Official Protocol Title:	**A Multi-Center, Open Label, Extension Study Evaluating the Safety and Efficacy of Bomedemstat for the Treatment of Patients with Myeloproliferative Neoplasms (MPNs) Enrolled in a Prior Bomedemstat Clinical Study**
NCT number:	NCT05223920
Document Date:	13-December-2023

Protocol Title:	A Multi-Center, Open Label, Extension Study Evaluating the Safety and Efficacy of Bomedemstat for the Treatment of Patients with Myeloproliferative Neoplasms (MPNs) Enrolled in a Prior Bomedemstat Clinical Study
Protocol No.:	IMG-7289-CTP-202 / MK-3543-005
Investigational Product:	Bomedemstat (IMG-7289 / MK-3543)
Indication:	Myeloproliferative Neoplasms
Study Phase:	Phase 2
EudraCT Number:	2021-002452-37
IND Number:	130,789
Sponsor:	Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc. 126 East Lincoln Avenue, Rahway, NJ 07065, USA
Version and Date:	
Amendment 02	**13 December 2023**

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 2	13-DEC-2023	This change was made to address study extension. Participants from this study will be eligible to enroll in another bomedemstat extension study at any point before this study ends.
Amendment 1	14-JUN-2023	This change was made to address Non-Merck protocol template. The rationale is further supported by acquisition of Imago BioSciences, Inc. by Merck & Co., Inc. This conversion resulted only in an entity name change and update to the address.
Original Protocol	11-JUL-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendment:

This change was made to address study extension. Participants from this study will be eligible to enroll in another bomedemstat extension study at any point before this study ends.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 9.4.1, End of Treatment (EoT)	Language added to allow eligible participants from this extension study to enroll in another extension study using bomedemstat	This change was made to address study extension. Participants from this study will be eligible to enroll in another bomedemstat extension study at any point before this study ends.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Title Page	Added complete address for Sponsor	To provide complete address for Sponsor
Section 2, Protocol Synopsis	Language added to allow eligible participants from this extension study to enroll in another extension study using bomedemstat	Refer to the rationale for Section 9.4.1
Section 5.1, Overview	Language added to allow eligible participants from this extension study to enroll in another extension study using bomedemstat	Refer to the rationale for Section 9.4.1
Section 9.4.2, End of Study/Early Termination Visit	Language added to allow eligible participants from this extension study to enroll in another extension study using bomedemstat	Refer to the rationale for Section 9.4.1
Section 11.2.5, For Participants Who Consent To Another Bomedemstat Extension Study	Added section	To provide guidance for investigator for reporting all AEs, SAEs, and other reportable safety events
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol

Table of Contents

1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
<, ≤, >, ≥	less than, less than or equal to, greater than, greater than or equal to
±	plus or minus
Ac	acetylation
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
ATP	Additional Treatment Period
BCR-ABL	breakpoint cluster region-Abelson
BM	bone marrow
Bomedemstat (IMG-7289 / MK-3543)	N-[(2S)-5-{[(1R,2S)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt
BMMC	bone marrow mononuclear cell
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	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Clinical Benefit	not meeting "progressive disease" criteria as per Section 16.4 (for MF patients) and Section 16.5 (for ET patients) and safely tolerating IMG-7289, as determined by the Principal Investigator
CMH	Cochran-Mantel-Haenszel
CoREST	Co-repressor for RE1-silencing transcription factor
COVID-19	Coronavirus disease-2019
CR	complete remission or response
CRO	contract research organization
CRP	c-reactive protein
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	co-efficient of variation
Cxcl	chemokine (C-X-C Motif) ligand
CXCR4	chemokine (C-X-C motif) receptor 4
CYP	cytochrome P450
D, d	day
DILI	Drug-induced liver injury

Abbreviation	Definition
DNA	deoxyribonucleic acid
DNMT	DNA-methyltransferase
D_{pi}	pharmacodynamic dose; the estimated dose of IMG-7289 needed in humans that provides sufficient exposure to inhibit normal hematopoiesis safely during a fraction of the 24-hour dosing cycle
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event free survival
ELN	European Leukemia Network
EMH	extramedullary hematopoiesis
EMR	electronic medical record
EoS	End of Study
EoT	End of Treatment
EPO	erythropoietin
ESC	embryonic stem cell
ET	essential thrombocythemia; Early Termination
FAD	flavin adenine dinucleotide
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
GGT	gamma glutamyltransferase
GM-CSF	granulocyte-macrophage colony stimulating factor
GMP	Good Manufacturing Practices
H	histone
HAV	hepatitis A virus
Hb	hemoglobin
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDAC	histone deacetylase
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HREC	Human Research Ethics Committee
HSC	hematopoietic stem cell
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

Abbreviation	Definition
IL	interleukin
IMG-7289	bomedemstat, *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
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent to Treat
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	leukemia initiating cell
LPE	Limited Physical Exam
LSD1	lysine-specific demethylase 1
LSDi	LSD1 inhibition or inhibitors
MAO; MAOI	monoamine oxidase(s); monoamine oxidase inhibitor(s)
MDS	myelodysplastic syndrome
me; Me	methyl; methylation
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
mg	milligram
mg/kg	milligram per kilogram
mg/kg/d	milligram per kilogram per day
mL	milliliter
MPL	myeloproliferative leukemia virus oncogene, thrombopoietin receptor
MPN	myeloproliferative neoplasias or neoplasms, myeloproliferative diseases
MPN10	The equivalent of the MPN-SAF TSS
MPN-SAF; MPN-SAF TSS	Myeloproliferative Neoplasm Symptom Assessment Form; Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score
MPP	multipotent progenitor
MRI	magnetic resonance imaging
mRNA	messenger RNA
MYB	V-Myb Avian Myeloblastosis Viral Oncogene Homolog
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
nM	nanomolar
NSAID	nonsteroidal anti-inflammatory drug
NuRD	nuclear remodeling and histone deacetylase
OCT4	octamer-binding transcription factor 4

Abbreviation	Definition
ONC	Office of the National Coordinator for Health Information Technology
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
PE	physical examination
PET-MF	post-essential thrombocythemia myelofibrosis
PFS	progression free survival
PGIC	Patient Global Impression of Change
Ph	phosphorylation
PI	Principal Investigator (at each site responsible for patient care)
PISCF	Participant Information Sheet/Consent Form
PMF	primary myelofibrosis
PR	partial remission or response
PT	prothrombin time
PV	polycythemia vera
QD	once daily
RBC	red blood cell
REST	RE-1 silencing transcription factor
RNA	ribonucleic acid
SAB	Safety Advisory Board
SABP	Safety Advisory Board Plan
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
sh	short hairpin
SOX2	sex determining region Y-box 2
SRM	Study Reference Manual
SRY	sex determining region Y
STAT	signal transducer and activator of transcription
TCP	tranylcypromine
TF	transcription factor
TP	Treatment Period
µL	microliter
µM	micromolar
Ub	ubiquitination
VPN	virtual private network
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of child-bearing potential

2 PROTOCOL SYNOPSIS

Protocol Title: A Multi-Center, Open Label, Extension Study Evaluating the Safety and Efficacy of Bomedemstat for the Treatment of Patients with Myeloproliferative Neoplasms (MPN) Enrolled in a Prior Bomedemstat Clinical Study

Protocol No: IMG-7289-CTP-202 / MK-3543-005

Amendment No: 01

Sites: Up to 25 sites in Australia, New Zealand, Italy, Germany, Hong Kong, UK and US. All sites will have previously participated in a bomedemstat study.

Study Objectives: The objectives of this extension study are to:

- Continue to assess the safety, tolerability and efficacy of bomedemstat in patients who received bomedemstat in a prior study
- Measure the extent and durability of bomedemstat treatment effects on exploratory endpoints including any impact of bomedemstat on the natural history of MF and ET

Investigational Drug: The active drug substance is identified as bomedemstat (also known as IMG-7289 / MK-3543). Bomedemstat is an irreversible inhibitor of LSD1. The chemical name is: *N*-[(2*S*)-5-{[(1*R*, 2*S*)-2-(4-fluorophenyl) cyclopropyl]amino}-1-(4- methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt. Bomedemstat will be supplied as capsules in multiple strengths. Reference the Pharmacy Manual for details.

Study Population: This study will enroll approximately 80 patients with an MPN that meet the eligibility criteria.

Methodology: This is a multi-center, open-label extension study to assess the long-term safety and efficacy of bomedemstat administered orally once daily in patients with an MPN who participated in a prior bomedemstat study such as, but not limited to, IMG-7289-CTP-102 and IMG-7289-CTP-201 (referred to hereafter as 'feeder studies'). Details of the extension study and a copy of the informed consent form (ICF) should be provided to the patient prior to their anticipated final visit in the feeder study. Informed consent should be obtained at, or before, the feeder study's final visit. It is intended that patients transition directly into this extension study with no interruption of dosing.

Under the following circumstances, provided the Principal Investigator (PI) deems it safe and clinically appropriate, patients may remain off bomedemstat for up to 2 weeks prior to entering the extension study:

- Patient does not provide consent by their final feeder study visit. Such patients will have an allowance of 14 days to consent to and initiate dosing in the extension study.
- Patient requires a dose hold per Titration Assessment
- There is an administrative need to interrupt bomedemstat dosing (i.e., pending any necessary health authority or local/site approvals).

Note: Fourteen (14) days without bomedemstat dosing prior to first dose in the extension study may not be exceeded without written Sponsor Medical Monitor approval.

A Safety Advisory Board (SAB) will perform reviews of safety parameters in accordance with a Safety Advisory Board Plan to assess the continued use of bomedemstat per protocol.

Study Conduct:

Eligibility criteria will be assessed based on the patient's final visit in their feeder study. The first visit in the extension study is the 'Transition Visit'. Ideally, patients will commence treatment upon completion of a Treatment Period (TP) in the feeder study; however, some patients will need to transition to this extension study at differing timepoints and so the final feeder study visit and the Transition Visit will need to be linked (i.e., patients completing their feeder study at the end of a TP will enter the extension study at TP1 Day 1; patients completing their feeder study at a 'Day 85' visit will enter the extension study at TP1 Day 85) to maintain the correct visit schedule. Patients will be dosed in TPs, with each TP comprised of daily treatment with bomedemstat for 169 days. Qualifying patients may continue to receive bomedemstat for multiple TPs, each comprising an additional 169 days of treatment.

CCI

days) post last procedure date in the feeder study.

At each Day 169 visit, a Qualification Assessment will be made to determine whether the patient is continuing to derive clinical benefit (defined as not meeting "progressive disease" criteria, as per Appendices 16.4 and 16.5 for MF and ET patients, respectively, and safely tolerating bomedemstat), thereby determining patient qualification for continued bomedemstat use *via* entry into another TP. Patients who qualify for another TP should transition without interruption in dosing. Patients who do not qualify will discontinue bomedemstat, immediately undergo an End of Treatment (EoT) visit and have the Follow-up Period End of Study (EoS) visit scheduled. If available, patients who qualify for another bomedemstat extension study can undergo an EoT visit and transition to the next extension study without the need for a Follow up Period/EoS visit.

Bomedemstat Dosing: All patients will be dosed with bomedemstat daily with dose-titration contingent on the Titration Assessment performed at every TP visit. Patients receiving their first extension study dose with no interruption in dosing will have a Titration Assessment performed at the Transition Visit to determine if a titration is needed. Patients requiring an interruption in dosing will have a Titration Assessment performed at the Transition Visit to determine if they will commence at the same daily dose of bomedemstat being taken at the conclusion of their feeder study or if a down-titration or dose hold is needed (up-titrations are not permitted). Titration targets and rules, specific to the underlying MPN, are detailed in the Study Reference Manual, Pharmacy Manual, and Appendix 16.1.3 and 16.1.4. The upper limit for titration is 6 mg/kg/day.

Study Duration: CCI [redacted].

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

*Patients entering the extension study at the final visit of the feeder study will undergo the asterisked procedures in association with the feeder study; the assessments should not be duplicated. Patients entering the extension study that require interruption of dosing must undergo the asterisked procedures.

Limited Physical Examinations (LPE): CCI [redacted] LPEs include weight, vital signs, a review of body systems to assess change from previous LPE and spleen measurement.

CCI [redacted]

following the last assessment in the feeder study for as long as the patient continues to qualify for treatment, and at the Suspected Relapse, EoT, EoS and ET visits. Bone marrow sampling will not be repeated if performed in the prior 5 weeks.

†Aspirate sample should be optimally obtained within the first pull. Do not collect after a second pull attempt.

Local Laboratory Assessments: The following panels (Section 10.1.1 details analytes) will be performed as per below, and at the Transition Visit*, Suspected Relapse, EoT, EoS and ET visits:

Genomic and Correlative Research Analyses: The following will be collected at the time-points noted below, and (unless bone marrow was performed in the prior 5 weeks) at the Suspected Relapse, EoT, EoS and ET visits. Genomic mutant allele burden will be analyzed. Also, some or all of each sample may be placed in long-term storage for potential correlative research studies.

Titration Assessment: At every visit during the TP, the local laboratory hematology panel will be assessed for potential dose titration in accordance with the titration rules detailed in the Study Reference Manual and Pharmacy manual.

Qualification Assessments: At Day 169 of each TP completed, Investigators will assess whether the benefit-risk of bomedemstat favors continued treatment, thereby determining patient qualification for entry into another TP. Qualifying patients may enter another TP upon completing the Day 169 visit. Patients who do not qualify will discontinue bomedemstat, undergo an EoT visit and proceed with the Follow-up Period EoS visit.

The below assessments are required **ONLY** if required in the feeder study:

ECOG Performance Status (Appendix 16.3): On Day 169 of each TP completed, and at the Suspected Relapse, EoT, EoS and ET visits.

CCI [redacted]

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.

Eligibility Criteria:

Patients must meet all Inclusion and no Exclusion Criteria.

Inclusion Criteria:

1. Completed at least one Treatment Period (TP) in a prior bomedemstat MPN protocol (such as, but not limited to, IMG-7289-CTP-102 or IMG-7289-CTP-201).
2. In the estimation of the Investigator, the risk-benefit favors continued dosing with bomedemstat.

Exclusion Criteria:

1. Ongoing participation in another investigational study (except observational studies).
2. A history of non-compliance in a prior bomedemstat study (excluding dose suspensions that were medically warranted).
3. Current use of a prohibited medication (e.g., romiplostim).
4. Medical, psychiatric, cognitive, or other conditions that, in the Investigator's opinion, compromise the patient's safety, ability to give informed consent, or comply with the trial protocol.
5. Females who are pregnant or breastfeeding or plan to become pregnant or breastfeed during the study.
6. CCI [redacted]

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

Patient Care Guidelines:

Patient care guidelines are provided for Investigator and site staff consideration and recognize the standard of care across global institutions will vary. The following are not protocol requirements.

For **all patients**:

1. In general, supportive care (transfusions, administration of anti-fungals, etc.) should be maintained in accordance with institutional policy. (Note: Transfusions must be adequately recorded in the source documents to facilitate data entry of the study required parameters [i.e., type of blood product transfused, units, total volume]).
2. Patients taking medications with the potential to induce or inhibit CYP3A4 or CYP2D6 should be monitored closely for potential effects of co-administration; particular attention should be given to anti-infectives in the azole class.
3. There are no restrictions to, or recommendations on the timing of, administration of vaccines (i.e., coronavirus disease 2019 [COVID-19] vaccination).
4. Cessation of bomedemstat is associated with a rebound in thrombopoiesis, and platelet counts may exceed baseline in the patient. **<u>When bomedemstat is discontinued, platelet counts must be monitored closely and the timing of the start of an alternative therapy should take the expected rebound of platelets into consideration.</u>**
    - CCI [redacted]

CCI [redacted]

5. CCI [redacted]
    - [redacted]
    - [redacted]

Prohibited Medications/Treatments:

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

1. All cytotoxic agents, with noted exception of hydroxyurea for MF patients as per Guidelines
2. All hematopoietic growth factors: romiplostim, eltrombopag, granulocyte and granulocyte-macrophage colony stimulating factor (G-CSF and GM-CSF) and erythropoietin (EPO)
3. Monoamine oxidase A and B inhibitors

4. Anticoagulant or nonsteroidal anti-inflammatory drug (NSAID; including aspirin) use, when patient platelet count is < 50 x 10^9/L

CCI [redacted]

5. CCI [redacted]

Management of Study Toxicities:

AE intensity will be evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5, published 27-NOV-2017. Refer to Section 8.2 for additional detail on management of study toxicities.

Contact the Medical Monitor to discuss bomedemstat dose modifications for clinically significant AE changes in platelets, neutrophil counts, or other hematologic parameters.

Stopping Rules:

Bomedemstat will be permanently discontinued, and the patients will undergo the Follow-up Period Visits (see Section 9.4) in the event of the following:

- Investigator or Medical Monitor deem it unsafe for the patient to continue bomedemstat.
- Following the temporary interruption of bomedemstat due to platelet counts below the applicable threshold (25 x 10^9/L for MF patients and 50 x 10^9/L for ET patients), the patient's platelet counts do not return to the required threshold (>50 x 10^9/L for MF patients and >150 x 10^9/L for ET patients) within 21 days. Note: new platelet thresholds may apply as additional feeder studies are conducted; such thresholds will be specified in the Study Reference Manual and Pharmacy Manual.

Criteria for Evaluation:

The parameters comprising safety and efficacy assessments are below. Details on endpoints and data analysis are provided in Sections 12.4 and 12.5, respectively.

CCI [redacted]

Safety

In **all patients**, safety will be assessed by:

- Evaluation of:
  - Adverse events (AEs)
  - Serious adverse events (SAEs)
  - Required laboratory tests (hematology, chemistry, coagulation and urinalysis)
  - Physical examinations, including vital signs

Efficacy

In **all patients**, efficacy will be assessed by evaluation of:

- Constitutional symptoms measured by continued completion of the version of the MPN-SAF tool associated with the feeder study
- Formal measures of response, including relapse, and disease transformation
- Fibrosis score

In **MF patients**, efficacy will also be assessed by:

- Spleen volume reduction

In **ET patients**, efficacy will also be assessed by:

- Patient reported change in clinical status as measured by the PGIC
- Durability in the reduction of platelet counts in the absence of new thromboembolic events
- Durability in the reduction of white blood cell count
- Evaluation of the incidence of thromboembolic events

3 INTRODUCTION

3.1 Background on the Disease to be Treated

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

3.2 Background on the Drug Target

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

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

LSD1 is localized to specific sites in the genome through the agencies of proteins that bind DNA directly, generally transcription factors (TFs) (Whyte *et al.*, 2012; Whyte *et al.*, 2013). Many TFs, both activators such as V-Myb Avian Myeloblastosis Viral Oncogene Homolog (MYB) and steroid hormone receptors, as well as repressors such as growth factor independence 1 transcription

repressor (GFI1) and RE-1 silencing transcription factor (REST), recruit LSD1 to specific genomic locations (Metzger *et al.*, 2005; Saleque *et al.*, 2007; Lin *et al.*, 2010). LSD1 is part of a larger protein complex, containing, e.g., Co-RE-1 silencing transcription factor (CoREST) or nucleosome remodeling and histone deacetylase (NuRD), which dictates the cell- and site-specific chromatin remodeling (Lee *et al.*, 2005; Foster *et al.*, 2010). These complexes may also include DNA methyltransferase 1 (DNMT1) and histone deacetylases 1, 2 and 3 (HDAC1, 2, and 3) activities all of which contribute to maintaining or modifying the epigenetic state at that specific genomic site (Shi *et al.*, 2005; Orkin and Hochedlinger, 2011). Thus, an important property of LSD1 beyond its own enzymatic activity is its function as a scaffold for other proteins and epigenetic enzymes that are co-recruited to genomic sites. Likewise, LSD1 bound to specific sites precludes the binding of other factors that may influence transcription.

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

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

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

to be stably activated with progressive methyl or acetyl additions on H3K4 and H3K27, respectively (Lara-Astiaso *et al.*, 2014).

3.3 Background on LSD1 in Myeloid Neoplasia Pre-Clinical Studies

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

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

LSD1 may play a direct role in regulating pathogenic signaling from the activated Janus Kinases (JAK) signal transducer and activator of transcription (STAT) pathway. The JAK-STAT signaling pathway is activated by the canonical MPN mutations in *MPL*, *JAK2* and *CALR via* the phosphorylation of STAT3 and STAT5, transcription factors that activate specific sets of genes with pleiotropic effects (Chen and Mullally, 2014). STAT3 activity as a transcription factor is modulated by methylation on lysine (K140) and is one of many reported non-histone substrates for LSD1 (Yang *et al*., 2010).

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

LSD1 inhibition also reduced the mutant cell burden. In a mouse model of AML in which *MLL-AF9* had been virally transduced into transplanted mouse HSCs along with the gene for green

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

3.4 Background on Bomedemstat (IMG-7289/MK-3543)

Bomedemstat is an orally available, irreversible inhibitor of LSD1, active against LSD1 and human AML cells at concentrations of <5 nM. Irreversible inhibitors of LSD1 include 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. Bomedemstat has >4000-fold selectivity for LSD over monoamine oxidase A and B, the mostly closely related human enzymes.

Pharmacokinetic studies in mouse, rat and dog and pharmacokinetic modeling in human systems suggest that once-daily dosing in humans would be sufficient to achieve therapeutic exposures. Twenty-six and thirty-nine week toxicologic studies in rat and dog, respectively, showed that CCI [redacted].

3.5 Potential Clinical Risks and Benefits when Dosing an LSD1 Inhibitor

The dosing effects with an LSD1 inhibitor (LSDi) are distinct from treatment with standard cytotoxic agents or with Janus Kinase (JAK)clo inhibitors.

LSD1 inhibition has specific effects on each myeloid lineage. LSD1 activity is needed for the differentiation of progenitors to red cells, platelets and granulocytes; LSD1 activity is not needed for monopoiesis. Hence, LSD1 inhibition changes the cellular composition in the marrow and the morphology of these cells. Likewise, distribution of blood cells based on lineage is also affected with an increase in the production of monocytes and a decreasing in the other myeloid cell types; the production of platelets appears to be more sensitive to LSD1 inhibition and red cell production the least. There is no evidence to date that inhibition of LSD1 has an effect on the function of platelets or neutrophils. CCI [redacted]

The morphologic and clinical pathology changes may not be familiar to clinicians and hematopathologists. CCI [redacted]

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

3.6 Bomedemstat 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 Bomedemstat Dose

In the Phase 2 study in MF patients (IMG-7289-CTP-102), the daily dose of bomedemstat needed by most patients to achieve a platelet count in the target range (50-75 x 10^9/L) is between 0.6 to 0.8 mg/kg/d with a dosing spectrum investigated of 0.4-1.5 mg/kg/d.

In the Phase 2 study in ET patients (IMG-7289-CTP-201), the daily dose of bomedemstat needed to reduce platelet counts into the target range (200-400 x 10^9/L) is also currently between 0.6 to 0.8 mg/kg/d.

To date, for both patient populations evaluated in clinical studies IMG-7289-CTP-102 and -201, the doses needed to reduce the platelet count to the target range do not appear to be correlated with the starting platelet count or antecedent hematologic history.

In the Phase 1 study in high-risk AML/ myelodysplastic syndrome (MDS) patients (IMG-7289-CTP-101), there was no maximum tolerated dose observed with doses up to 6 mg/kg/d.

Patients entering this study will have received bomedemstat for at least 6 months in their feeder study. All patients will be dosed with bomedemstat daily in the extension study, with dose-titration contingent on the Titration Assessment performed at every TP visit. Patients receiving their first extension study dose with no interruption in dosing will have a Titration Assessment performed at the Transition Visit to determine if a titration is needed. Patients requiring an interruption in dosing will have a Titration Assessment performed at the Transition Visit to determine if they will commence at the same daily dose of bomedemstat being taken at the conclusion of their feeder study or if a down-titration or dose hold is needed (up-titrations are not permitted).

The dose of bomedemstat needed to reduce platelets to the applicable target range is anticipated to be up to approximately 2 mg/kg once daily (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 upper limit for titration purposes is 6 mg/kg/d (**note:** this dose cannot be exceeded during the dose titration process).

3.6.2 Rationale for the Bomedemstat Dosing Schedule

This is an open-label extension study that intends to continue to dose patients with bomedemstat for as long as they are safely tolerating and receiving clinical benefit from its use. Patients entering this study will have received bomedemstat for at least 6 months in their prior feeder study. Dose-titration will continue to be contingent on the hematology assessments, specifically: platelets, hemoglobin and absolute neutrophil count (ANC). Titration targets and rules, including the frequency with which up- and down-titrations are permitted, and the associated titration increments/decrements are specific to the underlying MPN and are detailed in the Study Reference Manual and Pharmacy Manual.

Chronic daily administration of bomedemstat in rat, dog and humans has been well tolerated. No safety signals, per Safety Advisory Board reviews to date, have been observed in either the AML/MDS, myelofibrosis, or essential thrombocythemia studies with bomedemstat at doses up to 6 mg/kg/d and for CCI [redacted].

4 HYPOTHESIS AND OBJECTIVES

Hypothesis: Bomedemstat is safe and tolerable when administered long-term to patients with MPNs; inhibition of LSD1 by bomedemstat will provide long-term clinical benefit to patients with MPNs.

4.1 Objectives

The objectives of this extension study are to:

- Continue to assess the safety, tolerability and efficacy of bomedemstat in patients who received bomedemstat in a prior study
- Measure the extent and durability of bomedemstat treatment effects on exploratory endpoints including any impact of bomedemstat on the natural history of MF and ET

5 INVESTIGATIONAL PLAN

5.1 Overview

This is a Phase 2 multi-center, open-label extension study for patients with myeloproliferative neoplasms dosed with bomedemstat in a prior clinical study.

This study consists of Treatment Periods (TP) where patients will be treated daily for 169 days. The TPs are iterative and treatment may continue for an additional 169 days in those patients deriving clinical benefit (defined as not meeting "progressive disease" criteria as per applicable Appendix 16.4 or 16.5) and safely tolerating bomedemstat, as determined by the Investigator; this definition applies throughout the document and will not be repeated with each reference to clinical benefit.

Eligibility criteria will be assessed based on the patient's final visit in their feeder study. CCI [redacted]

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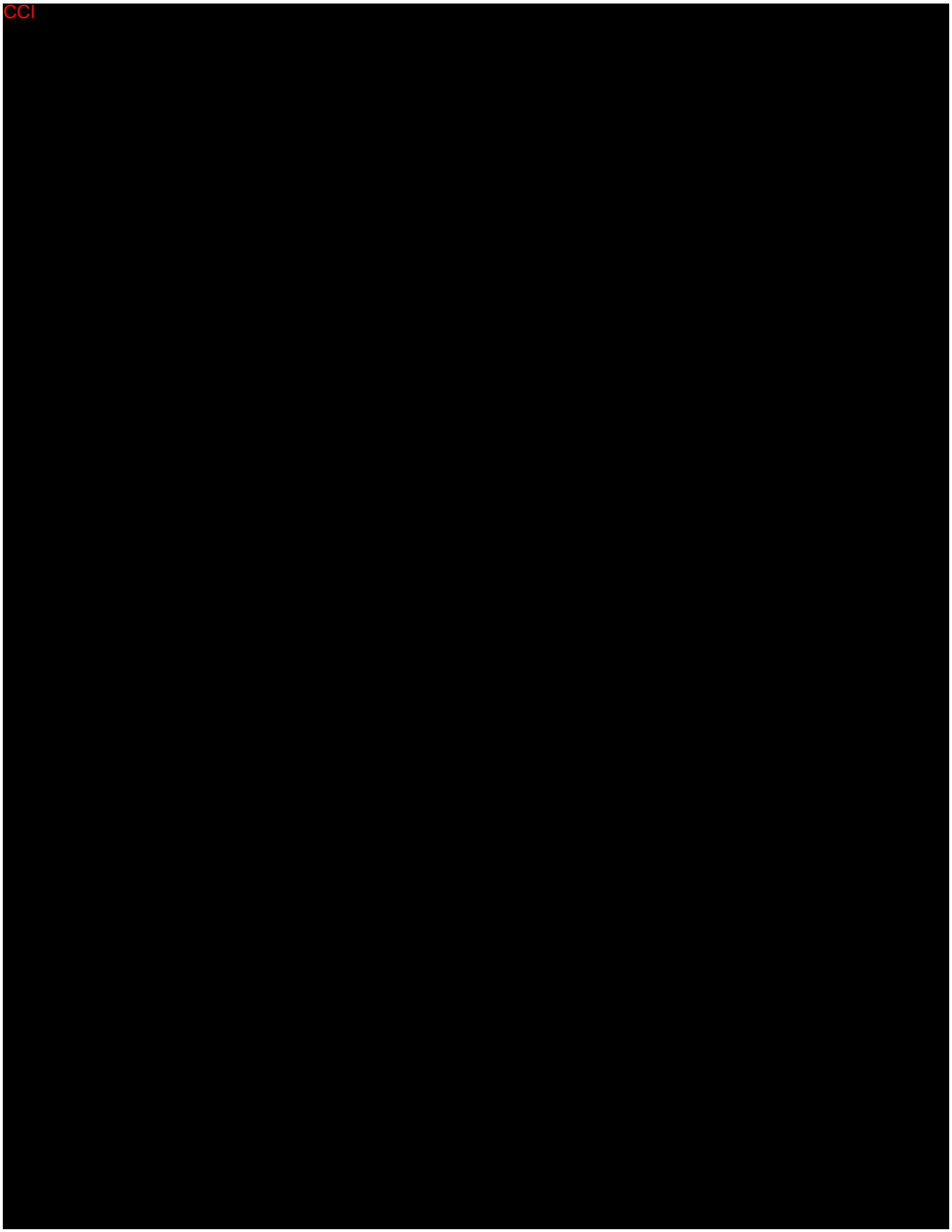
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6 STUDY POPULATION

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 the Treatment and Follow-up Periods, and withdrawal are not acceptable methods of contraception.

6.1.1 Inclusion Criteria

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

1. Completed at least one Treatment Period (TP) in a prior bomedemstat MPN protocol (such as, but not limited to, IMG-7289-CTP-102 or IMG-7289-CTP-201).
2. In the estimation of the Investigator, the risk-benefit favors continued dosing with bomedemstat.

6.1.2 Exclusion Criteria

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

1. Ongoing participation in another investigational study (except observational studies).
2. A history of non-compliance in a prior bomedemstat study (excluding dose suspensions that were medically warranted).
3. Current use of a prohibited medication (e.g., romiplostim).
4. Medical, psychiatric, cognitive, or other conditions that, in the Investigator's opinion,

compromise the patient's safety, ability to give informed consent, or comply with the trial protocol.

5. Females who are pregnant or breastfeeding or plan to become pregnant or breastfeed during the study.

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

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6.2 Patient Enrollment

This study will enroll approximately 80 patients with an MPN that meet the eligibility criteria.

6.3 Patient Withdrawal

In accordance with the Declaration of Helsinki, Good Clinical Practice (GCP), and International Council for Harmonisation (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. The patient's reason for withdrawal, if given, will be documented in the electronic case report form (eCRF). Patients will be requested to complete the Follow-up Period visits for post-dosing safety assessments as per Section 9.4.

Subjects may also be removed from the study by the Sponsor or Investigator. The Sponsor or Investigator may remove patients from the study for various reasons, including:

- Taking another investigational medicinal agent during the study;
- Use of a prohibited medication;
- Major violation of, or deviation from, study protocol procedures which, in the judgment of the Medical Monitor, could adversely affect the patient or the integrity of the study including missing an extended duration of bomedemstat doses or other evidence of major non-compliance;
- Withdrawal from the study is, in the Investigator's judgment, in the patient's best interest.

6.4 Patient Care Guidelines

Patient safety is paramount. The patient care guidelines below are intended to facilitate some consistency across sites by providing guidance to be used by the Investigator and the study staff

to ensure patient safety and recognize the standard of care across global institutions will vary. The guidelines are not protocol requirements and are not intended to supersede best clinical judgment by the Investigator. Please contact the Medical Monitor with any questions.

For **all patients**:

1. In general, supportive care (transfusions, administration of anti-fungals, etc.) should be maintained in accordance with institutional policy. (Note: Transfusions must be adequately recorded in the source documents to facilitate data entry of the study required parameters [i.e., type of blood product transfused, units, total volume]).
2. Patients taking medications with the potential to induce or inhibit CYP3A4 or CYP2D6 should be monitored closely for potential effects of co-administration; particular attention should be given to anti-infectives in the azole class.
3. There are no restrictions to, or recommendations on the timing of, administration of vaccines (i.e., COVID-19 vaccination).
4. Cessation of bomedemstat is associated with a rebound in thrombopoiesis, and platelet counts may exceed baseline in the patient. **When bomedemstat is discontinued, platelet counts must be monitored closely and the timing of the start of an alternative therapy should take the expected rebound of platelets into consideration.**
   - CCI [redacted]

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5. CCI [redacted]

6.5 Prohibited Medications

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

1. All cytotoxic agents with noted exception of hydroxyurea for MF patients as per Guidelines
2. All hematopoietic growth factors: romiplostim, eltrombopag, granulocyte and granulocyte-macrophage colony stimulating factor (G-CSF and GM-CSF) and erythropoietin (EPO)
3. Monoamine oxidase A and B inhibitors
4. Anticoagulant or nonsteroidal anti-inflammatory drug (NSAID; including aspirin) use, when patients platelet count is < 50 x 10^9/L

For **MF patients** only:

5. Prednisone or prednisolone > 10 mg/day or dexamethasone > 4 mg/day (doses exceeding these thresholds are permitted for management of gout). Maintenance supplemental corticosteroid therapy such as prednisone ≤ 10 mg/day or corticosteroid equivalent is allowed.

7 STUDY PRODUCT

7.1 Formulation, Labeling, Packaging and Storage

7.1.1 Formulation

The drug product bomedemstat (IMG-7289 / MK-3543) is a bis-tosylate salt. The free base of bomedemstat is the active moiety.

Bomedemstat will be supplied in capsules of multiple strengths. These strengths are based on bomedemstat free base (the active substance). The strengths may change over the duration of the study. Details on capsules 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.

7.1.2 Packaging and Labeling

Bomedemstat capsules will be supplied to the site pharmacy department by sponsor (or designee) in packaging in accordance with all applicable local regulatory requirements.

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

7.1.3 Storage

The recommended long-term storage condition for bomedemstat is a temperature not to exceed 25°C. Bomedemstat 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 bomedemstat-specific requirements. Bomedemstat supplies will be stored securely under the appropriate conditions according to the country, state and regional laws. Procedures for bomedemstat storage and accountability will be detailed in a Pharmacy Manual.

7.2 Dispensing, Administration, Dosage and Missed Doses

7.2.1 Dispensing

All material supplied is for use only in this clinical study and should not be used for any other purpose. Only patients enrolled in the study may receive bomedemstat, in accordance with all

applicable regulatory requirements. Only authorized site staff may dispense bomedemstat.

The Investigator must provide a prescription form every time bomedemstat is dispensed, including (but not limited to) the identification of the patient to whom bomedemstat is to be dispensed, the patient's weight, the requested dose in mg/kg/d and the Investigator (or designee's) signature.

Bomedemstat will be dispensed at doses in accordance with the dose chart provided and at the quantities detailed in the Pharmacy Manual. Since the bomedemstat dose and associated capsule strengths for each patient may change over time, minimize the patient retaining excess study drug capsules in their home.

Patients will be instructed to bring any unused bomedemstat in its dispensed packaging to each study visit for drug accountability. New bomedemstat supply will be dispensed at each visit. The Investigator and designated staff will maintain study drug accountability records (Section 14.5).

7.2.2 Administration

Appropriately trained study site personnel will provide patient instructions pertaining to bomedemstat administration and supervise the administration of bomedemstat, if taken in the clinic. It is, however, not required that bomedemstat 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.

Bomedemstat dosing will be based on the patient's established Dosing Weight from their feeder study. If during treatment the patient's weight changes by more than 10% from the established Dosing Weight, the amount of bomedemstat dispensed should be adjusted per the dose chart. The dispensing prescription form and source data must clearly document the weight used to calculate the dispensed daily dose.

Patients should be instructed to:

- Swallow the bomedemstat capsule(s) once daily, at approximately the same time.
    - While it would be recommended to take at night before bed, dose can be taken at any time during the day when convenient.
- Swallow the bomedemstat capsule(s) whole.
- Fast for 1 hour prior to and 30 minutes after a daily dose.
- Clear liquids are allowed during the fasting period.

7.2.3 Dosage

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7.2.4 Missed Doses

Patients who do not take their bomedemstat 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 temporary dosing interruption due to a medical or unforeseen patient situation, please consult the Medical Monitor for guidance on re-start of dosing. Patients who miss an extended duration of bomedemstat doses or exhibit serial non-compliance with treatment may be removed from the study at the discretion of the Investigator or Sponsor.

7.2.5 Interruption of Dosing

Patients requiring a Dose Hold according to the Titration and Rechallenge Rules, due to an (S)AE, or other unforeseen patient situation that interrupts daily dosing should undergo complete blood counts at least weekly for safety purposes and to enable re-challenge to commence as soon as counts return to the required level, if it is safe to do so.

8 SAFETY ADVISORY BOARD (SAB) REVIEWS AND MANAGEMENT OF STUDY TOXICITIES, INCLUDING STOPPING RULES

8.1 Safety Advisory Board (SAB) Reviews

Safety will be monitored throughout the study in accordance with a Safety Advisory Board Plan (SABP) by a SAB constituted by physicians with hematology expertise and clinical study experience. SAB reviews will occur at least quarterly as *per* the SABP. Reviews may also occur on an *ad hoc* basis when one of the following scenarios occurs:

- Fatal or life-threatening reaction assessed as related to bomedemstat (possibly, probably or definitely), regardless of expectedness, is reported
- Occurrence of other safety-related issues for patients receiving bomedemstat, such as evidence of unexpectedly severe effects on hematopoiesis, which pose a medical concern, and which may necessitate bomedemstat dose adjustment or discontinuation.

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

8.2 Management of Study Toxicities

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

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

Stopping rules are defined in Section 8.2.2.

8.2.1 Hematologic Toxicity

Hematologic values outside of the normal reference range are inherent features of MPNs and are expected effects of many therapeutic attempts to manage these diseases. MPN patients require doses of bomedemstat that are sufficient to reduce platelet counts and, to a lesser degree, absolute neutrophil counts. Any resulting reversible cytopenias can be managed clinically as needed with transfusions as well as broad-spectrum antibiotics, as *per* standard practice.

The effects of bomedemstat on normal myeloid hematopoiesis observed in non-clinical and clinical studies are expected; these are pharmacodynamic effects of LSD1 inhibition by bomedemstat, thus not regarded as adverse. Refer to the Investigator's Brochure for additional information.

8.2.2 Stopping Rules

Bomedemstat will be permanently discontinued and the patients will undergo the Follow-up Period visits (see Section 9.4) in the event of the following:

- PI or Medical Monitor deem it unsafe for the patient to continue bomedemstat.
- Following the temporary interruption of bomedemstat due to platelet counts below the applicable threshold (25 x 10^9/L for MF patients and 50 x 10^9/L for ET patients), the patient's platelet counts do not return to the required threshold (>50 x 10^9/L for MF patients and >150 x 10^9/L for ET patients) within 21 days. Note: new platelet thresholds may apply as additional feeder studies are conducted; such thresholds will be specified in the Study Reference Manual and Pharmacy Manual.

9 STUDY ASSESSMENTS

This section provides comprehensive detail on the visits and assessments required and should serve as the main guidance for use during study visits. The Schedule of Assessments (Section 16.1) contains these details in tabular form and is provided for use in a supportive/reference capacity only. To maintain clarity while facilitating a modicum of brevity, the 'Terms' in Table 1 below will be utilized in this section to encompass the broader 'Protocol Meaning' as stated.

Table 1 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 in the mid-clavicular line. Measure in the same manner at all visits.
	• Weight, measured (in kg)
	• Review of body systems for changes from previous visit
	• Vital signs, after patient has sat semi-supine for ~3 minutes, of:
	  ○ Heart rate
	  ○ Respiratory rate
	  ○ Temperature
	  ○ Systolic/diastolic blood pressure

Adverse Events and Concomitant Medications Collection	Use non-directive questions (i.e., "How are you feeling") to query patient regarding AEs that may have occurred and inquire about medication changes.
Full Local Lab Assessment	The following panels performed locally (Section 10.1.1 details analytes): • Hematology with automated differential • Biochemistry • Coagulation • Urinalysis • Serum pregnancy test for WOCBP
MPN Symptom Questionnaires	IRB/EC approved questionnaires will be completed based on the version required in the applicable feeder study. For example, the MPN-SAF TSS for IMG-7289-CTP-102 and the MPN-SAF for IMG-7289-CTP-201. Questionnaires will be completed weekly, ideally at the same time and day each week for consistency, through the EoS or ET Visit. The actual date of questionnaire completion, not the planned or collected date, must be documented on each questionnaire completed. On visit days, the questionnaire should be completed prior to the study visit. If the patient arrives without a completed questionnaire, the patient will complete it during the visit, and it will be collected by study staff prior to the patient departing.

Term	Protocol Meaning
	Importantly, multiple questionnaires will need to be provided to the patient for completion on a weekly basis between visits. Note, for patients undergoing monthly labs locally, consideration should be given to the use of a courier for provision and return of questionnaires.
Bone Marrow Sampling and Assessments	• Aspirate sample should be optimally obtained within the first pull. Do not collect after a second pull attempt, and biopsy collected as per site standard procedure. • A central laboratory will perform morphology review, fibrosis grading and store BMMCs for possible correlative research analysis (Section 10.1.2). • Note: Any results available from site routine bone marrow work-up, including morphology, cytogenetics, other genetic interrogations will be collected either via the eCRF or through collection of local reports.
Study Drug Dispensing and Dosing Instructions	• Administer bomedemstat in accordance with the Pharmacy Manual instructions. • Instruct patients to refer to their Dosing Card every day for details on bomedemstat dosing (Section 7.2.2) and handling of missed doses (Section 7.2.4)

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

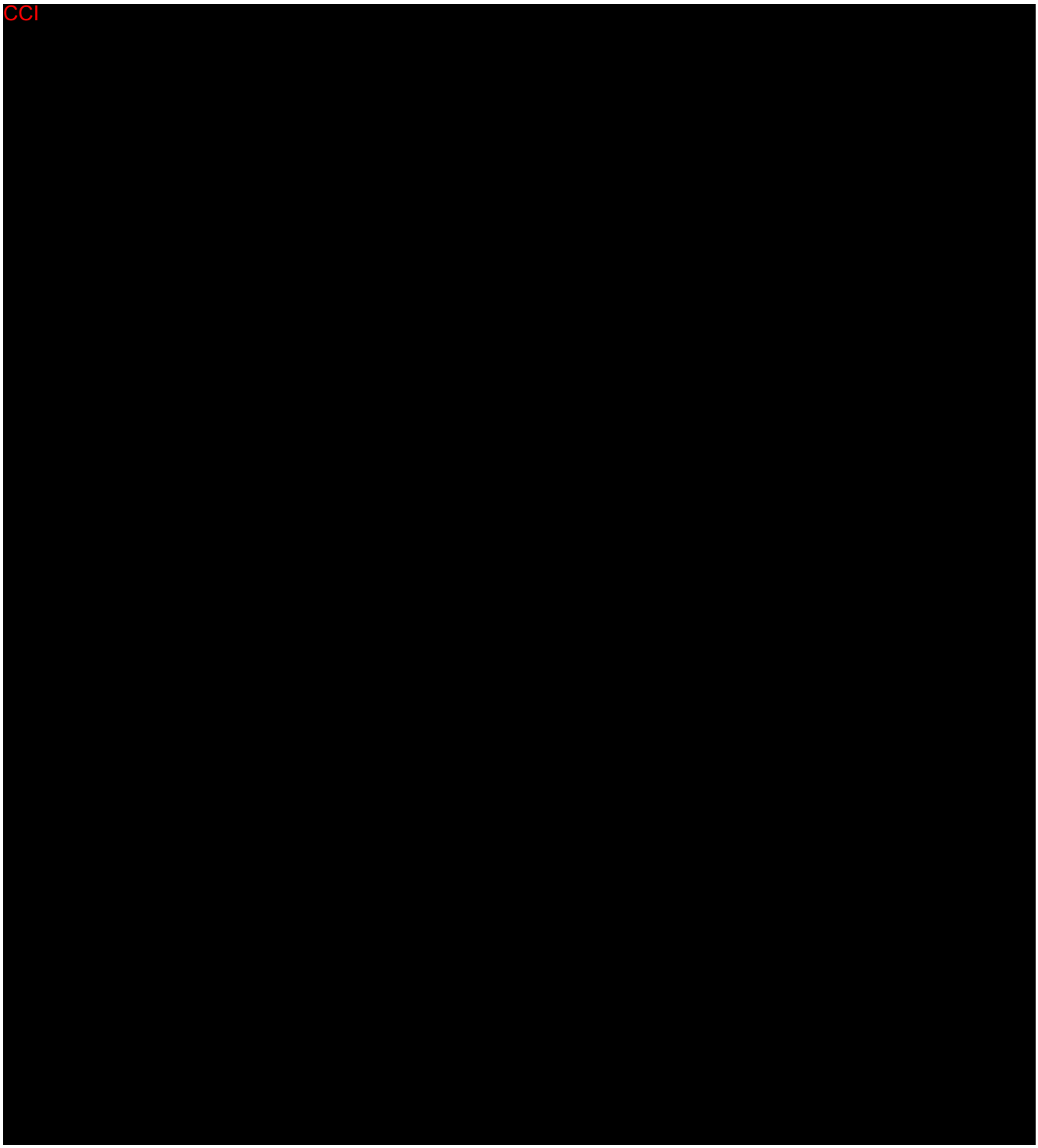
9.1 Enrollment Period

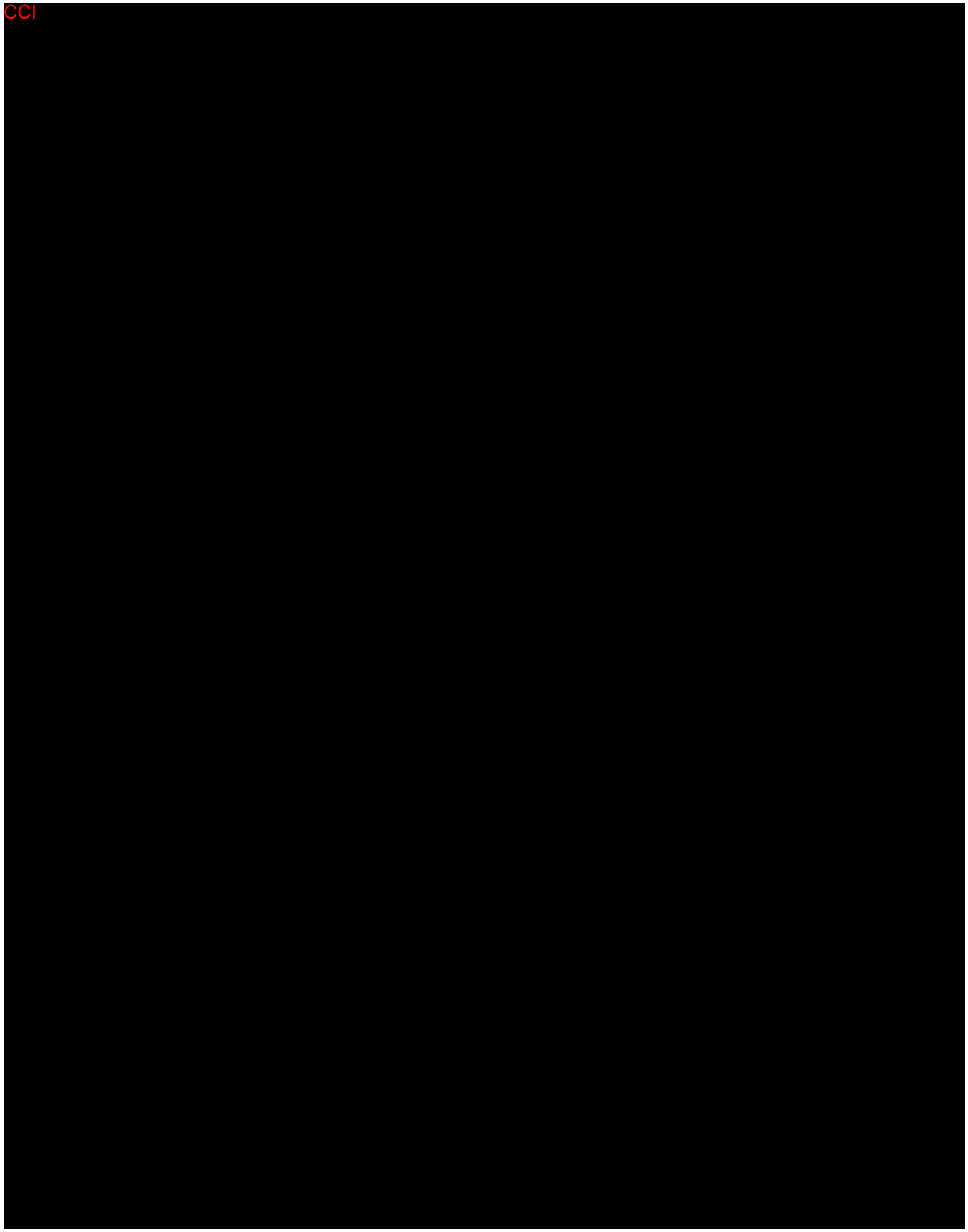
9.1.1 Informed Consent Visit

Details of the extension study and a copy of the Participant Information Sheet/Consent Form (PISCF) should be provided to the patient prior to their anticipated final feeder study visit. Informed consent should be obtained at, or before, the feeder study's final visit. Patients must provide documented informed consent before undergoing any study-related procedures. The PI, or designee, will explain to the patient the study purpose, 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 documented informed consent for their involvement in the study in the presence of the PI, or designee, who will also sign and date the PISCF. Time, date, name of the person taking consent and any questions raised by the patient must be documented in the source data.

9.1.2 Eligibility Assessment

Once consent has been obtained for participation in the extension study, the PI will assess whether the patient is eligible. If the patient meets all eligibility criteria, then they will be enrolled upon commencement of their first extension study visit (Section 9.1.4). Patients deemed ineligible should have the reason(s) documented in the patient's source data and on the Screening & Enrollment log.

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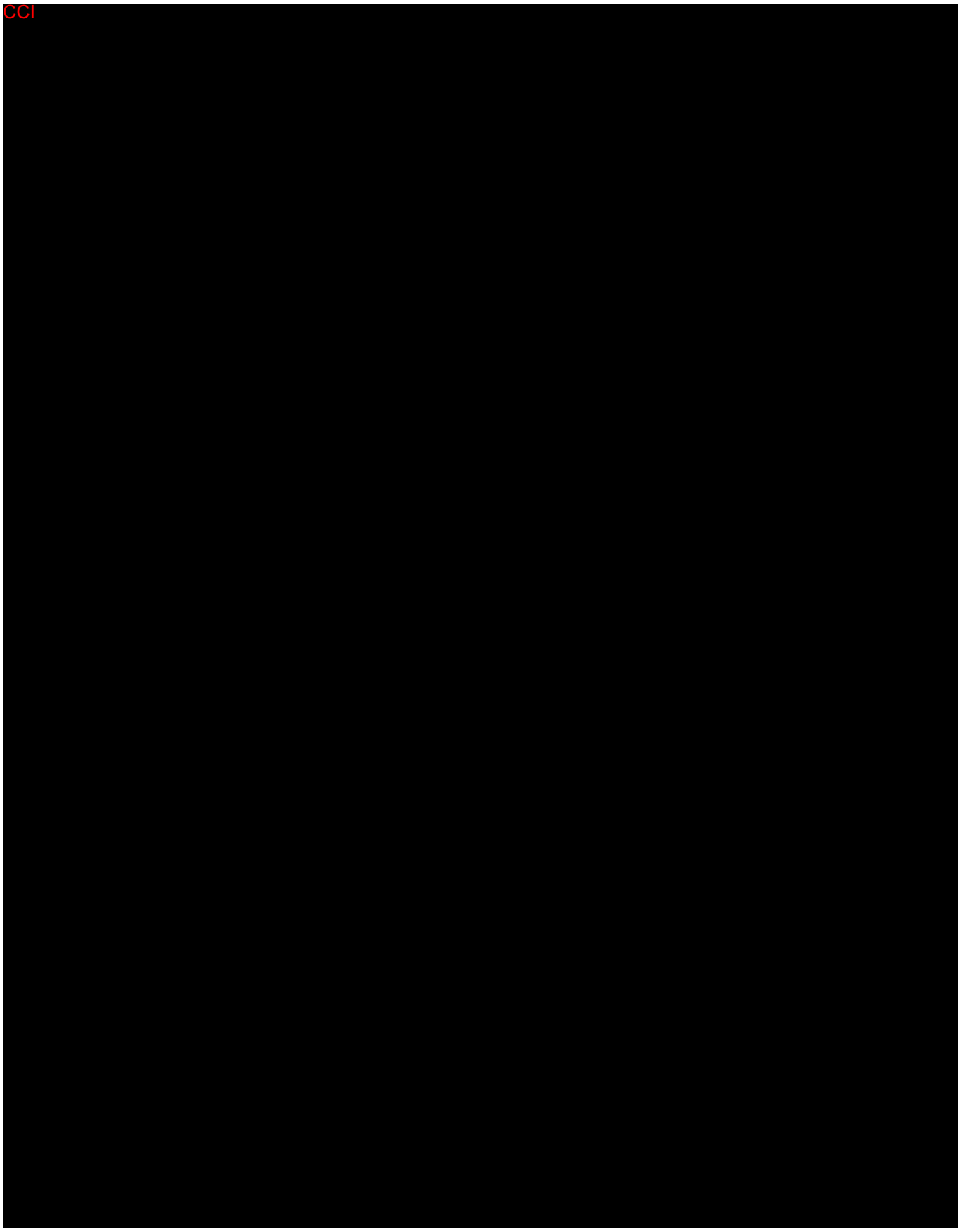

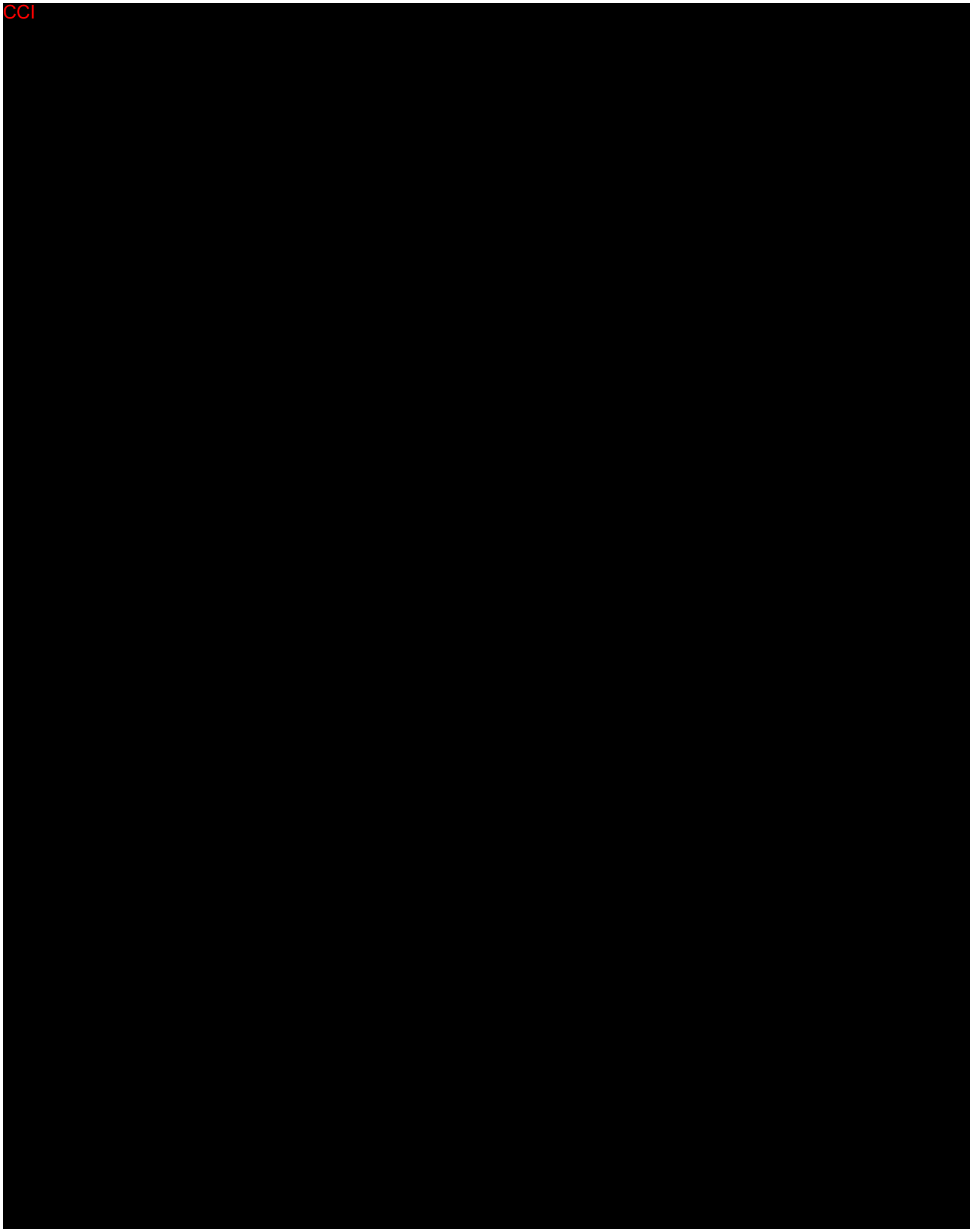
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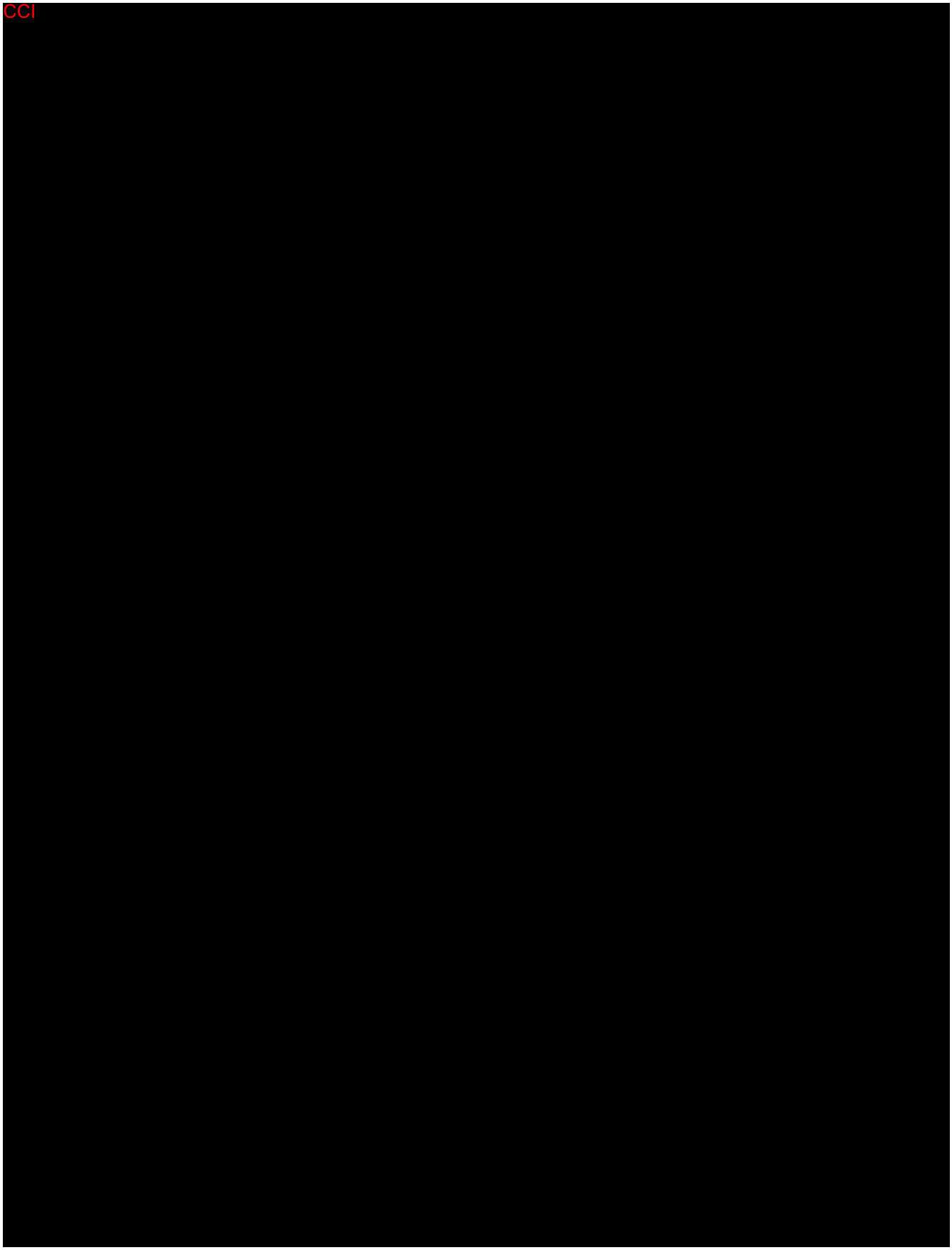

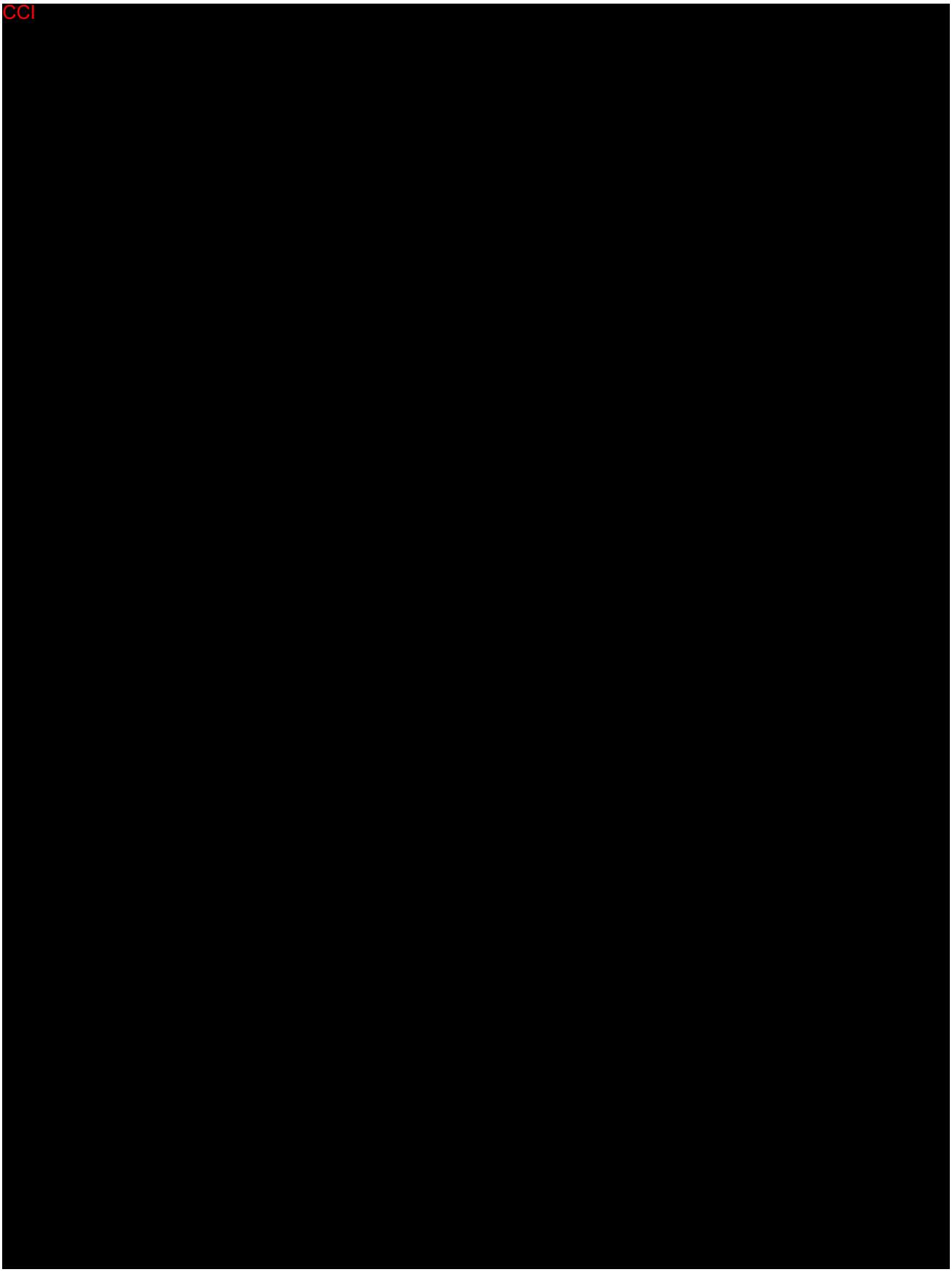
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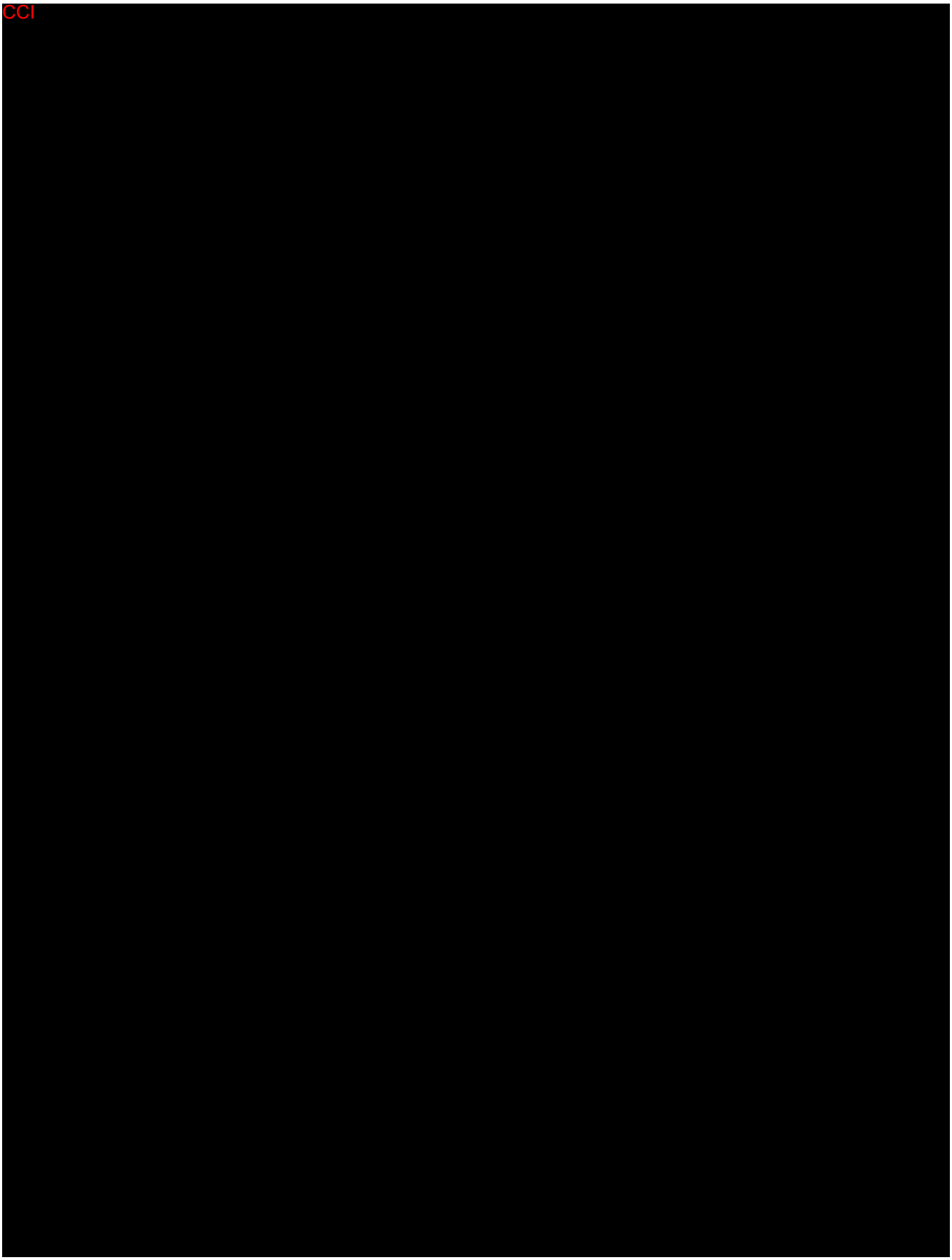

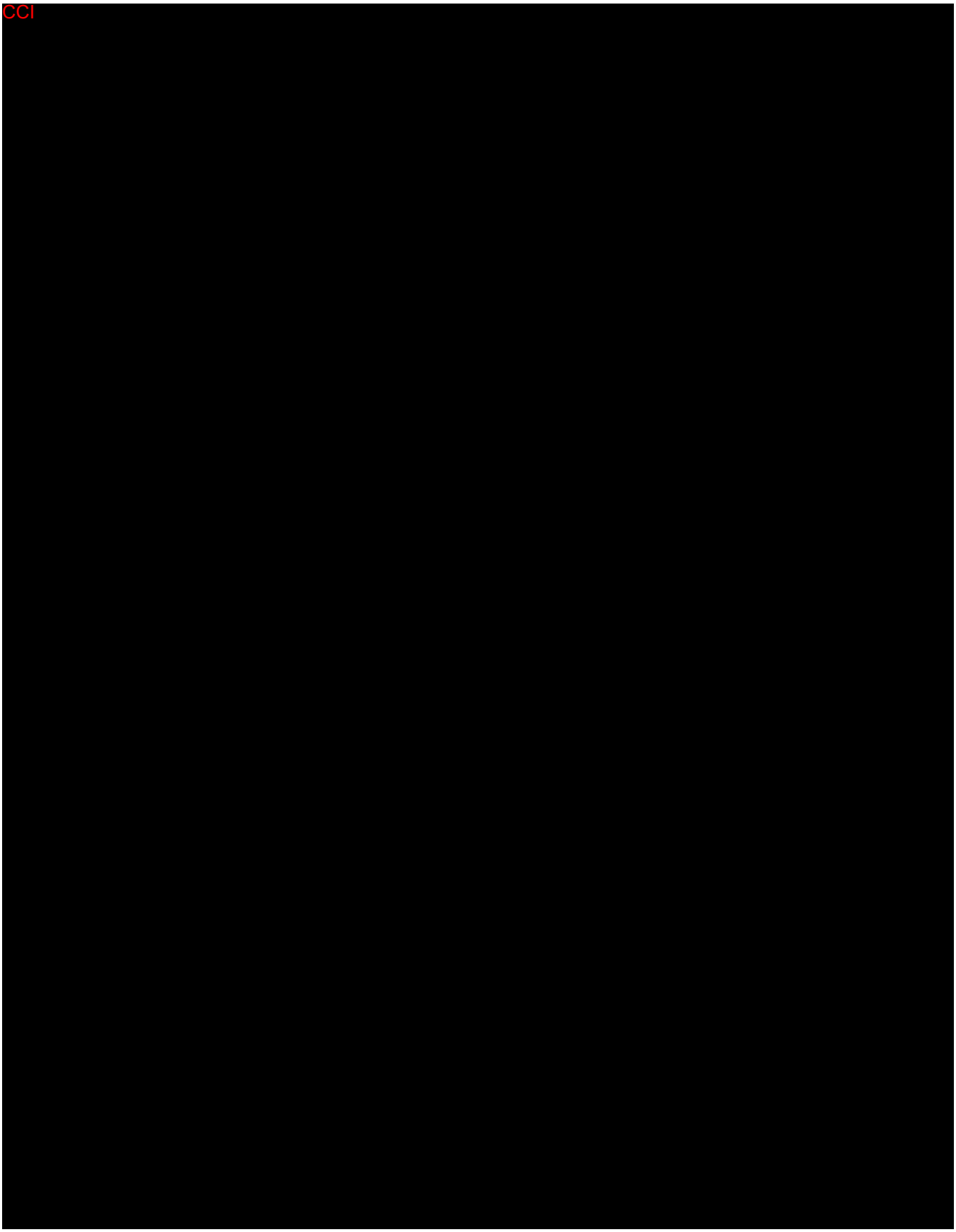
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10 LABORATORY SAMPLING FOR SAFETY AND PD ANALYSIS

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

The average of the blood volumes collected, which varies by local laboratory institution, is provided in EC/IRB approved the informed consent.

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

10.1.1 Local Laboratory Measures

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

Hematology: Hemoglobin, red blood cell count (RBC) (including nucleated RBC), red cell distribution width, hematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), platelets, mean platelet volume (MPV)*, white cell count and automated or manual assessment as needed to ensure the following results are generated: neutrophils, lymphocytes, monocytes, eosinophils, basophils, reticulocytes, promyelocytes, myelocytes, metamyelocytes and blasts.

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

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

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

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

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

Sample Processing: Sponsor 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 a Full Local Laboratory Assessment and a Hematology Local Laboratory Assessment varies by institution.

10.1.2 Central Laboratory Measures

Bone Marrow Sampling Requirements: Approximately 2-3 mL bone marrow aspirate sample for central analysis must be collected from the first pull, whenever possible, and no later than the second (except in the case of dry tap). A peripheral blood smear must also be provided the same day for review in conjunction with the bone marrow sample; additionally a de-identified copy of the hematology (CBC) report from the day of bone marrow sampling should be sent to the central lab with the bone marrow samples (or follow by email as soon as available). A 1-2 cm section of

trephine bone marrow sample must also be collected and sent to the central laboratory as a formalin fixed, paraffin embedded block (unless alternative arrangements have been agreed with sponsor). Measures to be performed centrally include: myelofibrosis grading and morphology review. Remaining bone marrow aspirate following preparation of the morphology slides may be used for analysis of mutant allele burden over the course of bomedemstat treatment. Genomic sample collection, handling, storage, and analysis will conform to all applicable national guidance and regulations.

Genomic Testing: At each required sample time-point approximately 20 mL peripheral blood sample will be collected for analysis. During the feeder protocols germline samples consisting of hair roots and a cheek swab were collected for analysis. If, upon analysis, the sample yield was found to be inadequate a repeat sample of either type may be requested as part of their feeder study or as part of this protocol. Genomic sample collection, handling, storage, and analysis will conform to all applicable national guidance and regulations.

Future Correlative Studies: Approximately 10 mL additional blood will be collected and stored in conjunction with each genomic blood sampling time-point for the purposes of potential correlative studies. If site process permits, samples collected and stored earlier in the course of their MPN, and any available genetic data may be requested.

Patients at specific sites/countries may need to provide specific consent for the analysis of these correlative samples but samples will be collected for all patients.

Sample Processing: Sponsor will provide a laboratory manual documenting the collection and handling of samples to be analysed centrally. Laboratory supplies will be provided for the collection of all central laboratory samples.

11 SAFETY

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

If the patient is withdrawn from treatment, the patient will discontinue study treatment and on that day or as soon as possible thereafter undergo an EoT visit and have the Follow-up Period EoS visit scheduled (see Section 9.4).

11.1 Pregnancy

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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 bomedemstat at the Transition Visit through to the EoS Visit (scheduled at 14 days post last bomedemstat dose). AE recording will continue for patients who discontinue study drug but remain in Follow-up Period, until their EoT and EoS Visits have been completed.

Note: Any medical event i.e., (S)AE which is ongoing from the feeder protocol study at the time of dosing with bomedemstat in this protocol must be documented in the patient's medical notes and will be recorded on the appropriate eCRF pages as AEs ongoing at the time of study entry.

New AEs 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 bomedemstat under this protocol until completion of the study.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient and/or observed by the Investigator or medical staff
- Findings at physical examinations
- Laboratory abnormalities of clinical significance
- Overdose defined as any dose exceeding the prescribed dose for bomedemstat

- Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

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

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the study drug 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

AE intensity will be evaluated using the NCI CTCAE version 5, published 27-NOV-2017. For AEs not included in the NCI CTCAE, the Investigator will be required to assess the 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 AE to the use of the drug or biologic. This may include, but is not limited, to the adverse experience being an expected outcome of a previously existing or concurrent disease, concomitant medication or procedure the subject experienced during their treatment period.
- Remote/Unlikely: AEs which are judged probably not related to the drug or biologic.
- Possible: There was no clear relationship of the AE to the use of the drug or biologic; however, one cannot definitively conclude that there was no relationship.
- Probable: While a clear relationship to the drug or biologic cannot be established, the event is associated with an expected AE (per the current Investigator Brochure or SAB findings) or there is no other medical condition or intervention which would explain the occurrence of such an experience.
- Definite: The relationship of the use of the drug or biologic to the experience is considered definitively established.

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

11.2.3 Serious Adverse Events

SAEs will be reportable from the time of first dose in the extension study through the EoS or ET Visit **or** until the Investigator and sponsor determine that follow-up is no longer necessary. SAEs that are suspected to be drug related will be reported even if they occur when the patient is no longer on the study.

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

Death

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

Required or prolonged inpatient hospitalization¥. The AE resulted in an initial inpatient hospitalization or prolonged an existing hospitalization of the patient. If a patient is hospitalized as part of the clinical use of the product, a period of normal hospitalization will be outlined in the

protocol or by the judgment of the Investigator. Hospitalizations longer than this period will be prolonged hospitalizations.

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

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

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

11.2.4 Reporting Serious Adverse Events

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

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

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

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

11.2.5 For Participants Who Consent To Another Bomedemstat Extension Study

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

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

12 ANALYSIS AND STATISTICAL CONSIDERATIONS

12.1 General Considerations

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

12.2 Power

There are no sample size calculations for this extension study. Sample size will be based on elective participation of patients who were enrolled into the feeder studies.

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 bomedemstat will be assessed by the analysis of adverse events (AEs), as well as changes in physical examinations, vital signs and laboratory values as detailed below.

- Monitoring of Adverse Events (AEs), serious adverse events (SAEs), and AEs. AEs will be assessed from time of entry into study until EoS or ET in terms of onset, duration, seriousness, severity and causality, using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.

- Changes in physical examinations, vital signs and laboratory values will also be assessed until EoS or ET. Information on the timing of these assessments is presented in the schedule of assessments. The following laboratory tests will be conducted:
    - Complete blood counts (CBC) and differential
    - Coagulation
    - Chemistry
    - Urinalysis

Additionally, in **MF patients**:

- Spleen volume reduction will be assessed based on spleen volume measured by MRI (or CT where applicable) approximately every 48 weeks.

Additionally, in **ET patients**:

- Reduction of platelet counts will be evaluated and assessed based on local laboratory measurements of platelet counts collected serially throughout the study.

12.4.2 Exploratory Endpoints

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12.5 Data Analysis

12.5.1 Safety and Tolerability Data Analysis

Demographics will be tabulated and summarized. Adverse events/ongoing medical event data at the time of study entry will be listed, as will Physical Examination data at time of study entry, 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 bomedemstat will be included in the safety analysis.

Laboratory values outside the laboratory normal ranges will be summarized and assessed for change from time of study entry and Day 1 in the feeder study.

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 and time of study entry, 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.

12.5.2 Efficacy Data Analysis

The primary efficacy objective for this study is to measure the extent and durability of bomedemstat treatment effects on the exploratory endpoints including any impact of bomedemstat on the natural history of MF and ET. The long-term effects of bomedemstat will be examined by summarizing the exploratory endpoints from feeder study baseline through the extension study.

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If applicable, progression free survival (PFS), event free survival (EFS), and overall survival (OS) will be calculated using the Kaplan-Meier method.

Additionally, for **MF Patients, s**pleen volume reduction will be assessed based on spleen volume measured by MRI (or CT where applicable).

Additionally, for **ET Patients**, the below endpoints, proportions and corresponding 95% confidence intervals will be based on the Clopper-Pearson method:

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13 STUDY ADMINISTRATION

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

13.1 Ethical Considerations

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

13.2 Participation Information Sheet/Consent Form (PISCF)

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

The PISCF must be documented 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

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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. CCI [redacted]

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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 ICHGCPs, including ICH E6, and ethical principles established by the Declaration of Helsinki.

13.5 Study Monitoring Requirements

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

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

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

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

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

13.6 Quality Assurance

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

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

13.7 Confidentiality

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

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

Information obtained during the conduct of this study will be collected, processed, and transmitted to or for the benefit of sponsor in accordance with the applicable regulations and principles of confidentiality for each participating country. Information contained therein will be maintained in accordance with applicable law protecting patient privacy, including the provisions of 46 CFR Part 164 promulgated under the Health Insurance Portability and Accountability Act (HIPAA) and may be inspected by the clinical researcher, the researcher's staff, Sponsor and its representatives, partners, advisors, affiliates, successors, and clinical research contractors and subcontractors to check, process, evaluate, and use the information collected during the study. The patient PISCF (or a separate data protection consent form if required

locally) will be used to obtain participant consent to 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 sponsor or its affiliates or successors in connection with the development of study drug, including possible filing of applications with governmental authorities for marketing approval, and for other pharmaceutical and medical research purposes. The study Investigator is obliged to provide Sponsor with complete test results and all data developed in this study. This information may be disclosed to other physicians who are conducting similar studies and to the applicable regulatory authorities as deemed necessary by sponsor. Patient-specific information may be provided to other appropriate medical personnel only with the patient's permission, as necessary and in accordance with other applicable privacy laws and regulations protecting patient health information.

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

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

14 INVESTIGATOR REQUIREMENTS

14.1 Protocol Adherence

Each Investigator must adhere to the protocol as detailed in this document and agrees that any changes to the protocol must be approved by sponsor's 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 sponsor. 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 sponsor (or disposal of the drug, if approved by sponsor) will be maintained by the clinical site. These records will adequately document that the patients were provided the drugs and doses as

specified in the protocol and should reconcile all study drugs received from sponsor. Accountability records will include dates, quantities, batch/serial numbers, expiry dates (if applicable), and patient numbers. Sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

14.6 Disposal of Study Drug

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

14.7 Training of Staff

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

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

14.8 Clinical Study Report

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

14.9 Retention of Records

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

15 REFERENCES

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

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

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

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

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

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

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

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

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

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

Jones A (VP Cliical Operation, Imago BioSciences). Global Study Reference Manual; Version 2.0. Redwood City (CA): Imago BioSciences, Inc.; 2021 Dec 2. 24 p. Protocol No.: IMG-7289-CTP-202.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Saleque, S., Kim, J., Rooke, H.M., Orkin, S.H., 2007. Epigenetic regulation of hematopoietic differentiation by Gfi-1 and Gfi-1b is mediated by the cofactors CoREST and LSD1. Mol Cell **27**, 562-572.

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

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

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

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

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

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

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

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

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

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

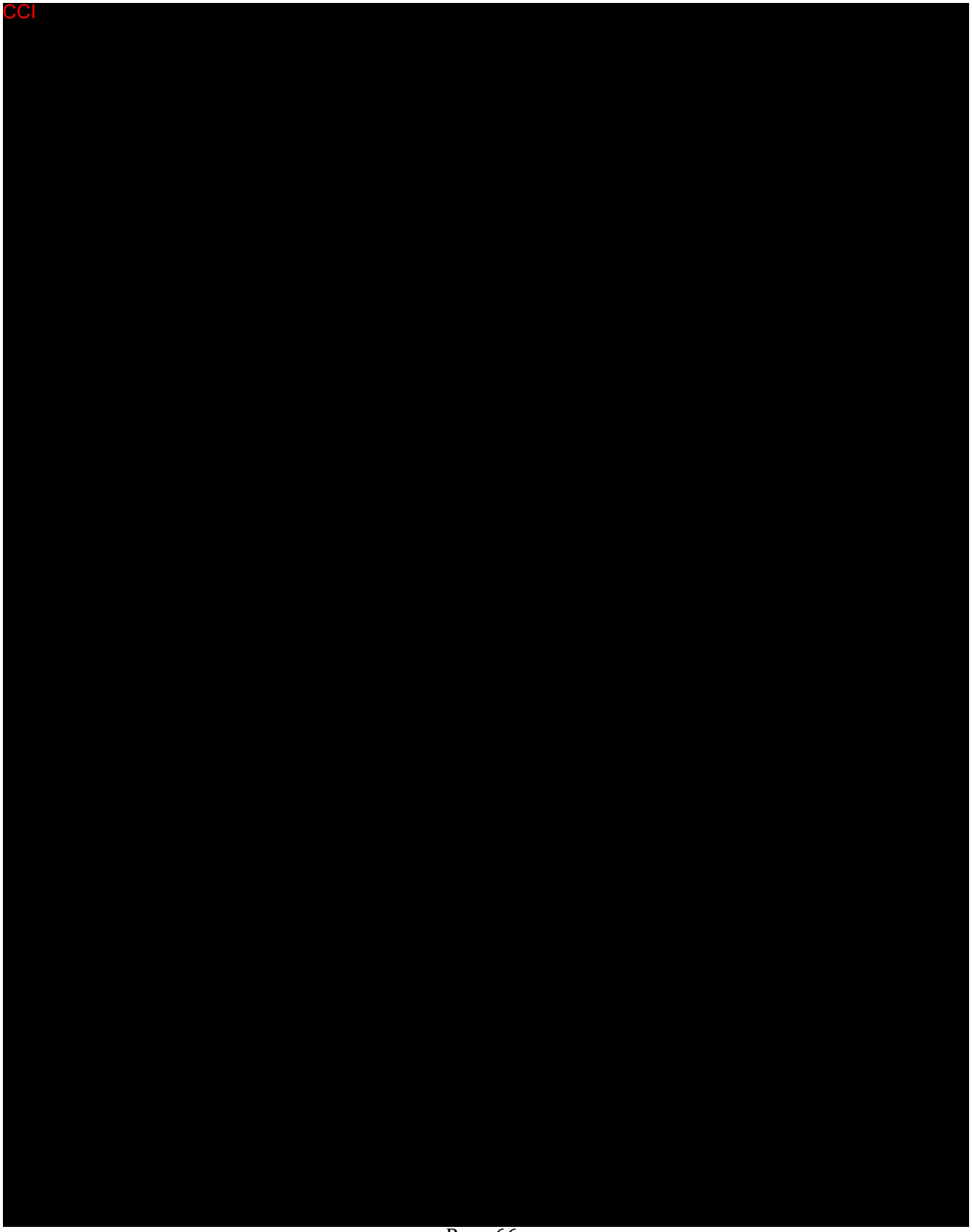
Whyte, W.A., Orlando, D.A., Hnisz, D., Abraham, B.J., Lin, C.Y., Kagey, M.H., Rahl, P.B., Lee, T.I., Young, R.A., 2013. Master transcription factors and mediator establish super-enhancers at key cell identity genes. Cell **153**, 307-319.

Wouters, B.J., Lowenberg, B., Erpelinck-Verschueren, C.A., van Putten, W.L., Valk, P.J., Delwel, R., 2009. Double CEBPA mutations, but not single CEBPA mutations, define a subgroup of acute myeloid leukemia with a distinctive gene expression profile that is uniquely associated with a favorable outcome. Blood **113**, 3088-3091.

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

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

16 APPENDICES

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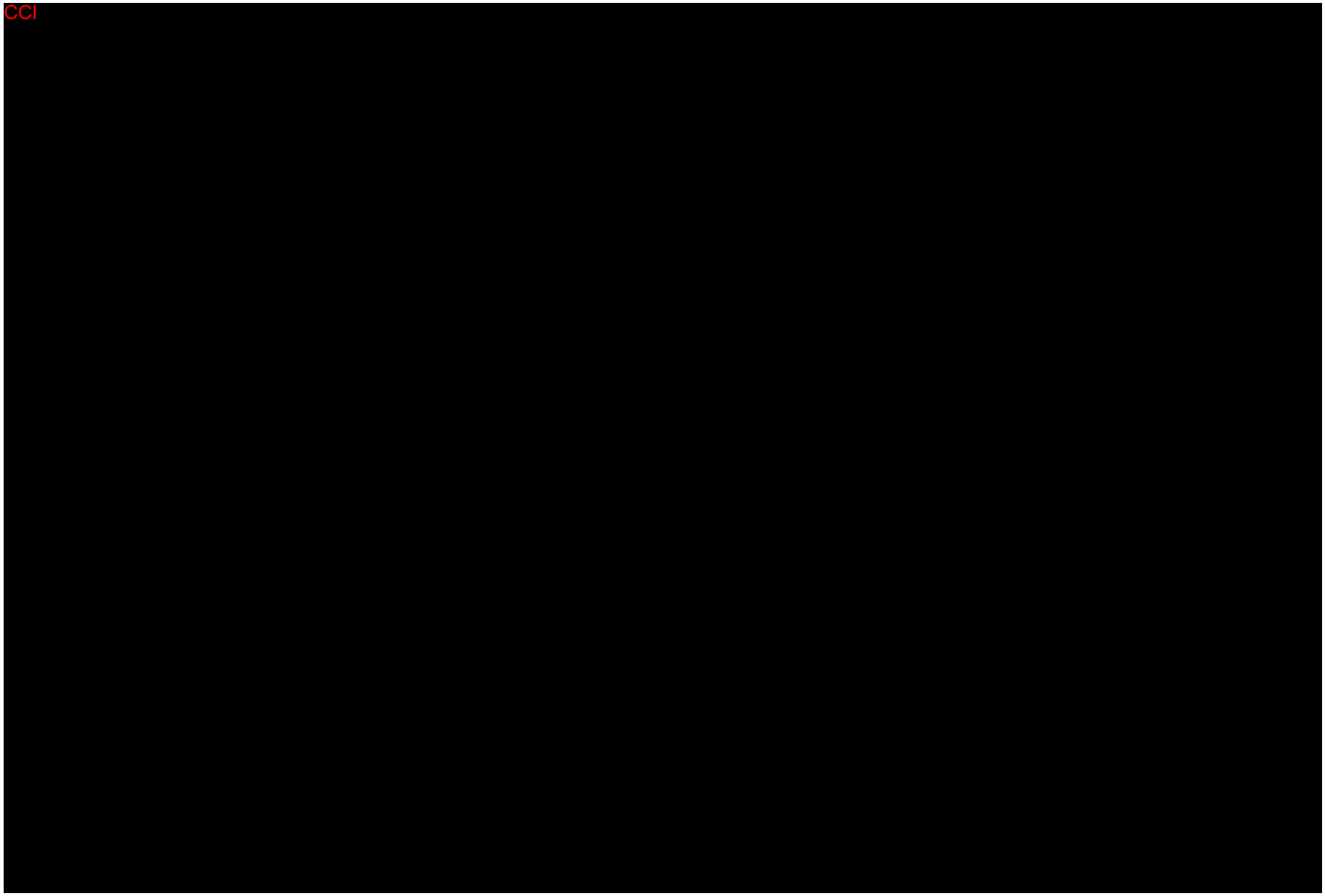
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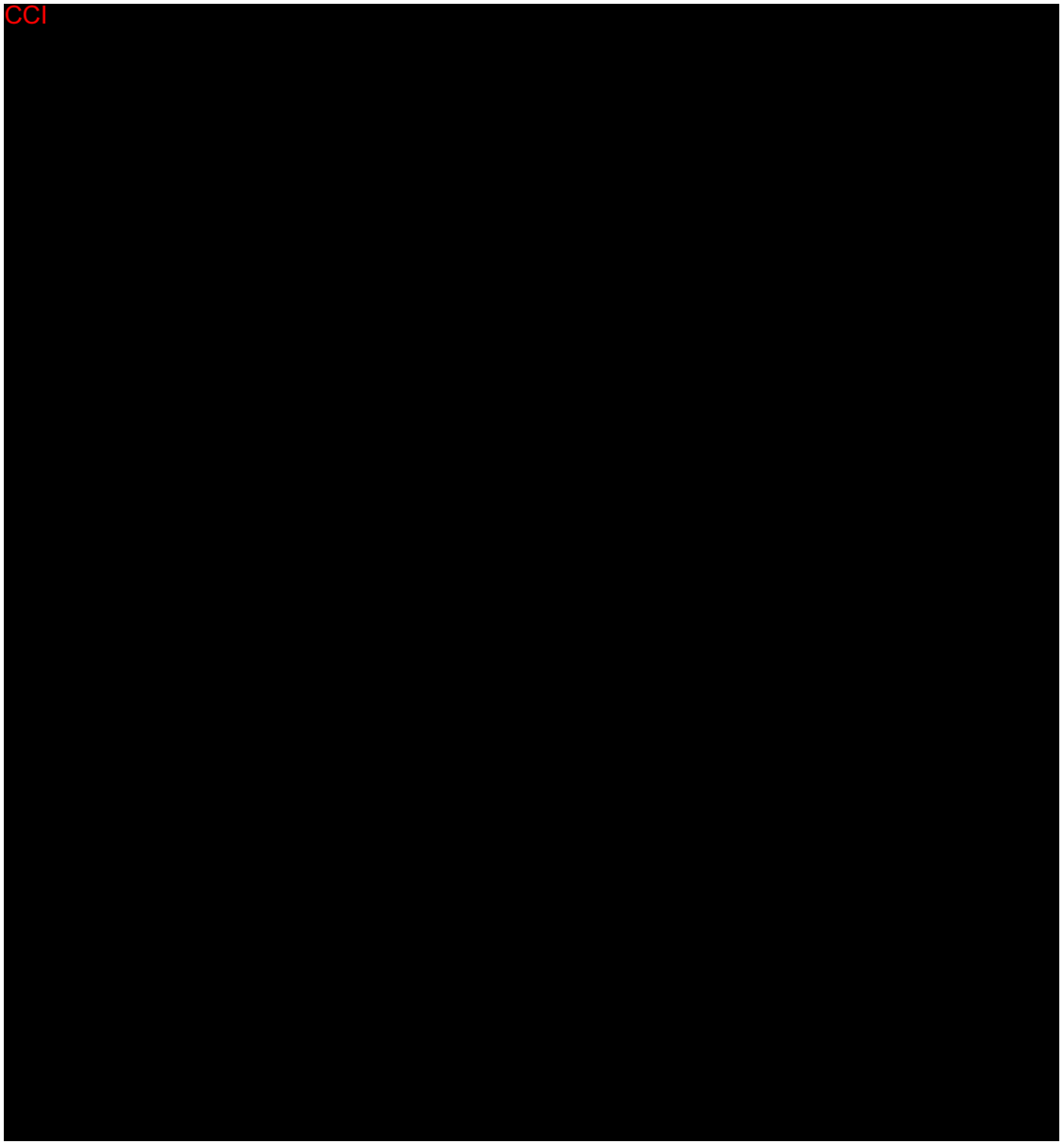
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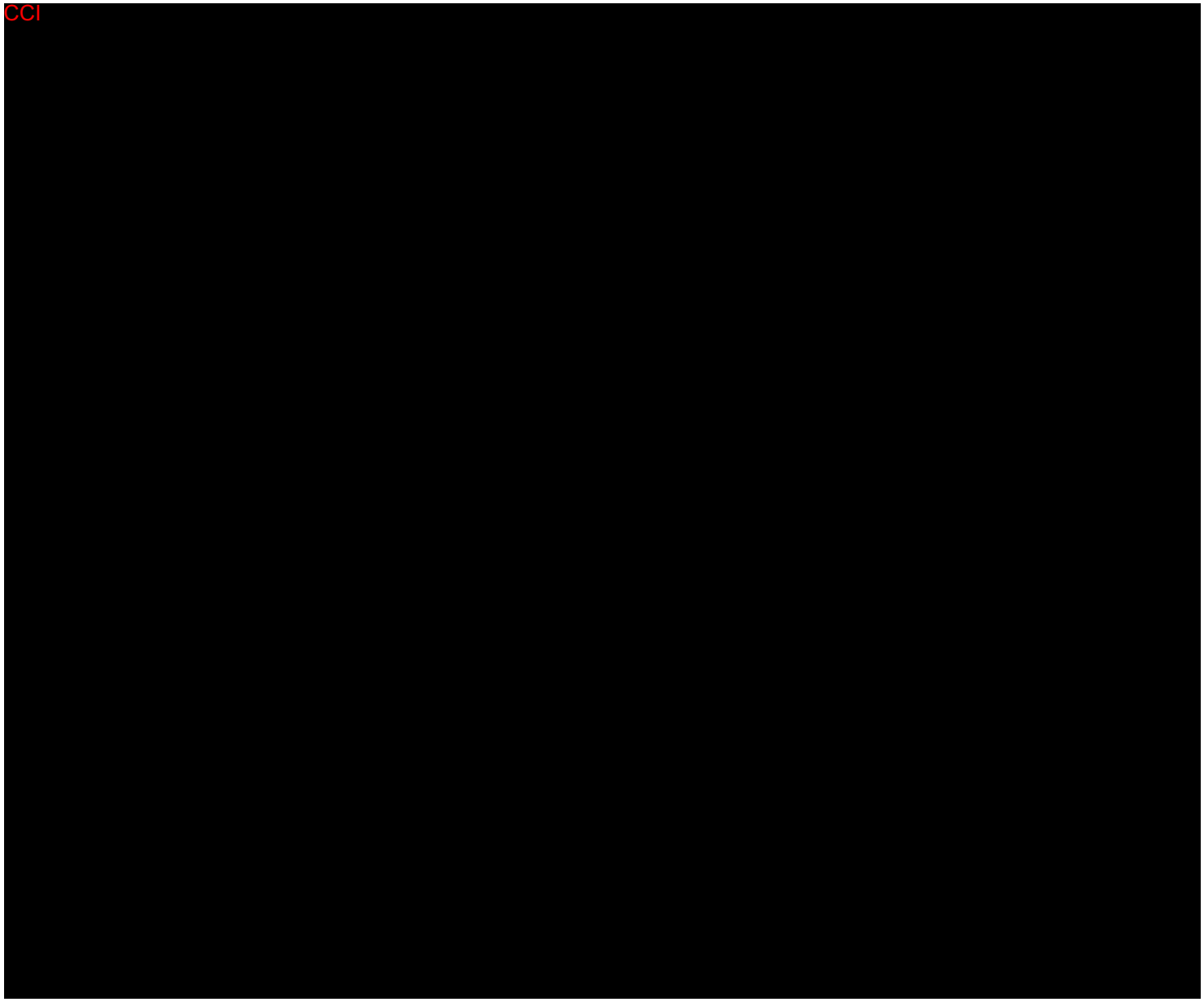

16.2 Criteria for Grading Myelofibrosis (Arber *et al.*, 2016)*

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]

*Slightly modified from the European Consensus Criteria as presented in Thiele *et al.*, 2005
Semiquantitative grading of BM fibrosis with minor modifications concerning collagen and osteosclerosis. Fiber density should be assessed only in hematopoietic areas.

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

16.3 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

16.4 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{
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.
ʕTransfusion 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.

16.5 Revised Response Criteria for ET: IWG-MRT and ELN Consensus 2013 (Barosi et al., 2013)

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

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

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

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

IMG-7289 -CTP-202
Patient Information: __ __ __ - __ __ __ (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 is required *weekly* during your participation in the IMG-7289-CTP-202 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-202; V1, 12May2021 7-DAY RECALL

16.7 Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)

IMG-7289 -CTP-202
Patient Information: __ __ __ - __ __ __ (Site # Screen #) ___/___/___ (Initials) Completion Date: ____/_____/_____ (dd mmm yyyy)

Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)

Instructions: Please fill out all questions, as best able, reflecting how these symptoms affected you over the **LAST WEEK** unless directed otherwise.

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

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

1

For use by participants in: IMG-7289-CTP-202; 12May2021

IMG-7289 -CTP-202

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

Circle the one number that describes, during the past Week, how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal pain	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with headaches	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Dizziness/ Vertigo/ Lightheadedness	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/ Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Difficulty sleeping	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Depression or sad mood	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with sexual desire or Function	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Cough	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100˚F / 37˚C)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
What is your overall quality of life?	(As good as it can be) 0 1 2 3 4 5 6 7 8 9 10 (As bad as it can be)

16.8 Patient Global Impression of Change

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

Patient Global Impression of Change (PGIC)

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

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

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

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

For use by participants in: IMG-7289-CTP-202; 27Apr2021

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

16.9 Remote Data Review

16.9.1 Risk Assessment

Sponsor will remain responsive where possible, to the remote data review requirements of each individual site regarding how patient visits and monitoring visits can occur remotely, when possible.

16.9.2 Security Measures

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

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

16.9.3 Processes

As outlined in Section 13.5, remote data review is intended to encompass as many activities performed in a routine on-site monitoring visit as is functionally possible, and as permitted by site policy and procedure. The source documents/source data to be made available for remote data review include those related to the primary endpoint and exploratory endpoints, safety, study drug dispensation and return and the reasons for exclusion of a subject from the trial.

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

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

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

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

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

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

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

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

- The video call/conference may only occur using a Syneos Health approved information and communication technology.
- Video review of documentation only is permitted.
- No recording of the interaction is permitted.
- No document upload is permitted.
- No document storage is permitted.
- Usage must comply with applicable local regulations/regulatory guidance.
- During remote data review by video call/conferencing care will be taken to avoid inadvertent viewing of individuals who should not be part of the interaction.

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

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

confirm an individual data-point.

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

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

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

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

- Scanned images via secure email (encrypted email or password protected email attachment. If the latter, the password will be provided to Monitor via telephone)
- A secure platform for document exchange

- A set of the prepared source document package, including transmittal form, will be retained in the Investigator's Site File. Note: These documents will not be retained in Germany.