data review through the processes detailed below in Sections 16.10.3.1 and 16.10.3.2 (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 an IQVIA/IQVIA Biotech office, at home in private area for home-based staff.
    - Examples of prohibited locations include: Open plan desk space in IQVIA/IQVIA Biotech 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. IQVIA/IQVIA Biotech office internet or secure personal internet after logging into IQVIA Biotech virtual private network (VPN). Use of a public internet, hot spot or hotel internet is prohibited.
- Device: remote data review is permitted only through IQVIA/IQVIA Biotech 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.

16.10.3 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 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.

16.10.3.1 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.

16.10.3.2 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 an IQVIA Biotech 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.

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

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

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

  Certified Copy: *A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. (International Council for 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 and the correct subject identification code added.
    - 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.