Official Protocol Title:	A Multi-Center, Open Label Study to Assess the Safety,Steady-State Pharmacokinetics and Pharmacodynamics of IMG-7289 with and without ATRA (Tretinoin) in Patients with Advanced Myeloid Malignancies
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Protocol No.:	IMG-7289-CTP-101
Investigational Product:	IMG-7289
Indication:	Advanced Myeloid Malignancies
Study Phase:	Phase 1/2a
Sponsor:	Imago BioSciences, Inc. 2729 Debbie Court San Carlos, CA 94070 - USA PPD Imago BioSciences, Ltd. Church Cottage 28 Broadway Chilton Polden Somerset TA7 9DP United Kingdom PPD
Principal Medical Monitor:	PPD Imago BioSciences, Inc. PPD
Clinical Operations:	PPD Imago BioSciences, Inc. PPD
Version and Date Final:	Original Protocol: 05 April 2016 Amendment 1: 29 June 2016 Amendment 2: 19Jan2017 Addendum 1: 13Jun2017 **Amendment 3: 29Aug2017**

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

PPD

Signature

29 Aug 2017

Date

INVESTIGATOR SIGNATURE PAGE

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Sponsor:	Imago BioSciences, Inc. 2729 Debbie Court San Carlos, CA 94070 - USA PPD Imago BioSciences, Ltd. Church Cottage 28 Broadway Chilton Polden Somerset TA7 9DP United Kingdom PPD

Declaration of Investigator

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

_____ _____

Investigator Signature Date

_____ _____

Investigator Name (Print)

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

1.1 List of Abbreviations

Abbreviation	Definition
<, ≤, >, ≥	less than, less than or equal to, greater than, greater than or equal to
±	plus
6-MP	6-mercaptopurine
6-TG	6-thioguanine
7+3	seven days of cytarabine and three days of an anthracycline, generally daunorubicin or idarubicin
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
ANC	absolute neutrophil count
APL	acute promyelocytic leukaemia
A_sO_3	arsenic trioxide
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
ATRA	all-*trans* retinoic acid; tretinoin; Vesanoid®
AUC	area under the drug concentration time curve
AUC_{0-24}	area under the drug concentration time curve from time zero to 24 hours post-dose
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
°C	degrees Centigrade
C	cohort
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CL/F	apparent total clearance of drug after oral administration
C_{max}	maximum observed blood concentration
C_{min}	minimum observed plasma concentration at 24 hours from last dose
CNS	central nervous system
CR	complete remission or response
CRi	complete remission or response, with incomplete recovery
CRF	case report form

Abbreviation	Definition
CSF2	colony-stimulating factor 2
CSF3	colony-stimulating factor 3
CXCR4	chemokine (C-X-C motif) receptor 4
CTCAE	Common Terminology Criteria for Adverse Events
CV	co-efficient of variation
Cycle	duration comprised by the dosing and rest period; also referred to as treatment cycle
d	day
D_i	dose needed to inhibit normal myeloid haematopoiesis
DIC	Disseminated Intravascular Coagulation
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
D_p	pharmacodynamic dose; the dose needed to effect desired pharmacodynamics changes in malignant cells
D_s	starting dose
DSMC	Data Safety Monitoring Committee
DSMP	Data Safety Monitoring Plan
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event free survival
EOS	end of study
EOT	end of treatment
EPO	erythropoietin
ESC	embryonic stem cell
EVI-1	ecotropic viral integration site 1
°F	degrees Fahrenheit
FAB	French American British
FACS	fluorescence-activated flow cytometry
FC	flow cytometry
FISH	fluorescent *in-situ* hybridisation
FPFV	first patient first visit
Free base of IMG-7289	*N*-[(2*S*)-5-{[(1*R*,2*S*)-2-(4-fluorophenyl)cyclopropyl]amino}-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl]-4-(1H-1,2,3-triazol-1-yl)benzamide, **free base**
g or gm	gram
g/dL	gram per deciliter
GCP	good clinical practice
G-CSF	gram colony stimulating factor
GFR	glomerular filtration rate

Abbreviation	Definition
GGT	gamma glutamyltransferase
GI	gastrointestinal
GLP	good laboratory practice
GM-CSF	granulocyte-macrophage colony stimulating factor
GMP	Good Manufacturing Practices
GVHD	graft *versus* host disease
H	histone
HbF	fetal haemoglobin
HED	human equivalent dose
HIV	human immunodeficiency virus
HMA	hypomethylating agent
HREC	Human Research Ethics Committee
HSC	haematopoietic stem cell
HSCT	haematopoietic stem cell transplant
IC	inhibitory concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL8	Interleukin 8
IMG-7289	*N*-[(2*S*)-5-{[(1*R*,2*S*)-2-(4-fluorophenyl)cyclopropyl]amino-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl}-4-(1*H*-1,2,3-triazol-1-yl)benzamide, **bis-tosylate salt**
INR	International normalized ratio
IPF	immature platelet fraction
IPSS	International Prognostic Scoring System
IPSS-R	IPSS-Revised
IRB	Institutional Review Board
IUD	intrauterine device
IWG	International Working Group
K	lysine
KD	knockdown
KDM1A	lysine-specific demethylase 1
K_{el}	elimination rate constant
kg	kilogram
L	liter
LC/MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LDH	lactate dehydrogenase
LPLV	last patient last visit
LSC	leukaemia stem cell

Abbreviation	Definition
LSD1	lysine-specific demethylase 1
LSDi	LSD1 inhibition or inhibitors
m^2	meters squared
MAO	monoamine oxidases
MCH	mean cell haemoglobin
MCHC	mean cell haemoglobin concentration
MCV	mean cell volume
MDS	myelodysplastic syndromes
me	methyl
MEOI	Medical Events of Interest
mg	milligram
mg/kg	milligram per kilogram
mg/kg/d	milligram per kilogram per day
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
mL/min	milliliters/minute
MPP	multipotent progenitor
MPN	myeloproliferative neoplasias or neoplasms
MPV	mean platelet volume
mRNA	messenger RNA
MTD	maximally tolerated dose
MTDu	maximally tolerated duration
MV4;11	a human AML cell line
NCI	National Cancer Institute
ng·hr/mL	nanogram an hour per milliliter
nM	nanomolar
NOD/SCID	non-obese diabetic/severe combined immunodeficiency
NPM1	nucleophosmin 1
OS	overall survival
p53	tumour protein p53
PD	pharmacodynamics
PE	physical examination
PFS	progression free survival
PI	Principal Investigator (at each site responsible for patient care)
PI	Product Information document
PISCF	Participant Information Sheet/Consent Form
PK	pharmacokinetics

Abbreviation	Definition
PKAP	Pharmacokinetic Analysis Plan
PML	promyelocytic leukaemia
PML-RARα	PML-retinoic acid receptor alpha
PR	partial remission or response
PSA	prostate specific antigen
QD	once daily
RBC	red blood cell
RD	resistant disease
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation
Sh	short hair
SOA	schedule of assessments
SOC	standard-of-care
SRM	Study Reference Manual
$t_{1/2}$	half-life
t-AML	treatment related AML
T_{max}	time to maximum concentration
TCP	tranylcypromine
TF	transcription factor
TPO	thrombopoietin
µL	microliter
µM	micromolar
VAF	variant allele frequency
V_z/F	apparent volume of distribution during terminal phase after oral administration
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of child-bearing potential

2 PROTOCOL SYNOPSIS

Protocol Title: A MULTI-CENTER, OPEN LABEL STUDY TO ASSESS THE SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF IMG-7289 WITH AND WITHOUT ATRA (TRETINOIN) IN PATIENTS WITH ADVANCED MYELOID MALIGNANCIES

Protocol No: IMG-7289-CTP-101

Investigator/Study Centers: Approximately 8 sites in Australia; additional sites and countries may be added as needed.

Study Hypothesis and Objectives:

Hypothesis: IMG-7289 with and without all-*trans* retinoic acid (ATRA; tretinoin) is a safe and tolerable orally available agent when administered to patients with advanced myeloid malignancies including high risk acute myeloid leukaemia (AML) and high risk myelodysplastic syndromes (MDS); lysine-specific demethylase 1 (LSD1) inhibition (LSDi) by IMG-7289 will have a negative impact on leukaemic and dysplastic cells, an effect which may be further enhanced *via* synergistic mechanisms when administered in combination with ATRA.

Objectives: The following objectives will be evaluated in patients with advanced myeloid malignancies, including high risk AML and high risk MDS, treated with IMG-7289 with and without ATRA:

Primary:

- Safety and tolerability
- Pharmacokinetics
- The adequacy of dose and duration in producing a pharmacodynamic effect

Secondary:

- The association of plasma concentrations (C_{max} and C_{min}) and exposure (AUC) on haematopoiesis (both short[+] and longer-term[ǂ] measures)
- The kinetics of recovery of haematopoiesis for a given dose and for a given duration of dosing

CCI [redacted]

[+]Short term measures may include reticulocyte counts, absolute neutrophil counts (ANC), platelet volume.

[ǂ]Longer-term measures may include return of counts to baseline or better.

CCI [redacted]

Investigational Drug: The drug product is identified as IMG-7289, a bis-tosylate salt. The free base of IMG-7289 is an irreversible inhibitor of LSD1. The chemical name is: *N*-[(2*S*)-5-{[(1*R*,2*S*)-2-(4-fluorophenyl)cyclopropyl]amino-1-(4-methylpiperazin-1-yl)-1-oxopentan-2-yl}-4-(1*H*-1,2,3-triazol-1-yl)benzamide, bis-tosylate salt.

IMG-7289 will be supplied as capsules in multiple strengths. CCI

CCI

Additional Medication: Tretinoin (all-*trans* retinoic acid; ATRA; Vesanoid®) is an approved retinoid for the indication of induction of remission in acute promyelocytic leukaemia (APL; FAB classification AML-M3). Chemically, tretinoin is 3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl) nona-2,4,6,8-all-*trans*-retinoic acid.

Tretinoin is available as oval, soft gelatin capsules; one half of each capsule is opaque orange-yellow the other half opaque reddish brown. One capsule strength will be provided: 10 mg. The Product Information (PI) document will be provided to each Principal Investigator.

Note: Tretinoin will be referred to as ATRA throughout the remainder of this protocol.

Study Population: Approximately 40 patients, eighteen years of age or older, with high risk AML or high risk MDS (as defined in the Inclusion/Exclusion Criteria) will be treated. A minimum of 3 patients per cohort/sub-cohort are required to complete the entirety of Cycle 1 (i.e., the applicable dosing and rest periods). All patients will be unique; no patient will be allowed to be dosed in more than one cohort. Contingent on the number of prior DLTs within a cohort/sub-cohort, non-completers of Cycle 1 will be replaced.

Note: 'Sub-cohort' (generally) refers to different treatment arms within the dose-finding Cohort.

Methodology: This is a multi-center, open-label study evaluating the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of IMG-7289 administered orally once daily (QD), with and without ATRA, to patients with advanced myeloid malignancies.

CCI

Accordingly, as a measure of precaution, a starting dose of 0.75 mg/kg QD, representing the estimated $<IC_{10}$ for inhibiting human platelet production has been selected as the starting dose and designated the D_s.

CCI

CCI [redacted]

The study consists of two phases in which IMG-7289 will be dosed with and without ATRA: the dose-finding phase, and the duration-finding phase. During both phases, a Data Safety Monitoring Committee (DSMC) will review safety parameters, pharmacodynamic markers and pharmacokinetic parameters to draw conclusions around the safety and pharmacodynamic effect of differing doses, treatment regimens and dosing durations. DSMC reviews are critical, as neither a new dose-finding sub-cohort, nor a duration-finding cohort may commence without DSMC review and recommendation to do so. Refer to Section 8 for details pertaining to DSMC reviews, and management of study toxicities.

CCI [redacted]

CCI [redacted] phase, will be used to establish and confirm the IMG-7289 D_i and the D_p in patients, as well as provide samples sufficient to establish the pharmacokinetic parameters of IMG-7289 at several dose levels and, with and without ATRA. Patients assigned to combination therapy will receive IMG-7289 in combination with ATRA.

The second phase of the study, the duration-finding phase, will be used to identify the safety and clinical effects of IMG-7289 treatment for durations longer than 7 days as well as provide samples sufficient to establish drug concentrations at steady state, with and without ATRA.

A DSMC review will be conducted after a minimum of 3 patients in a cohort/sub-cohort have completed Cycle 1 to determine the safety of each dose and different treatment durations, with and without ATRA. The DSMC will also assess the impact of each dose on normal myeloid haematopoiesis, the PD impact of that dose on malignant cells, and whether a further cohort/sub-cohort in the respective phase is appropriate. Changes in the clearance of IMG-7289, with and without ATRA, based on drug concentrations at C_{min} will be reviewed as

available. As DSMC review of data continues throughout the study, the DSMC may also recommend a different cohort progression than is currently outlined in the protocol.

Importantly, if a specific dose, treatment regimen or dosing duration is found by the DSMC to be associated with greater therapeutic benefit, patients that have *fully completed* their initially allowed IMG-7289 cycles and are receiving either a different dose, treatment regimen (i.e., IMG-7289 alone *versus* combination therapy) or dosing for a different dosing duration will be transitioned to the more optimal dose, treatment regimen or dosing duration at the start of their next cycle. Such transition may occur more than once, as different doses, treatment regimens and dosing durations continue to be evaluated.

Patients will be followed closely for both Adverse Events (AEs) and signs of toxicity by frequent monitoring of clinical signs and symptoms and by peripheral blood and urine analyses. Pharmacodynamic effects will also be closely monitored by frequent haematology assessments of peripheral blood and bone marrow aspirates and biopsies, as required.

All patients will undergo End-of-Treatment (EOT), pre-End-of-Study (pre-EOS), and End-of-Study (EOS) visits approximately 7, 14 and 28 days, respectively, after last Cycle last dose.

Study Phases, Doses and Duration:

Dose-Finding Phase: Cohort 1 (*via* sub-cohorts, as needed) comprises the dose-finding Cohort. Cohort 1 patients, including the combination therapy sub-cohorts, will be dosed with IMG-7289 for 7 days and initially allowed to receive up to **4 cycles** of IMG-7289, provided IMG-7289 (with or without ATRA) continues to be tolerated.

The IMG-7289 alone component of the dose-finding phase is summarized below.

Sub-cohort 1a: Dosing will begin on Day 1 at the D_s, 0.75 mg/kg/d IMG-7289 free base.

Note: Though not expected, contingencies are in place in the case that unacceptable toxicity is seen at the D_s and sub-cohorts at lower doses are required. Please refer to Section 7.2.2.2.

Dose escalation will proceed in sub-cohorts (i.e., Sub-cohorts 1b, 1c, etc.) provided that:

1. A minimum of 3 patients from the previous sub-cohort have completed Cycle 1, both the applicable dosing and rest periods
2. The number of patients who experience DLT is within the guidelines (Section 8.2.2)
3. DSMC review of the previous sub-cohort has determined that:
   a. The dose administered appears safe
   b. Further dose escalation is appropriate

If the DSMC determines dose escalation should proceed, then additional sub-cohorts (Sub-cohorts 1b, 1c, etc.) will be dosed with increasing doses as per below.

Sub-cohort 1b: Dosing will begin on Day 1 at 1.5 mg/kg/d IMG-7289 free base.
Sub-cohort 1c: Dosing will begin on Day 1 at 3 mg/kg/d IMG-7289 free base.

There are two potential dose-escalation pathways for Sub-cohort 1d: 6 and 10 mg/kg/d. The dose to be administered in Sub-cohort 1d will be determined at the discretion of the DSMC. Therefore, upon completion of a minimum of 3 patients in Cycle 1 of Sub-cohort 1c, the DSMC will assess the safety and pharmacodynamic effects of the earlier sub-cohorts, and reach consensus on:

1. Whether dose escalation should proceed at all, and if so…
2. Whether the appropriate escalation for Sub-cohort 1d is a doubling or a tripling of the 3 mg/kg/d dose administered in Sub-cohort 1c.

Sub-cohort 1d: Dosing will begin on Day 1 at either 6 or 10 mg/kg/d IMG-7289 free base.

Sub-cohort 1e: Dosing will begin on Day 1 at 10 mg/kg/d IMG-7289 free base, if not previously administered in Sub-cohort 1d.

If appropriate, an additional sub-cohort will commence at a 2x multiple of the last sub-cohort's dose, followed by further sub-cohorts with dose escalation continuing in such increments until the DSMC determines that no further dose escalation is anticipated[Ω]. Upon such confirmation, the combination therapy sub-cohorts will commence.

[Ω]The DSMC may revisit dose escalation after having progressed to combination therapy.

If the DSMC determines a specific IMG-7289 dose is associated with greater therapeutic benefit, patients who have fully completed their initially allowed IMG-7289 treatment cycles and are at a different dose will be titrated to the more optimal dose at the start of their next cycle.

The table below summarizes the IMG-7289 alone component of the dose-finding phase by sub-cohort, dose, dosing duration, rest period, and number of initially allowed IMG-7289 cycles.

Sub-cohort	IMG-7289 Dose (free base)	IMG-7289 Cycle		No. of Initial IMG-7289 Cycles**
		Dosing Duration	Rest Period*	
1a	**0.75 mg/kg/d = D_s**	**7 days**	**7 days**	**4**
1b	1.5 mg/kg/d			
1c	3 mg/kg/d			
1d[Φ]	6 or 10 mg/kg/d			
1e***	10 mg/kg/d			

*The duration of the rest period may be adjusted based on an assessment by the DSMC that either a specific patient or an entire sub-cohort could benefit from an extended rest period. This decision could be taken if there is no clear indication of the restoration of normal haematopoiesis in the 7 day period or analysis of the pharmacokinetic parameters in the earlier sub-cohorts suggest the rest period duration requires adjusting; for example, if the half-life of IMG-7289 is unexpectedly long. Investigators will be notified of any such change.
**Additional cycles may be allowed, contingent on clinical benefit/patient response.
[Φ]The dose to be used in Sub-cohort 1d, either 6 mg/kg/d or 10 mg/kg/d, will be determined by the DSMC based on review of safety and pharmacodynamic data from earlier dose-finding sub-cohorts.
***If 10 mg/kg/d was not studied in Sub-cohort 1d, and if deemed appropriate by the DSMC, then 10 mg/kg/d will be studied in Sub-cohort 1e. If deemed appropriate by the DSMC, then additional sub-cohorts beyond Sub-cohort 1e will commence with up-titration of dosing continuing in such increments until the D_p is identified.

The IMG-7289 administered in combination with ATRA component of the dose-finding phase is summarized below.

Sub-cohort 1χ: Dosing will begin on Day 1 with IMG-7289 (dose to be determined by the DSMC) dosed for 7 days on followed by 7 days off, in combination with ATRA 45 mg/m^2 per day dosed for 7 days on followed by 7 days off.

Additional combination therapy sub-cohorts may follow (i.e., Sub-cohort 1ω, Sub-cohort 1ν, etc.) as the DSMC continues to review data on an ongoing basis, provided that:

1. A minimum of 3 patients from the previous sub-cohort have completed Cycle 1, both the applicable dosing and rest periods
2. The number of patients who experience DLT is within the guidelines (Section 8.2.2)
3. DSMC review of the previous sub-cohort has determined that:
   a. The doses administered in combination appear safe
   b. Further combination therapy is appropriate

If the DSMC determines combination therapy should proceed, then additional sub-cohorts will commence.

Sub-cohort 1ω: Dosing will begin on Day 1 with IMG-7289 (dose to be determined by the DSMC) dosed for 7 days on followed by 7 days off, in combination with ATRA 45 mg/m^2 per day dosed for 21 days^{ϱ} on followed by 7 days off.

^{ϱ}Patient's enrolled in Sub-cohort 1χ will continue their current treatment regimen until completion of their initially allowed treatment cycles and pending DSMC review of the sentinel patient in Sub-cohort 1ω, after which transition to the new (21 day ATRA) regimen may occur at the start of the next cycle.

As DSMC review of data continues throughout the study, the DSMC may recommend extending the dosing duration of IMG-7289, reducing the ATRA dose and/or adjusting the ATRA dosing duration. The IMG-7289 dose may be either increased or decreased to a dose studied in an earlier sub-cohort, or decreased to an intermediary dose, by the DSMC.

If the DSMC determines combination therapy offers greater therapeutic benefit as compared to single agent IMG-7289 therapy, patients who have fully completed their initially allowed IMG-7289 treatment cycles and are receiving a different treatment regimen (i.e., IMG-7289 alone) will be transitioned to combination therapy at the start of their next cycle.

The table below summarizes the IMG-7289 in combination component of the dose-finding phase by sub-cohort, drug, dose, dosing duration, rest period, and number of initially allowed IMG-7289 cycles.

Sub-cohort	IMG-7289 Dose (free base)	IMG-7289 Cycle		No. of Initial IMG-7289 Cycles**
		Dosing Duration	Rest Period*	
1χ	**TBD**¥	**7** days on	**7** days off	4
	Administered in combination with			
	ATRA§ 45 mg/m^2/d for **7** days^{ϱ} on followed by 7 days off			
1ω^{ß}	**TBD**¥	**7** days on	**7** days off	4
	Administered in combination with			
	ATRA§ 45 mg/m^2/d for **21** days on followed by **7** days off			

*The duration of the rest period may be adjusted based on an assessment by the DSMC that either a specific patient or an entire sub-cohort could benefit from an extended rest period. This decision could be taken if there is no clear indication of the restoration of normal haematopoiesis in the 7 day period or analysis of the pharmacokinetic parameters in the earlier sub-cohorts suggest the rest period duration requires adjusting; for example, if the half-life of IMG-7289 is unexpectedly long. Investigators will be notified of any such change.

**Additional cycles may be allowed, contingent on clinical benefit/patient response.

¥The IMG-7289 dose for administration with ATRA will be determined by the DSMC based on ongoing review of safety and pharmacodynamic data.

§The ATRA dose may be reduced or the dosing and/or rest period duration adjusted by the DSMC based ongoing review of safety and pharmacodynamic data.

^{ß}If deemed appropriate by the DSMC, then additional sub-cohorts beyond 1ω will commence.

^{ϱ}Patient's enrolled in Sub-cohort 1χ will continue their current treatment regimen until completion of their initially allowed treatment cycles and pending DSMC review of the sentinel patient in Sub-cohort 1ω, after which transition to the new (21 day ATRA) regimen may occur at the start of the next cycle.

Upon DSMC confirmation that no further dose-finding sub-cohorts are anticipated, and safety permitting (the DSMC must have determined it safe to extend the duration of IMG-7289 treatment), the study will progress to assess the effect of IMG-7289 dosing duration.

Duration-Finding Phase: Cohorts 3, 3χ, 4 and 4χ comprise the duration-finding cohorts. Patients will be dosed with IMG-7289 at the D_p^* (determined by the DSMC) for either 14 or 21 days, with or without ATRA. The number of initially allowed IMG-7289 cycles differs by cohort, in conjunction with the duration of IMG-7289 dosing, to a total of 28 days IMG-7289 dosing.

*May change as data from earlier sub-cohorts becomes available and different durations continue to be evaluated.

There are two potential duration-extension pathways for the duration-finding cohorts: duration extension with IMG-7289 alone, or IMG-7289 administered in combination with ATRA. Therefore, prior to opening a duration-finding cohort, the DSMC will assess the safety and pharmacodynamic effects of the earlier sub-cohorts, and reach consensus on:

1. Whether it appears safe to extend the duration of IMG-7289 dosing
2. Whether there appears to be greater therapeutic benefit with IMG-7289 dosed in combination with ATRA.

Based on the above assessments, one of the below duration-finding cohorts will commence.

Cohort 3: Dosing of IMG-7289 at the D_p will begin on Day 1 for a duration of 14 days.

Cohort 3χ: The above IMG-7289 regimen in combination with ATRA 45 mg/m^2 per day for 14 days.

Cohorts 3 and 3χ will initially be allowed to receive **2 cycles** of IMG-7289, provided IMG-7289 (with or without ATRA) continues to be tolerated.

The duration of dosing will be extended in subsequent cohorts provided that:

1. A minimum of 3 patients from the previous cohort have completed Cycle 1, both the applicable dosing and rest periods
2. The number of patients who experience DLT is within the guidelines (Section 8.2.2)
3. DSMC review of the previous cohort has determined that:
   a. The duration of dosing appears safe
   b. Further duration extension is appropriate

If the DSMC determines further duration extension is appropriate, then additional cohorts will be dosed with extending durations to determine if a more optimal duration can be identified; possible cohorts are outlined below.

Cohort 4: Dosing of IMG-7289 will begin on Day 1 for a duration of 21 days.

Cohort 4χ: The above IMG-7289 regimen in combination with ATRA 45 mg/m^2 per day for 21 days.

Cohorts 4 and 4χ will initially be allowed to receive **1 cycle** of IMG-7289.

If the DSMC determines a specific dosing duration is associated with greater therapeutic benefit, patients who have fully completed their initially allowed IMG-7289 cycles and are at a different dosing duration will be transitioned to the more optimal dosing duration at the start of their next cycle.

The table below summarizes the duration-finding phase by cohort, dosing duration, treatment regimen, rest period and number of initially allowed IMG-7289 cycles.

Cohort	IMG-7289 Dose (free base)	IMG-7289 Cycle		No. of Initial IMG-7289 Cycles**
		Dosing Duration	Rest Period*	
3	D_p¥	**14** days	**7 days**	2
3χ	The Cohort 3 IMG-7289 regimen, administered in combination with ATRA§ 45 mg/m^2/d for **14** days on followed by **7** days off			
4	D_p¥	**21** days	**7 days**	1
4χ	The Cohort 4 IMG-7289 regimen, administered in combination with ATRA§ 45 mg/m^2/d for **21** days on followed by **7** days off			

*The duration of the rest period may be adjusted based on an assessment by the DSMC that either a specific patient or an entire cohort could benefit from an extended rest period. This decision could be taken if there is no clear indication of the restoration of normal haematopoeisis in the 7 day period or analysis of the pharmacokinetic parameters in Cohort 1 suggest the rest period duration requires adjusting. Investigators will be notified of any such change.

**Additional cycles may be allowed, contingent on clinical benefit/patient response.

¥The IMG-7289 dose for administration will be determined by the DSMC based on ongoing review of safety and pharmacodynamic data.

§The ATRA dose may be reduced or the dosing and/or rest period duration adjusted by the DSMC based ongoing review of safety and pharmacodynamic data.

Throughout all phases of the study, if it appears that either a maximally tolerated dose (MTD) or maximally tolerated duration (MTD_u) is reached (see Section 8.2.3), the DSMC will convene to evaluate further dose escalation, combination therapy and/or extended dosing duration.

Dose reductions may be made in consultation with the Medical Monitor, should an adverse event (AE) requiring a dose reduction occur.

Additional Cycles: Upon completion of the number of initially allowed IMG-7289 cycles per sub-cohort, patients deriving clinical benefit and safely tolerating IMG-7289, as determined by the Principal Investigator, may continue to receive IMG-7289, with additional dose titration, treatment regimen and/or duration changes occurring in consultation with the Medical Monitor, until disease progression or unacceptable toxicity ensues. During the additional cycle period, the rest period may be extended from the 7 day standard to a maximum of 56 days, but only after: 1) the patient has received a minimum of 28 IMG-7289 doses; and, 2) consultation with or recommendation by the DSMC. Such recommendation may be made for a variety of reasons including evidence of tumour reduction, marked hypocellularity in the marrow consistent with myelosuppression, or to enable the return of normal haematopoiesis. For protocol purposes, a rest period extending beyond the 7 day standard will be referred to as the extended rest period (see Section 9.10).

Patients who either fail to demonstrate stable disease, demonstrate progressive disease after achieving partial remission (PR) or stable disease, or relapse after achieving complete remission (CR), CR with incomplete recovery (CRi) or PR (see **Table 14** and **Table 15**) are the equivalent of treatment failures, and will discontinue study drug and enter the follow-up period.

Study Duration: Screening procedures may commence up to 28 days prior to the start of treatment. Depending on the duration of dosing in each cohort, patients may initially undergo four, three, two or one treatment cycles while on study to a total of approximately 28 days of dosing, with Rest Periods between each cycle anticipated to last approximately 7 days. Patients should be followed for 28 days post last dose. As such, the length of patient participation will vary by cohort. For Cohort 1 this will be ~15 weeks from first patient-first visit (FPFV) to last patient-last visit (LPLV), for Cohort 3/3χ ~13 weeks, and for Cohort 4/4χ ~11 weeks. As described above, additional cycles may be given, contingent on patient response.

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Adverse events (AEs) will be assessed throughout the study after the first IMG-7289 dose to the End of Study visit (EOS). AE frequency, causality, and severity will be evaluated as measures of safety and tolerability. Febrile neutropenia admissions will also be assessed.

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Clinical laboratory measures:

Cycle 1

- Haematology with differential* will be performed at Screening, Baseline, pre-dose on Day 1, and approximately every 3 days.
- Coagulation* will be performed at Screening, Baseline, pre-dose on Day 1, and then at least once weekly throughout the study.
- Biochemistry* will be performed at Screening, Baseline, pre-dose on Day 1, and then as follows:
  - Cohort 1: Days 3 and 7 of dosing, and Days 9, 11 and 14 of the rest period.
  - All other Cohorts, pending DSMC review of Cohort 1 data:
    - If clinically significant trends are noted by the DSMC, or an opinion has not yet been formed, then either focused panels or full biochemistry will be performed at least twice weekly throughout the Cycle.
    - If clinically significant trends are not noted by the DSMC, then full biochemistry panels will be performed at least once weekly throughout the Cycle.
- Urinalysis with microscopy will be performed at Screening, pre-dose on Day 1, and then at least once weekly throughout the study.
- Red Cell Haemoglobin F (HbF)** will be measured pre-dose on Day 1, at the end of dosing (sample timing will vary depending on the duration of the Cohort), and then on the last day of the rest period.
- Prostate Specific Antigen (PSA)** will be measured in males pre-dose on Day 1 and then on the last day of the rest period.

*To be performed at EOT, pre-EOS, and EOS visits.
**To be performed at EOT.

Cycle 2 and beyond, all Cohorts

- Haematology with differential (diff) will be performed pre-dose on Day 1 and approximately every 3 days throughout the duration of the study, at the EOT, pre-EOS, and EOS visits, and upon suspicion of relapse.
- Coagulation will be performed pre-dose on Day 1 and then at least once weekly throughout the study, at the EOT, pre-EOS, and EOS visits and upon suspicion of relapse.
- Biochemistry: Pending DSMC review of Cycle 1 data, biochemistry will be performed:
  - If clinically significant trends are noted by the DSMC, or an opinion has not yet been formed, then either focused panels or full biochemistry will be performed twice weekly throughout the Cycle.
  - If clinically significant trends are not noted by the DSMC, then full biochemistry panels will be performed at least once weekly throughout the Cycle.
  - At the EOT, pre-EOS, and EOS visits and upon suspicion of relapse.
- Urinalysis with microscopy will be performed pre-dose on Day 1 and then at least once weekly throughout the study, at the EOT, pre-EOS, and EOS visits and upon suspicion of relapse.
- HbF will be measured on the last day of the rest period of the final initially allowed Cycle for Cohorts 1 and 3 (i.e., Cohort 1 = Cycle 4, Day 14; Cohort 3/3χ = Cycle 2, Day 21), and on Rest Day 7 of every other Cycle during the additional treatment phase in all Cohorts.
- PSA will be measured on the last day of the rest period of the final initially allowed Cycle for Cohorts 1 and 3 (i.e., Cohort 1 = Cycle 4, Day 14; Cohort 3/3χ = Cycle 2, Day 21), and on Rest Day 7 of every other Cycle during the additional treatment phase in all Cohorts.

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Effective Dose Assessment: The DSMC will assess the impact of each dose on normal myeloid haematopoeisis, and the pharmacodynamic impact of each dose on malignant cells (see Study Endpoints Section 12.4). This assessment will be made using a combination of pharmacodynamic and pharmacokinetic markers. Indicators evaluated may include: peripheral white blood cell count, peripheral blast count, reticulocyte count, platelet count, bone marrow blast count, changes in immunophenotype, changes in variant allele frequency (VAF), changes in cytokine profiles, and changes in PSA. These metrics will be evaluated in the context of PK parameters such as C_{max} and AUC, as available.

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

Inclusion Criteria:

1. Willing and able to sign the approved informed consent.
2. Age: 18+ years old at Screening.
3. Diagnosis (a., b., and c. required) of **EITHER** Acute Myeloid Leukaemia:
   a. By World Health Organization (WHO) criteria regardless of etiology, sub-type or treatment history.
   b. High risk AML* diagnosis in accordance with one of the following classifications:
      - ≥ 60 years of age with AML who are ***not*** candidates for (based on parameters such as performance scores, co-morbidities and cytogenetic studies), or have refused, standard chemotherapy
      - 18+ year old with *de novo* or secondary AML (MDS/AML or treatment-related (t)-AML) who are ***not*** expected to benefit from standard remission-induction chemotherapy (unfavorable cytogenetics)
      - Relapsed/refractory AML after no more than 3 previous lines of chemotherapy, including hypomethylating agents, for whom no standard therapies are available
   c. Eastern Cooperative Oncology Group (ECOG) performance status score ≤2.

   *All forms of AML (M0–M7) diagnosed by morphologic, histochemical or cell surface marker criteria.

   OR

   Myelodysplastic Syndromes:

   a. By WHO criteria regardless of sub-type.
   b. High Risk MDS diagnosis in accordance with one of the following classifications:
      - MDS patients who have failed first-line therapy, demonstrated by resistance to, or relapse following a minimum of 4 cycles with a hypomethylating agent (HMA)
      - Treatment-related MDS, except if it is associated with favorable cytogenetics, and ***not*** a candidate for stem cell transplantation
   c. Either an International Prognostic Scoring System (IPSS) score equivalent to intermediate-2 risk or higher, or a Revised International Prognostic Scoring System (IPSS-R) score equivalent to intermediate risk or higher.
4. Prior autologous stem cell transplant is allowed if a minimum of 3 months has elapsed from the time of transplant and the patient has recovered from transplant-associated toxicities.
5. Prior allogeneic stem cell transplant is allowed, provided all of the following criteria are met:
   - Transplant was >120 days prior to study enrollment
   - No immunosuppressive medications have been taken for at least 1 month
   - No active graft versus host disease (GVHD), excluding Grade 1 skin GVHD
6. WBC ≤ 30 x 10^9/L (30,000/μL) for at least one week prior to first dose, with hydroxyurea use to achieve this value acceptable.

7. Platelet count ≥ 30 x 10^9/L (30,000/μL) prior to first dose, with transfusions to reach this limit acceptable.
8. Life expectancy >12 weeks.
9. Willing to discontinue all existing anti-neoplastic therapies (with the exception of hydroxyurea) for the 3 weeks prior to first dose of IMG-7289, total duration of dosing, and 1 week after last dose.
10. Amenable to serial bone marrow evaluation, blood, and urine sampling during the study.
11. Able to swallow capsules.
12. Agrees to use an approved method of contraception from Screening and until 28 days after the last administration of the study drug. Agreed methods of contraception may include: condom; use of birth control pills, patches, implants or injections, diaphragm with vaginal spermicide, intrauterine device (IUD) and/or surgical sterilization (vasectomy or tubal ligation at least six months prior to dosing). Patients practicing abstinence must agree to use an approved method of contraception should they become sexually active during the study.

Exclusion Criteria:

1. Has received either: immunotherapy within <8 weeks; chemotherapy within <3 weeks (with the exception of hydroxyurea); radiation therapy to >30% of marrow-bearing bone within <2 weeks prior to starting study treatment; or, has not yet recovered from the effects of such therapies (excluding alopecia).
2. Has undergone major surgery ≤4 weeks prior to starting study drug or has not recovered from side effects of such surgery.
3. Has undergone any surgical procedure within 2 weeks, excluding minor procedures (i.e., skin biopsy or central venous catheter placement/removal) prior to starting study drug.
4. Scheduled haematopoietic stem-cell transplant.
5. Current use of a prohibited medication including anticoagulants or platelet inhibitors or expected to require any of these medications (outside of such use permitted as per the Prohibited Medications section) during treatment with the investigational drug.
6. Current use of monoamine oxidase A and B inhibitors (MAOIs).
7. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to IMG-7289, LSD1 inhibitors, or ATRA that contraindicates participation.
8. Uncontrolled active infection.
9. Clinical evidence of central nervous system (CNS) or pulmonary leukostasis, disseminated intravascular coagulation, or CNS leukaemia.
10. A concurrent second active and non-stable malignancy (patients with a concurrent second active but stable malignancy, such as non-melanoma skin cancers, are eligible).
11. Known human immunodeficiency virus (HIV) infection or known active Hepatitis B or Hepatitis C virus infection.
12. History of any illness/impairment of gastrointestinal (GI) function that might interfere with drug absorption (e.g., chronic diarrhea), confound study results or pose an additional risk to the patient by their participation in the study; patients with gastric bypass surgery.

13. Refractory to platelet transfusion (but not excluding patients receiving HLA–matched platelets that increment appropriately).
14. Evidence at the time of Screening of risk of bleed, including any one of the following:
    a. Activated partial thromboplastin time (aPTT) ≥ 1.3 x the local upper limit of normal
    b. International normalized ratio (INR) ≥ 1.3 x the local upper limit of normal
    c. History of severe thrombocytopenia unrelated to AML, MDS or treatment for either
    d. Known bleeding disorder (e.g., dysfibrinogenemia, factor IX deficiency, haemophilia, Von Willebrand's disease, Disseminated Intravascular Coagulation [DIC], fibrinogen deficiency, or other clotting factor deficiency)
    e. Receiving therapeutic anticoagulation
15. Evidence at the time of Screening of significant renal or hepatic insufficiency (unless due to haemolysis, or leukaemic infiltration) as defined by any one of the following local lab parameters:
    a. Calculated glomerular filtration rate (GFR) < 40 mL/min or serum creatinine > 1.5 x the local upper limit of normal
    b. Aspartate transaminase (AST) or alanine aminotransferase (ALT) ≥ 2 x the local upper limit of normal
16. Use of an investigational agent within less than 14 days, or the equivalent of at least 7 half-lives of that agent, whichever is the longer, prior to the start of study treatment.
17. Pregnant or lactating females.

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IMG-7289 Dose Limiting Toxicity (DLT): Dose Escalation, Combination Therapy and Duration Extension Decision Making Rules; and, Maximum Tolerated Dose (MTD), Maximum Tolerated Duration (MTD_u):

Adverse event intensity will be evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, published 14 June 2010.

Definitions:

Haematologic Toxicity: Haematologic values outside of the normal reference range are inherent features of AML and MDS, and are expected effects of many therapeutic attempts to manage these diseases. The effects of IMG-7289 on normal myeloid haematopoiesis observed in non-clinical studies are expected in humans; these are pharmacodynamic effects of LSD1 inhibition by IMG-7289, thus are not regarded as adverse. These events, with the

exceptions noted below, will not be considered DLTs. Additional information pertaining to haematologic toxicity, DLTs, dose escalation/duration extension rules, and MTDs is provided in Section 8.2.

Dose limiting toxicity (DLT): Any one of the following AEs that occurs during the first cycle and is considered by the Investigator possibly, probably or definitely related to IMG-7289:

- A clinically significant bleeding event;
- Any Grade 4 or 5 non-haematologic adverse event;
- Any Grade 3 non-haematologic adverse event with failure to recover to Grade 1 within 7 days of drug cessation, with the following exceptions:
  - ≥ Grade 3 nausea, vomiting or diarrhoea that responds to standard medical care
  - ≥ Grade 3 aesthenia lasting less than 14 days
- Any Grade 3 electrolyte abnormality unrelated to the underlying malignancy and persisting greater than 24 hours.

Patients who experience a DLT may have their dose adjusted downward if the Medical Monitor and Principal Investigator deem it safe for the patient to continue on IMG-7289. To ensure a minimum of 3 Cycle 1 completers, and contingent on the number of prior DLTs within the cohort, such patients may be replaced.

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

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

IMG-7289 Dose Escalation, Combination Therapy and Duration Extension Decision Rules:

The DSMC will convene and review safety data after a minimum of 3 patients in a sub-cohort/cohort have completed Cycle 1 (both the treatment and rest periods). If 0-1 of 3 patients experience a DLT, and if the DSMC deems safe, then dose escalation will proceed to the next higher dose with the opening of the applicable sub-cohort/cohort. If 2 out of 3 patients experience a DLT, then the safe dose has been exceeded, enrollment in the sub-cohort/cohort will close and dose escalation cease.

The table below outlines these rules.

Patients with DLT at a Given Dose	**Escalation Decision Rules***
0-1 out of 3	Open subsequent sub-cohort/next dose
2 out of 3	Dose escalation will be stopped

*The above instruction applies in kind for combination therapy and duration extension decision making.

As this study is not investigating the effects of cytotoxic agents, the 2 DLT/3 patient rule should provide an adequate safety margin to patients, while allowing escalation to doses that could offer greater therapeutic benefit. This study design does not conform to the traditional 3+3 dose escalation study which is based on pre-specified rules using actual observations of target events such as dose-limiting toxicity. The traditional 3+3 design was developed in an era of cytotoxic drugs and is appropriate when the toxicity is directly proportional to exposure. This study takes the alternative model-based approach more appropriate for a targeted, non-cytotoxic drug such as IMG-7289, in which there is no observed monotonic relationship between exposure and toxicity (Le Tourneau, *et al.*, 2009). Specifically, this

study employs the dose-toxicity model developed in rat and dog relating the plasma concentration of drug 24 hours after last dose at steady state needed to inhibit platelet production, a process dependent on the activity of LSD1.

Additionally, the DSMC may review safety data and, even in the absence of 2 DLTs, deem that the safe dose has been exceeded. Were this to occur, dose escalation would cease.

IMG-7289 Maximum Tolerated Dose (MTD) and Maximum Tolerated Duration (MTD_u)$^{\Phi}$:

MTD: The highest dose below or at which <2 out of 3 patients experiences DLT.

MTD_u: The longest duration below or at which <2 out of 3 patients experiences DLT.

$^{\Phi}$MTD and MTD_u definitions also apply to combination therapy sub-cohorts.

The MTD may not be reached in this study if the highest dose tested is found to be safe.

ATRA Toxicity: Decisions on IMG-7289 and ATRA dose interruption, reduction and re-challenge due to observed toxicity will be made by the Investigator in consultation with Medical Monitor and DSMC.

Expected toxicities for ATRA can be found in the PI.

3 INTRODUCTION

3.1 Background Information

3.2 The Diseases to be Treated

Acute myeloid leukaemia (AML) is a lethal haematologic malignancy resulting in the accumulation of abnormal myeloid blasts ($CD13^+$ and $CD33^+$) in the bone marrow (Estey, 2013). These blasts interfere with normal haematopoiesis causing cytopenias, and accumulate in peripheral blood and infiltrate the lung and the central nervous system (CNS). AML accounts for approximately 80% of all adult acute leukaemias with a median age at diagnosis of 67 years (Pollyea *et al.*, 2011). AML can arise *de novo* without a prior history of haematologic disease but can also evolve from other clonal myeloid disorders such as myelodysplastic syndromes (MDS) or myeloproliferative neoplasias (MPNs), or secondary to prior DNA-damaging treatment (Lindsley *et al.*, 2015).

AML is a devastating and difficult disease to treat. Despite intense efforts, the treatment for AML has changed very little in almost 40 years. Standard-of-care (SOC) induction with intensive chemotherapy consists of seven days of cytarabine and three days of an anthracycline ("7+3"), generally daunorubicin or idarubicin, with many additional agents used specific to clinical sites. Patients attaining a complete remission (CR) are subject to additional cycles of high-dose cytarabine and/or haematopoietic stem cell transplantation (HSCT) (Dombret and Gardin, 2016; Cornelissen and Blaise, 2016). The addition of other agents to SOC, however, has not proven to provide additional clinical benefit (Stein and Tallman, 2012). Improved supportive care, as opposed to more effective treatment, has been the primary means for extending life in these patients.

The five-year overall survival rate is approximately 25%, but closer to 10% for patients over 65 years of age primarily because of co-morbidities, a disproportionate number of adverse genetic abnormalities, treatment-related mortality and unsuitability for HSCT (Pollyea *et al.*, 2011; Roboz, 2012). While standard chemotherapy and bone marrow transplantation are curative in up to 40% of younger (<40) AML patients, most patients are not cured of their disease. AML is, after all, a disease of older people (>60) and these patients are the most difficult to cure (Appelbaum *et al.*, 2006; Burnett, 2012; Burnett, 2013). Although more than 60% of AML patients treated with standard therapy will achieve a CR, at least 70% of these patients will relapse (Burnett *et al.*, 2012).

A core objective of improving outcomes is the identification of novel target(s) ideally present in all malignant cells; the greatest need is for those with either resistant disease or who cannot endure intensive SOC treatment.

3.3 Lysine (K)-Specific Demethylase 1 (LSD1)

LSD1, also known as KDM1A, was first described as an enzyme that removes mono- and dimethyl groups from critical lysines (K), K4 and K9 in histone (H) H3 (Shi *et al.*, 2004). Methylation of histone H3K4 and H3K9 is a post-translational modification associated with changes in rates of gene transcription (Bannister and Kouzarides, 2011; Beisel and Paro, 2011). By virtue of altering the local state of chromatin, LSD1 is an epigenetic regulator of gene expression. The lysine (K) sites

on histone H3 and the degree of methylation on those sites (1, 2 or 3 methyl groups) are associated with specific functions, e.g., enhancers and super-enhancers are characterized by H3K4me1 marks, whereas H3K4me2 is more often found in the proximal promoters and enhancers of actively transcribed genes (Campos and Reinberg, 2009; Gardner *et al.*, 2011; Rando, 2012). The inhibition of LSD1 (LSDi) can result in an increase or decrease of specific messenger RNAs (mRNAs) dependent on those local chromatin marks and associated transcription factors (TFs).

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 short-term haematopoietic stem cells (HSCs) and progenitor cells (Sprussel *et al.*, 2012). An inducible *LSD1* KD resulted in profound but reversible thrombocytopenia, neutropenia and anaemia; monocyte counts were increased. *LSD1* KD for 27 days led to an increase in circulating multipotent progenitors (MPPs) and HSCs, with a concomitant down-regulation of chemokine (C-X-C motif) receptor 4 (CXCR4), without affecting the size of the quiescent long-term HSC pool (Sprussel *et al.*, 2012).

LSD1 plays a key role in regulating the progression from pluripotency to terminal differentiation and balancing self-renewal and proliferation (Adamo *et al.*, 2011; Wang *et al.*, 2007; Whyte *et al.*, 2012). LSD1 is also required for normal cell cycle progress, differentiation and prevention of apoptosis (Wang *et al.*, 2009; Foster *et al.*, 2010; Whyte *et al.*, 2012).

Over-expression of *LSD1* mRNA and excess LSD1 protein have been observed in many tumour types, including poorly-differentiated neuroblastoma, squamous cell carcinoma, Ewing's sarcoma, AML, neuroendocrine carcinomas and epithelial tumours such as breast, prostate, bladder, small cell lung and colon cancers (Metzger *et al.*, 2005; Kahl *et al.*, 2006; Schulte *et al.*, 2009; Lim *et al.*, 2010). The role of LSD1 in neoplasia has, however, been most thoroughly studied in AML. LSD1 activity is present in a high proportion of AML cells. In one survey of newly diagnosed primary AML cells of multiple sub-types, LSD1 activity was elevated in 80% of cases; in primary AML cells from patients with refractory or relapsing disease, 100% of cases had elevated LSD1 activity (Lin *et al.*, 2011). Expression of LSD1 was highest in the minimally differentiated M1 sub-type of AML compared to other more morphologically differentiated sub-types (Rhodes *et al.*, 2007; Wouters *et al.*, 2009). LSD1 gene expression is among the highest in immunophenotypically stem/progenitor populations of leukaemic cells (Goardon *et al.*, 2011). Similar findings in mouse model of AML confirm that LSD1 expression is correlated with immunophenotypically and functionally defined leukaemic stem cells (LSC) (Somervaille *et al.*, 2009; Harris *et al.*, 2012).

Inhibition of LSD1 in AML cells de-represses or induces the expression of genes associated with differentiation including markers of monocytic maturation such as CD14 and CD86 (Huang *et al.*, 2009; Lynch *et al.*, 2013). This phenomenon of drug-induced differentiation is reminiscent of the effects of all-*trans* retinoic acid (ATRA) combined with arsenic trioxide (As_2O_3) on acute promyelocytic leukaemia (APL M3) cells: inducing the degradation of the onco-fusion protein promyelocytic leukaemia-retinoic acid receptor alpha (PML-RARα) relieves the block to differentiation (Lallemand-Breitenbach *et al.*, 1999). Indeed, LSD1 inhibition sensitizes non-APL

AML cells to differentiation by ATRA as well as reducing leukaemic stem cell potential (Schenk *et al.*, 2012).

Non-clinical studies indicate that the maximal differentiation and cell killing of AML cells is a result of complete inhibition of the enzyme. Accordingly, IMG-7289, an irreversible inhibitor, was developed to enhance the probability that LSD1 activity would be fully inactivated during drug exposure. Additional reasons IMG-7289 was selected for clinical development include: its high potency, chemical stability and its half-life in plasma in non-clinical animal models.

Irreversible inhibitors of LSD1 include tranylcypromine (TCP) which has been used for the treatment of depression for decades. The targets of TCP therapy, however, are the monoamine oxidases (MAO). TCP inactivates LSD1 in a manner identical to its action on MAO-A and MAO-B because these three enzymes share a similar oxidative mechanism of action. Despite the lack of specificity and low potency of TCP for LSD1, there are currently at least two actively recruiting clinical trials in which TCP is being used for the treatment of AML (NCT02273102 and NCT02261779). TCP derivatives with improved specificity for LSD1 over MAO-A and MAO-B have recently been developed with the therapeutic purpose of inhibiting LSD1 activity in cancer – these include IMG-7289. Other molecules in development include ORY-1001 identified by Oryzon Genomic SA and now being developed by Roche; and, GSK2879552, a molecule being developed by GlaxoSmithKline (NCT02177812) for the treatment of AML and for small cell lung cancer. Both companies are presently recruiting AML patients for these studies, though no clinical results have been published.

In summary, the scientific evidence available in the literature shows that inhibition of LSD1 offers the promise of targeting an enzyme that participates in many essential neoplastic functions in AML cells including self-renewal, a phenotype that characterizes the major reservoir of treatment-resistant-cells, the leukaemic stem cell population. The pathological process in MDS that leads to neoplastic transformation is similar in many aspects to the evolution of AML and hence is thought to be subject to the same therapeutic thesis. That AML cells employ LSD1 in a similar fashion suggests that with continued inhibition the population of both leukaemic blasts and stem cells might be eroded and eventually eradicated. These data, and the successful treatment of various animal models of AML through the inhibition of LSD1, is the foundation for taking development of the Imago molecule, IMG-7289, into clinical trials in the AML population.

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3.4 Background to All-*Trans* Retinoic Acid (ATRA; tretinoin) Use in Acute Leukaemia

The standard "7+ 3" treatment regimen can be expected to achieve a complete remission rate approximating 80%. AML is, however, infrequently cured with chemotherapy. The outstanding exception is acute promyelocytic leukaemia (APL) which, when treated with all-*trans* retinoic acid (ATRA) in combination with other agents such as As_2O_3, can achieve a *cure* rate approaching 90% (Wang and Chen 2008; Lo-Coco *et al.,* 2013). The primary mechanism by which ATRA is thought to achieve its therapeutic effects is by converting the fusion oncoprotein PML-RARα from a transcriptional repressor to a transcriptional activator and inducing its own proteolysis. Transcriptional activation drives myeloid differentiation, but that alone is not sufficient to clear leukaemic stem cells; ligand-induced degradation of this oncoprotein is more closely linked to clinical efficacy (de The' *et al.,* 2012; dos Santos *et al.,* 2013). Granulocytic differentiation can be induced at low ATRA doses, but higher doses are required to induce PML-RARα proteolysis and reduce the frequency of leukaemic stem cells (Nasr *et al.,* 2008). Thus, with APL, differentiation alone is not sufficient for cure.

While ATRA as monotherapy induces haematologic remission in virtually all cases of APL, patients invariably relapse because of residual disease; a surviving population of leukaemic stem cells (Warrell *et al.,* 1991) present at remission. This remnant of disease may be partially owing to inadequate exposure to ATRA. Orally administered ATRA is rapidly metabolized with a plasma elimination half-life of 0.8 hours (Muindi *et al.,* 1992b). When administered over a period of as

little as a week, C_{max} and exposure (AUC) are reduced by as much as 50% and 90%, respectively (Muindi *et al.,* 1992a; Adamson *et al.,* 1995). That a liposomal formulation of the drug effected cures as monotherapy in treatment-naive APL patients supports the notion that ATRA exposure must attain, and remain, above a certain threshold to achieve maximal clinical effects (Tsimberidou *et al.,* 2006).

The activity of ATRA has been studied in non-clinical models of, non-APL AML. Primary cells from AML patients over-expressing ecotropic viral integration site 1 (*EVI-1*) showed greater sensitivity to ATRA suggesting that this sub-group might benefit clinically were ATRA added to their regimen (Verhagen *et al.,* 2016 Blood). In cells carrying nucleophosmin 1 (*NPM1*) mutations, ATRA exposure significantly increased the proportion of annexin V-positive and $CD11b^+$ cells, while inducing p53 (El Hajj *et al.,* 2016). The clinical benefit afforded by adding ATRA to standard chemotherapy has also been studied. Two studies report no improvement with the addition of ATRA to a SOC regimen (Burnett *et al.,* 2010; Nazha *et al.,* 2013), while Schlenk and colleagues reported that relapse-free and overall survival at four years in AML patients older than 60 years were superior to standard chemotherapy when ATRA was added (Schlenk et al., 2004; Schlenk *et al.,* 2009).

3.5 Rationale for IMG-7289 and ATRA Combination Therapy

The rationale for combining ATRA with an LSD1 inhibitor is based on enhanced anti-leukaemic activity observed by various groups. ATRA does not abolish the self-renewal or engraftment of leukaemic stem cells, whereas LSD1 inhibitors have been shown to reduce self-renewal, induce differentiation, inhibit engraftment and promote cell death in leukaemia stem cells (Zheng *et al.,* 2007; Harris *et al.,* 2012; Schenk *et al.,* 2012). A study of the combination of the non-specific LSD1 inhibitor, tranylcypromine (TCP), and ATRA was active against AML cells in culture and impaired engraftment in patient-derived AML cells transplanted to non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice (Schenk *et al.,* 2012). In this combination study, the CD11b marker was induced and the percentage of cells undergoing apoptosis was enhanced compared to monotherapy. The proposed mechanism of this synergism is the collective induction and de-repression of genes needed for differentiation.

In *in vitro* and *in vivo* studies, the LSD1 inhibitor IMG-7289 was synergistic with ATRA in inhibiting AML cell growth in culture. In a mouse xenograft model implanting the human AML cell line MV4;11, the combination of ATRA and the free base of IMG-7289 inhibited the growth of tumour volume more than either agent alone.

As discussed in Section 3.3, there are currently at least two actively recruiting clinical trials in which TCP (an irreversible inhibitor of LSD1) is being used for the treatment of AML (NCT02273102 and NCT02261779). Compared to IMG-7289 with a mean IC_{50} for inhibiting LSD1 of 10 nM, the IC_{50} for TCP against LSD1 *in vitro* is approximately 10 µM, a C_{max} plasma concentration difficult to achieve with standard TCP dosing because of dose-limiting toxicity, but this has not dampened enthusiasm for the combination. The dose of ATRA being used in these studies is 45 mg/m^2 daily given in divided doses, the same as for the treatment of APL.

As with ATRA treatment for APL, the doses of IMG-7289 and ATRA needed to induce AML cell death (apoptosis) and reduce leukaemic stem cell potential may be higher than those needed to induce differentiation.

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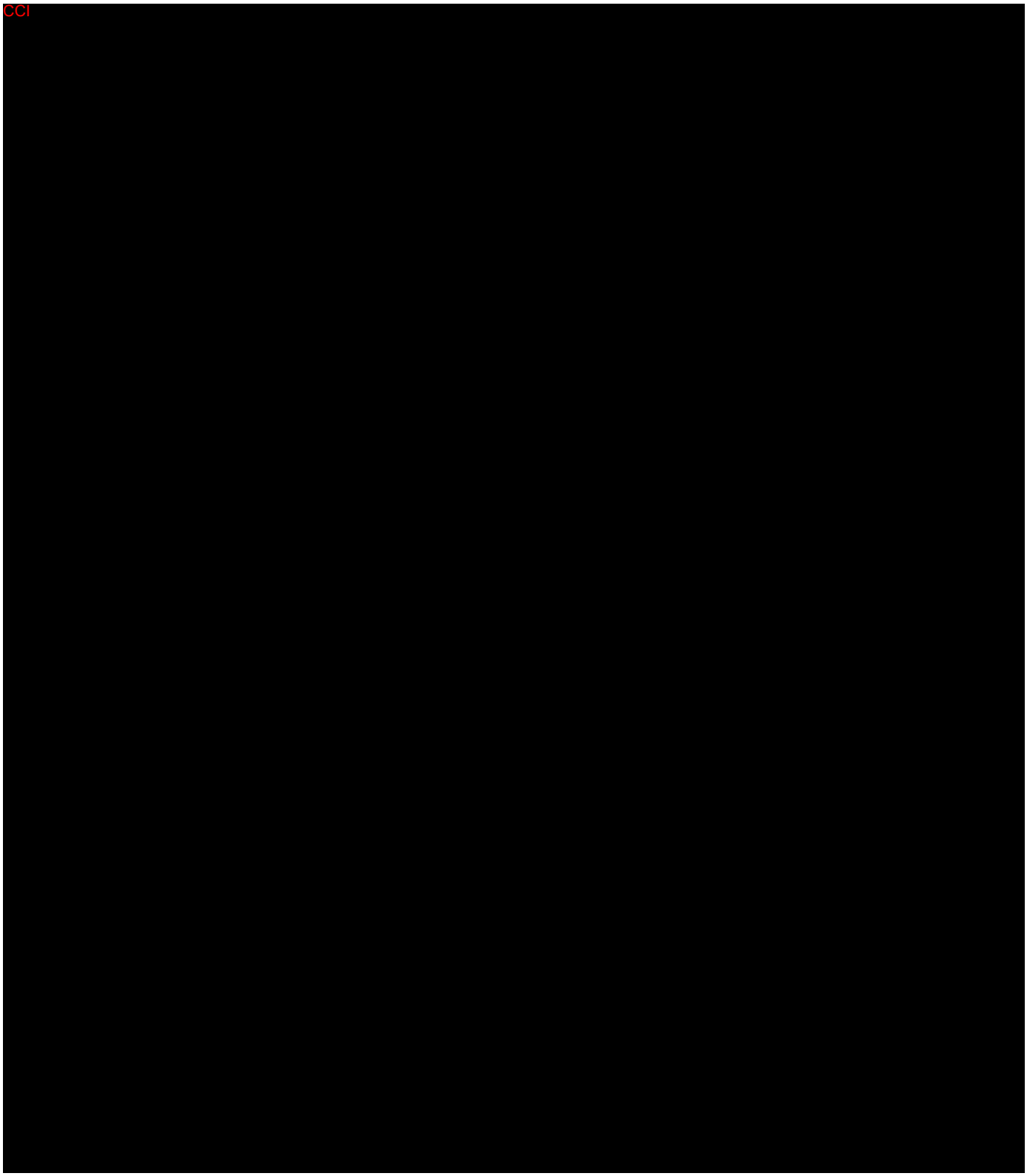

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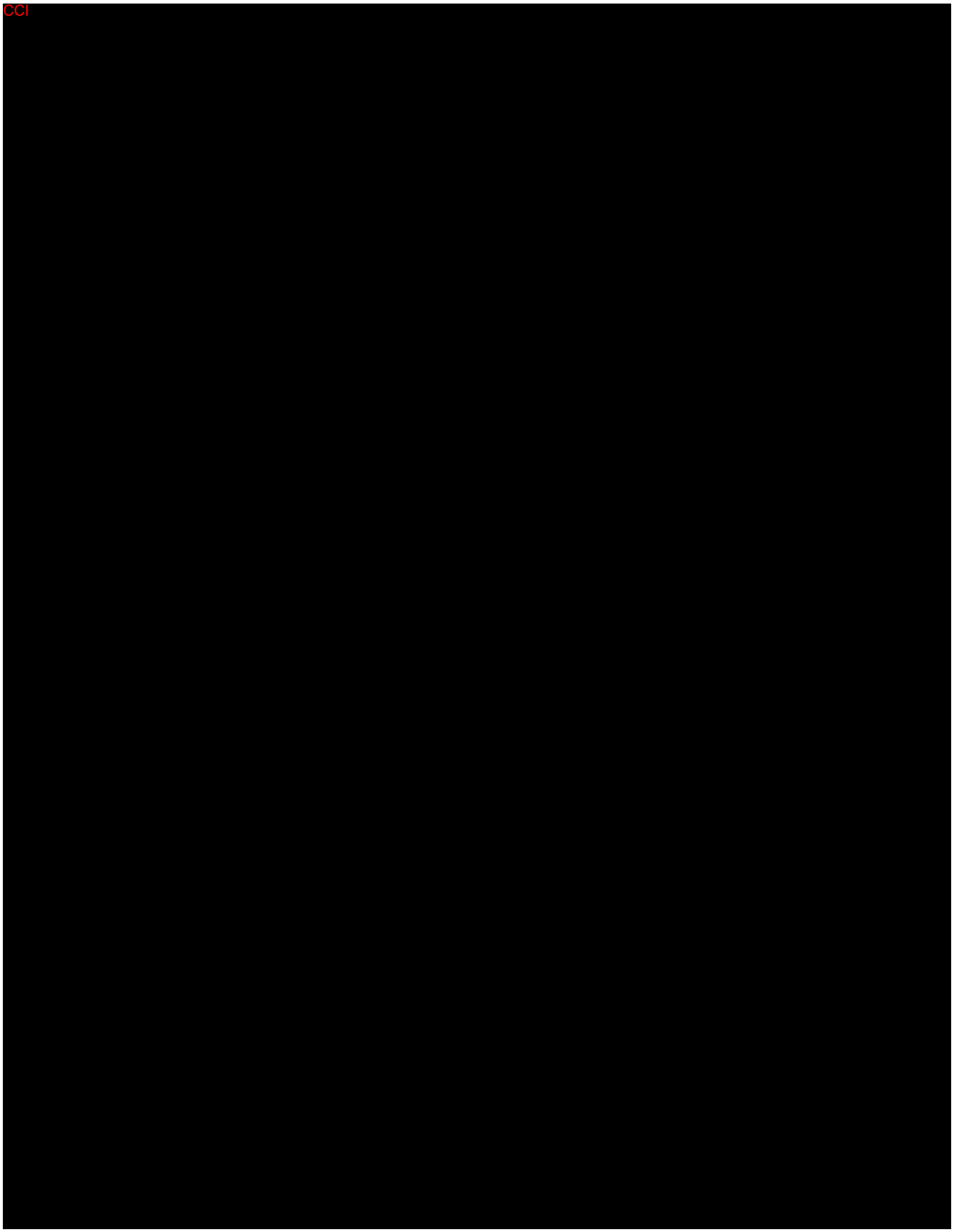

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3.7 ATRA Dose and Duration in Non-APL AML

There are no clinical studies comparing doses of ATRA in the treatment of APL. The standard dose is 45 mg/m^2 per day in divided doses, though some reports suggest that a reduced dose of 25 mg/m^2 is equally effective (Tallman and Altman 2009). Daily dosing of ATRA is typically continued until complete remission (CR) by clinical measures has been achieved, as long as the patient is tolerating treatment well. Patients who have received ATRA for at least two weeks but were discontinued because of toxicity even eventually achieved CR. After the induction of CR, APL patients receive intermittent ATRA for up to 2 years to achieve a molecular remission.

Though very low doses of ATRA in combination with IMG-7289 were needed to induce differentiation in cultured AML cells, higher exposure to ATRA than that needed for differentiation may be required to induce AML cell death (apoptosis) and potentially reduce the leukaemic stem cell pool. Hence, in combination with IMG-7289, the proposed dose of ATRA is 45 mg/m^2 per day divided into two doses.

The objective of this phase of the study is to expose leukaemic cells to a combination of both IMG-7289 and ATRA. Non-clinical models had suggested the half-life of IMG-7289 was less than 24 hours. The PK parameters now available for the first four dose-finding sub-cohorts indicate a drug half-life of 4-5 days. Thus, what was originally defined as the 7 day "rest" period is one during which patients are still exposed to IMG-7289 at or above the IC_{50} of the drug. This degree of exposure has, however, been demonstrated to be well tolerated. Thus, to match more closely the exposure of ATRA to IMG-7289, ATRA will be given at the planned dose of 45 mg/m^2, but for 21 days, followed by a rest period of 7 days. This dosing schedule of ATRA is regarded as safe as it affords less exposure than standard recommended treatment regimens of ATRA for acute promyelocytic leukaemia in which 45-60 days of daily ATRA at 45 mg/m^2 would be most common.

4 HYPOTHESIS AND OBJECTIVES

4.1 Hypothesis

IMG-7289 with and without all-*trans* retinoic acid (ATRA; tretinoin) is a safe and tolerable orally available agent when administered to patients with advanced myeloid malignancies including high risk AML and high risk MDS; LSDi by IMG-7289 will have a negative impact on leukaemic and dysplastic cells, an effect which may be further enhanced *via* synergistic mechanisms when administered in combination with ATRA.

4.2 Objectives

The following primary, secondary and exploratory objectives will be evaluated in patients with advanced myeloid malignancies, including high risk acute myeloid leukaemia and high risk myelodysplastic syndromes, treated with IMG-7289 with and without ATRA:

4.2.1.1 Primary

- Safety and tolerability
- Pharmacokinetics
- The adequacy of dose and duration in producing a pharmacodynamic effect

4.2.1.2 Secondary

- The association of plasma concentrations (C_{max} and C_{min}) and exposure (AUC) on haematopoiesis (both short[+] and longer-term[‡] measures)
- The kinetics of recovery of haematopoiesis for a given dose and for a given duration of dosing

4.2.1.3 Exploratory[Φ]

- The impact of therapy on disease burden as measured by malignant-cell specific nucleic markers (DNA or mRNA)[*]
- The effect of treatment on the immunophenotype of leukaemic and dysplastic cells[**]
- The effect of treatment on cytokine profiles[***]
- The relationship between genetic and cytogenetic aberrations in leukaemic cells on pharmacodynamic response
- The association of conventional clinical responses[****] with molecular assessments of response

[+]Short term measures may include reticulocyte counts, absolute neutrophil counts (ANC), platelet volume.

[‡]Longer-term measures may include return of counts to baseline or better.

[Φ]Some or all may be analysed time and cost permitting.

*Nucleic markers include tumour-specific transcripts and DNA mutations detected by sequencing.

** Immunophenotyping by fluorescence-activated cell sorting or flow cytometry (FACS; FC).

***Serum cytokine quantification.

****Conventional clinical response parameters may comprise: CBC including platelets, red and white blood cell (RBC and WBC) and leukaemic blast cell counts; transfusion requirements; cellular composition of the bone marrow (% marrow blasts); and, markers of differentiation.

5 INVESTIGATIONAL PLAN

5.1 Overview

Note: 'Sub-cohort' (generally) refers to different treatment arms within the dose-finding Cohort.

This is a multi-center, open-label, multiple ascending dose- and duration-finding study assessing the safety, pharmacokinetics and pharmacodynamics of IMG-7289, with and without ATRA, in patients with advanced myeloid malignancies. Following their consent, patients will undergo Screening to confirm eligibility. A sufficient number of patients will be screened to enroll and treat approximately 40 patients with high risk AML/MDS. Screening may commence up to 28 days prior to the start of IMG-7289 treatment on Day 1. Patients meeting all applicable Inclusion and no Exclusion Criteria will be enrolled into the study and assigned to a Cohort. All patients will be unique; no patient will be allowed to be dosed in more than one cohort. Contingent on the number of prior DLTs within a cohort, non-completers of Cycle 1 will be replaced.

Non-clinical studies indicate that the maximal differentiation and cell killing of AML cells is a result of complete inhibition of the enzyme. The dose of IMG-7289 (free base) estimated to provide in

humans a plasma concentration sufficient to inhibit the LSD1 enzyme throughout the 24 hour dosing cycle has been designated the D_i. Non-clinical studies indicate that an oral dose resulting in a C_{min} unbound plasma concentration at 24 hours post-dose of between 1 and 2 ng/mL of the free base of IMG-7289 is sufficient to fully inhibit LSD1 during the dosing cycle and hence, arrest normal myeloid haematopoiesis in mouse, rat and dog. This concentration approximates the IMG-7289 concentration needed to inhibit LSD1 activity fifty percent (IC_{50}) *in vitro* as well as the IC_{50} for killing cultured AML cells (6-9 nM free base). Based on pharmacokinetic modeling, the IMG-7289 free base dose needed to achieve this concentration in humans at 24 hours is approximately 3 mg/kg. The non-clinical and modeling data may not be precise enough to accurately predict the pharmacokinetic parameters in humans. Accordingly, as a measure of precaution, a starting dose of 0.75 mg/kg QD representing the estimated $<IC_{10}$ for inhibiting human platelet production has been selected as the starting dose and designated the D_s.

The D_s of 0.75 mg/kg QD (free base) is likely to be below the D_i, the dose anticipated to achieve an unbound plasma concentration of drug across the dosing interval sufficient to inhibit normal myeloid haematopoiesis. If, as expected, normal myeloid haematopoiesis is not significantly affected at the D_s, then planned dose escalation in subsequent sub-cohorts above the D_s are intended to identify the D_i. Similarly, the D_i may not be the equivalent of the dose needed to achieve the desired PD effects on malignant cells in high risk AML/MDS patients, a dose designated the D_p; the D_p, which will be determined by the DSMC, may be higher *or* lower than the D_i. NB: the D_p may vary based on the IMG-7289 dose, treatment regimen (i.e., IMG-7289 alone *versus* combination therapy) or dosing duration. If the anticipated PD responses are not demonstrated at the D_i, then titrations above or below the D_i are intended to identify the D_p. Any potential dose titrations will be made with appropriate consideration to safety.

The study consists of two phases in which IMG-7289 will be dosed with and without ATRA: the dose-finding phase, using multiple ascending doses of IMG-7289; and the duration-finding phase, during which multiple IMG-7289 durations may be assessed. During both phases, a Data Safety Monitoring Committee (DSMC) will convene to review safety parameters, pharmacodynamic markers and pharmacokinetic parameters to draw conclusions around the safety and pharmacodynamic effects of differing doses, treatment regimens and dosing durations. DSMC reviews are critical, as neither a new dose-finding sub-cohort, nor a duration-finding cohort may commence without DSMC review and recommendation to do so. Refer to Section 8 for details pertaining to DSMC reviews, DLT management, dose escalation/duration extension rules, and MTDs.

At least three patients will enroll in each cohort/sub-cohort, with a minimum of 3 patients per cohort/sub-cohort required to complete the entirety of Cycle 1 (i.e., the applicable IMG-7289 dosing and rest periods). Each dose-finding sub-cohort will include a sentinel patient to be dosed for 7 days, the safety of which will be determined by the DSMC before the remainder of the sub-cohort is treated; duration-finding cohorts will not include sentinel patients. Therefore, with the exception of a sentinel patient in each dose-finding sub-cohort, patients will be enrolled on a rolling basis. As there is no evidence in non-clinical studies of acute toxicity with IMG-7289, even at extremely high doses, it is believed that one sentinel patient for each dose-finding sub-cohort is sufficient to establish the acute safety of IMG-7289 dosed with and without ATRA. Since this study is not

investigating the effects of cytotoxic agents, enrolling patients on a rolling basis facilitates progression to later cohorts that could offer greater therapeutic benefit.

Patients will be treated with IMG-7289 in cycles, each cycle comprised of one IMG-7289 dosing period followed by one rest period. The number of initially allowed IMG-7289 cycles differs by cohort, as does the duration of IMG-7289 dosing. Patients may initially undergo four (Cohort 1), two (Cohort 3/3χ) or one (Cohort 4/4χ) IMG-7289 treatment cycles while on study to a total of approximately 28 days of IMG-7289 dosing. During the initially allowed IMG-7289 treatment cycles and regardless of the dosing duration, the rest period will remain at 7 days, unless assessment is made by the DSMC that either a specific patient or an entire cohort could benefit from an extended rest period. This decision could be taken if there is no clear indication of the restoration of normal haematopoiesis in the 7 day period or analysis of the IMG-7289 pharmacokinetic parameters in the earlier sub-cohorts suggest the rest period duration requires adjusting. As IMG-7289 treatment may lead to cytopenias, transfusions may be administered in accordance with standard institutional guidelines.

The initial dose-finding phase of the study will be used to establish and confirm the IMG-7289 D_i and the D_p in patients, as well as to provide samples sufficient to establish the pharmacokinetic parameters of IMG-7289 at several dose levels, with and without ATRA. It is anticipated that dose escalation of IMG-7289 as well as IMG-7289 administered in combination with ATRA will proceed in sub-cohorts (i.e., Sub-cohort 1b, 1c, 1χ, 1ᴡ) in accordance with Section 7.2.2.1, following DSMC reviews as detailed in Section 8.1 and the rules outlined in Section 8.2.2. (Note: Though not expected, contingencies are in place in the case that unacceptable toxicity is demonstrated at the D_s and sub-cohorts at lower doses are therefore required. Please refer to Section 7.2.2.2.) The IMG-7289 dosing duration and associated rest period will remain at 7 days dosing followed by a 7 day rest period throughout the entirety of the dose-finding phase (includes all sub-cohorts)*. Patients will be initially allowed to receive up to 4 cycles of IMG-7289, provided that IMG-7289 (with and without ATRA) continues to be tolerated.

Upon DSMC confirmation that no further dose-finding sub-cohorts are anticipated, and safety permitting (the DSMC must have determined it safe to extend the duration of IMG-7289 treatment), the duration-finding phase will commence. The duration-finding phase will be used to identify the safety and clinical effects of IMG-7289 treatment for durations longer than 7 days as well as provide samples sufficient to establish drug concentrations at steady state, with and without ATRA. Duration-finding cohorts will be dosed with IMG-7289 at the D_p (determined by the DSMC), with or without ATRA. The D_p may change as data from earlier sub-cohorts becomes available and different durations continue to be studied. The duration of dosing will be extended in cohorts in accordance with Section 7.2.2.3, following DSMC reviews as detailed in Section 8.1 and the rules outlined in Section 8.2.2; each dosing duration will be followed by a 7 day rest period*. Patients will be initially allowed to receive **2 cycles** of 14 days IMG-7289 dosing for Cohorts 3/3χ, and **1 cycle** of 21 days IMG-7289 dosing for Cohorts 4/4χ; each dosing duration will be followed by a 7 day rest period.*

*The duration of the rest period may be adjusted based on an assessment by the DSMC that either a specific patient or an entire cohort could benefit from an extended rest period. This decision could be taken if there is no clear indication of the restoration of normal haematopoiesis in the 7 day period or analysis of the

pharmacokinetic parameters in earlier cohorts (or sub-cohorts) suggest the rest period duration requires adjusting. Investigators will be notified of any such change.

Importantly, if the DSMC determines a specific dose, treatment regimen or dosing duration is associated with greater therapeutic benefit, patients who have *fully completed* their initially allowed cycles and are receiving a different dose, treatment regimen (i.e., IMG-7289 alone *versus* combination therapy) or dosing duration will be transitioned to the more optimal dose, treatment regimen or dosing duration at the start of their next cycle. Such transition may occur more than once, as different doses, treatment regimens and dosing durations continue to be evaluated.

Throughout all phases of the study, if it appears that either a maximally tolerated dose (MTD) or maximally tolerated duration (MTD_u) is reached (see Section 8.2.3), the DSMC will convene to evaluate further dose escalation, combination therapy and/or extended dosing duration.

Upon completion of the number of initially allowed IMG-7289 cycles per cohort, patients deriving clinical benefit and safely tolerating IMG-7289, as determined by the Principal Investigator, may continue to receive IMG-7289 with additional dose titration, treatment regimen and dosing duration changes occurring in consultation with the Medical Monitor until disease progression or unacceptable toxicity ensues. During the additional cycle period, the rest period may be extended from the 7 day standard to a maximum of 56 days but only after: 1) the patient has received a minimum of 28 IMG-7289 doses; and, 2) consultation with or recommendation by the DSMC. Such recommendation may be made for a variety of reasons including evidence of tumour reduction, marked hypocellularity in the marrow consistent with myelosuppression, or to enable the return of normal haematopoiesis. For protocol purposes, a rest period extending beyond the 7 day standard will be referred to as the extended rest period (see Section 9.10).

Patients who either fail to demonstrate stable disease, demonstrate progressive disease after achieving partial remission (PR) or stable disease, or relapse after achieving complete remission (CR), CR with incomplete recovery (CRi), or PR (see **Table 14** and **Table 15**) are the equivalent of treatment failures, and will discontinue study drug and enter the follow-up period.

Patients will be followed closely for both Adverse Events (AEs) and signs of toxicity by frequent monitoring of clinical signs and symptoms and by blood and urine analyses both during the IMG-7289 treatment period and the rest period. Pharmacodynamic effects will also be closely monitored by frequent haematology assessments of peripheral blood and bone marrow aspirates, as required.

All patients will undergo End-of-Treatment (EOT), pre-End of Study (pre-EOS), and End-of-Study (EOS) visits approximately 7, 14, and 28 days, respectively, after last Cycle last dose.

A detailed description by-cohort, by-cycle, of assessments to be performed is provided in Section 9. Additionally, a by-cohort schema of assessments is included in Section 16.1, Schedule of Assessments.

6 STUDY POPULATION

6.1 Study Entry Criteria

6.1.1 Inclusion Criteria

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

1. Willing and able to sign the approved informed consent.
2. Age: 18+ years old at Screening.
3. Diagnosis (a., b., and c. required) of **EITHER** *Acute Myeloid Leukaemia:*
   a. By World Health Organization (WHO) criteria regardless of etiology, sub-type or treatment history.
   b. High risk AML* diagnosis in accordance with one of the following classifications:
      - ≥ 60 years of age with AML who are ***not*** candidates for (based on parameters such as performance scores, co-morbidities and cytogenetic studies), or have refused, standard chemotherapy
      - 18+ year old with *de novo* or secondary AML (MDS/AML or treatment-related (t)-AML) who are ***not*** expected to benefit from standard remission-induction chemotherapy (unfavorable cytogenetics)
      - Relapsed/refractory AML after no more than 3 previous lines of chemotherapy, including hypomethylating agents, for whom no standard therapies are available
   c. Eastern Cooperative Oncology Group (ECOG) performance status score ≤2.

   *All forms of AML (M0–M7) diagnosed by morphologic, histochemical or cell surface marker criteria.

   OR *Myelodysplastic Syndromes:*
   a. By WHO criteria regardless of sub-type.
   b. High Risk MDS diagnosis in accordance with one of the following classifications:
      - MDS patients who have failed first-line therapy, demonstrated by resistance to, or relapse following a minimum of 4 cycles with a hypomethylating agent (HMA)
      - Treatment-related MDS, except if it is associated with favorable cytogenetics, and ***not*** a candidate for stem cell transplantation
   c. Either an International Prognostic Scoring System (IPSS) score equivalent to intermediate-2 risk or higher, or a Revised International Prognostic Scoring System (IPSS-R) score equivalent to intermediate risk or higher.
4. Prior autologous stem cell transplant is allowed if a minimum of 3 months has elapsed from the time of transplant and the patient has recovered from transplant-associated toxicities.
5. Prior allogeneic stem cell transplant is allowed, provided all of the following criteria are met:
   a. Transplant was >120 days prior to study enrollment
   b. No immunosuppressive medications have been taken for at least 1 month
   c. No active graft versus host disease (GVHD), excluding Grade 1 skin GVHD

6. WBC ≤ 30 x 10^9/L (30,000/μL) for at least one week prior to first dose, with hydroxyurea use to achieve this value acceptable.
7. Platelet count ≥ 30 x 10^9/L (30,000/μL) prior to first dose, with transfusions to reach this limit acceptable.
8. Life expectancy >12 weeks.
9. Willing to discontinue all existing anti-neoplastic therapies (with the exception of hydroxyurea) for the 3 weeks prior to first dose of IMG-7289, total duration of dosing, and 1 week after last dose.
10. Amenable to serial bone marrow evaluation, blood, and urine sampling during the study.
11. Able to swallow capsules.
12. Agrees to use an approved method of contraception from Screening and until 28 days after the last administration of the study drug. Agreed methods of contraception may include: condom; use of birth control pills, patches, implants or injections, diaphragm with vaginal spermicide, intrauterine device (IUD) and/or surgical sterilization (vasectomy or tubal ligation at least six months prior to dosing). Patients practicing abstinence must agree to use an approved method of contraception should they become sexually active during the study.

6.1.2 Exclusion Criteria

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

1. Has received either: immunotherapy within <8 weeks; chemotherapy within <3 weeks (with the exception of hydroxyurea); radiation therapy to >30% of marrow-bearing bone within <2 weeks prior to starting study treatment; or, has not yet recovered from the effects of such therapies (excluding alopecia).
2. Has undergone major surgery ≤4 weeks prior to starting study drug or has not recovered from side effects of such surgery.
3. Has undergone any surgical procedure within 2 weeks, excluding minor procedures (i.e., skin biopsy or central venous catheter placement/removal) prior to starting study drug.
4. Scheduled haematopoietic stem-cell transplant.
5. Current use of a prohibited medication including anticoagulants or platelet inhibitors or expected to require any of these medications (outside of such use permitted as per the Prohibited Medications section) during treatment with the investigational drug.
6. Current use of monoamine oxidase A and B inhibitors (MAOIs).
7. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to IMG-7289, LSD1 inhibitors, or ATRA that contraindicates participation.
8. Uncontrolled active infection.
9. Clinical evidence of central nervous system (CNS) or pulmonary leukostasis, disseminated intravascular coagulation, or CNS leukaemia.
10. A concurrent second active and non-stable malignancy (patients with a concurrent second active but stable malignancy, such as non-melanoma skin cancers, are eligible).

11. Known human immunodeficiency virus (HIV) infection or known active Hepatitis B or Hepatitis C virus infection.
12. History of any illness/impairment of gastrointestinal (GI) function that might interfere with drug absorption (e.g., chronic diarrhea), confound study results or pose an additional risk to the patient by their participation in the study; patients with gastric bypass surgery.
13. Refractory to platelet transfusion (but not excluding patients receiving HLA–matched platelets that increment appropriately).
14. Evidence at the time of Screening of risk of bleed, including any one of the following:
    a. Activated partial thromboplastin time (aPTT) ≥ 1.3 x the local upper limit of normal
    b. International normalized ratio (INR) ≥ 1.3 x the local upper limit of normal
    c. History of severe thrombocytopenia unrelated to AML, MDS or treatment for either
    d. Known bleeding disorder (e.g., dysfibrinogenemia, factor IX deficiency, haemophilia, Von Willebrand's disease, Disseminated Intravascular Coagulation [DIC], fibrinogen deficiency, or other clotting factor deficiency) or
    e. Receiving therapeutic anticoagulation
15. Evidence at the time of Screening of significant renal or hepatic insufficiency (unless due to haemolysis, or leukaemic infiltration) as defined by any one of the following local lab parameters:
    a. Calculated glomerular filtration rate (GFR) < 40 mL/min or serum creatinine > 1.5 x the local upper limit of normal
    b. Aspartate transaminase (AST) or alanine aminotransferase (ALT) ≥ 2 x the local upper limit of normal
16. Use of an investigational agent within less than 14 days, or the equivalent of at least 7 half-lives of that agent, whichever is the longer, prior to the start of study treatment.
17. Pregnant or lactating females.

6.2 Patient Enrollment

A sufficient number of patients who fulfil the inclusion and exclusion criteria documented in Section 6.1 will be screened to ensure approximately 40 patients are enrolled and treated in this study. As patients are screened and become eligible for the study, they will be assigned to the currently open cohort. This process will be detailed in the Study Reference Manual (SRM).

6.3 Patient Withdrawal

In accordance with the Declaration of Helsinki, Good Clinical Practice (GCP), and International Conference on Harmonization (ICH) Guidelines and applicable regulations governing human subject protection, a subject has the right to withdraw from the study at any time for any reason. Subjects may also be removed from the study by the Sponsor or Investigator. The reason for withdrawal, if given, will be provided to the Sponsor and documented on the CRF. Patients will be requested to return for follow-up beginning with an End of Treatment visit as per Section 9.12.1.

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

- Taking another investigational medicinal agent during their involvement in the study
- Major violation of, or deviation from, study protocol procedures which, in the judgment of the Medical Monitor, could adversely affect the patient or the integrity of the study including missing more than 2 consecutive doses or other evidence of major non-compliance;
- Withdrawal from the study is, in the Investigator's judgment, in the patient's best interest;
- Experiencing a Dose Limiting Toxicity (DLT), as per Section 8.2.1.

6.4 Replacement of dropouts

A minimum of 3 patients per cohort/sub-cohort are required to complete the entirety of Cycle 1 (including the applicable treatment and rest periods). Contingent on the number of prior DLTs within a cohort/sub-cohort, non-completers of Cycle 1 will be replaced to ensure a minimum of 3 patients complete Cycle 1 of each cohort/sub-cohort.

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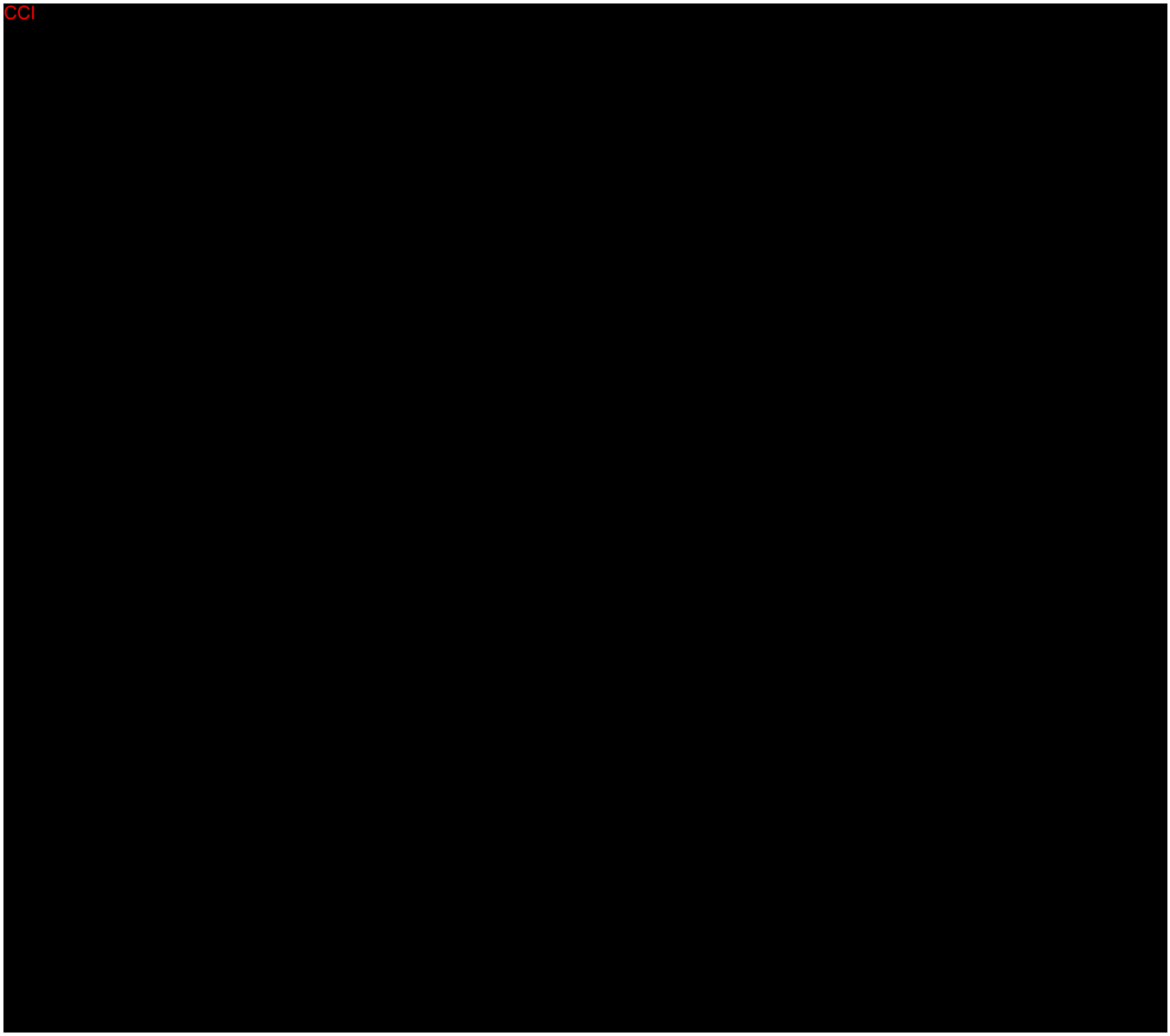

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6.7 Patients Who Terminate Early or Discontinue Study Medication

All patients who finish the study early, or who discontinue study medication will be requested to return for follow-up visits, beginning with an End of Treatment visit as detailed in Section 9.12.1. If a patient refuses to enter follow up, perform an Early Termination visit as detailed in Section 9.12.3 Patients who discontinue study medication due to a DLT will be asked to continue follow-up.

6.8 Treatment Failure

Patients who either fail to demonstrate stable disease, demonstrate progressive disease after achieving partial remission or stable disease, or relapse after achieving CR, CRi or PR (see **Table 14** and **Table 15**) are the equivalent of treatment failures, and will discontinue study drug and enter the follow-up period.

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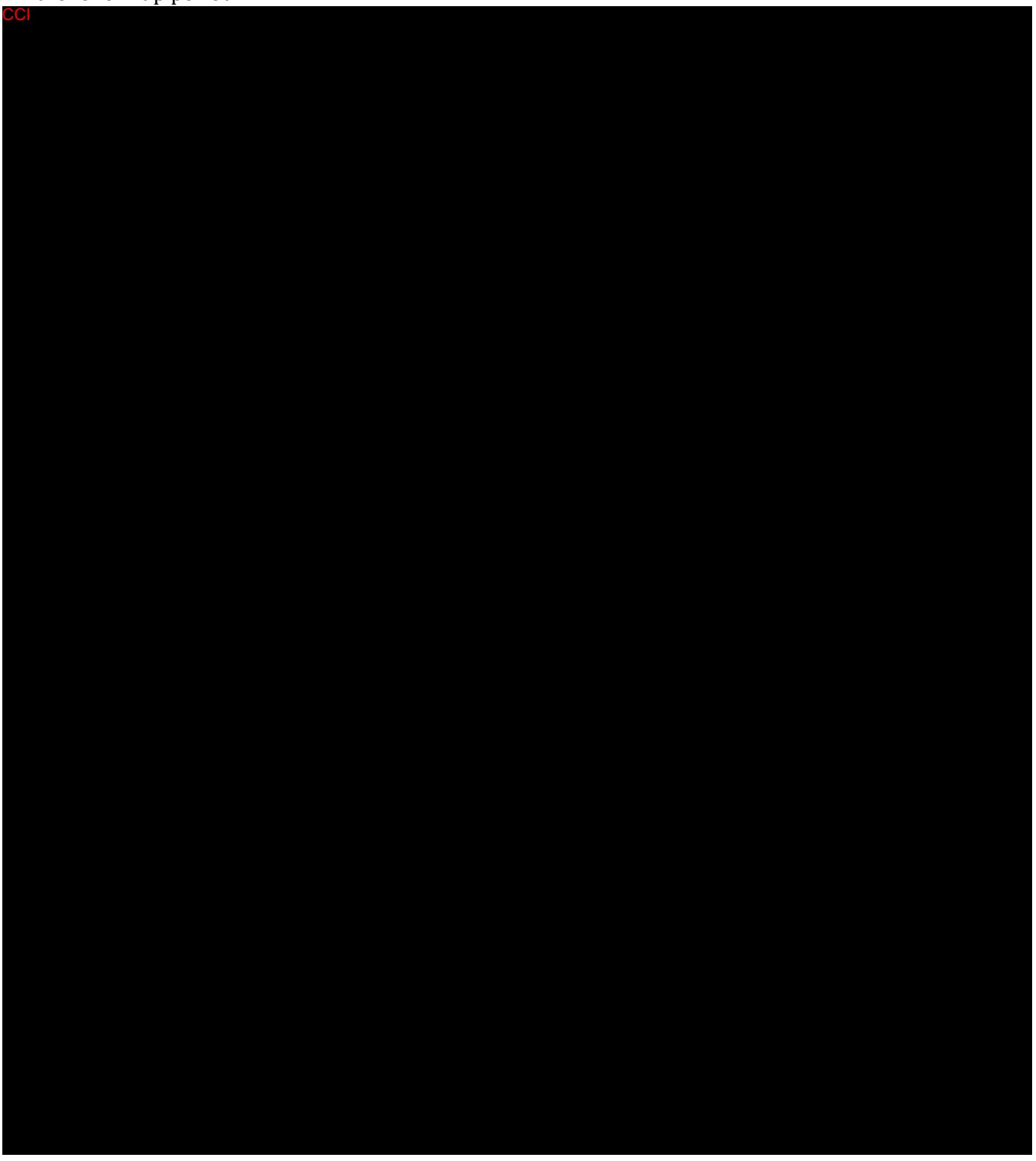

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7.2.2 Dosage and Duration of Treatment

Throughout both the dose- and duration-finding phases, patients will be treated with IMG-7289 in cycles comprised by one IMG-7289 dosing period followed by one rest period. Regardless of IMG-7289 dosing duration, the rest period will remain at 7 days, unless assessment is made by the DSMC that either a specific patient or an entire cohort could benefit from an extended rest period. This decision could be taken if there is no clear indication of the restoration of normal haematopoiesis in the 7 day period or analysis of the IMG-7289 PK parameters in earlier sub-cohorts suggest the rest period duration requires adjusting.

Throughout all phases of the study, if it appears that either a maximally tolerated dose (MTD) or maximally tolerated duration (MTD_u) is reached (see Section 8.2.3), a DSMC review will convene to evaluate further dose escalation, combination therapy and/or duration extensions.

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

Details on dosage, combination therapy and duration of treatment by study phase are detailed in the sections below.

7.2.2.1 Dosage and Duration of Treatment During the Dose-finding Phase

Details on the selection of and rationale for the starting dose can be found in Section 3.6.1. Details on the rationale for IMG-7289/ATRA combination therapy can be found in Section 3.5. Cohort 1 (*via* sub-cohorts, as needed), the dose-finding cohort, is outlined below.

Patients assigned to a dose-finding sub-cohort will receive 7 days of IMG-7289 dosing and be initially allowed to receive up to **4 cycles** of IMG-7289, provided IMG-7289 (with or without ATRA) is tolerated.

The IMG-7289 alone component of the dose-finding phase is summarized below.

Sub-cohort 1a: Dosing will begin on Day 1 at the starting dose (D_s), 0.75 mg/kg/d IMG-7289 free base.

It is anticipated that dose escalation will proceed in sub-cohorts in accordance with the below, following DSMC reviews as detailed in Section 8.1 and in accordance with the rules outlined in Section 8.2.2. (Note: though not expected, contingencies are in place in the case that unacceptable toxicity is demonstrated at the D_s and lower doses are therefore required. Please refer to Section 7.2.2.2.

If the DSMC determines that dose escalation should proceed, then additional sub-cohorts (Sub-cohorts 1b, 1c, etc.) will be dosed with increasing doses as outlined below.

Sub-cohort 1b: Dosing will begin on Day 1 at 1.5 mg/kg/d IMG-7289 free base.

Sub-cohort 1c: Dosing will begin on Day 1 at 3 mg/kg/d IMG-7289 free base.

There are two potential dose-escalation pathways for Sub-cohort 1d: 6 and 10 mg/kg/d. The dose to be administered in Sub-cohort 1d will be determined at the discretion of the DSMC.

Sub-cohort 1d: Dosing will begin on Day 1 at either 6 or 10 mg/kg/d IMG-7289 free base.

Sub-cohort 1e: Dosing will begin on Day 1 at 10 mg/kg/d IMG-7289 free base, if not previously administered in Sub-cohort 1d.

Note: If appropriate, an additional sub-cohort will commence at a 2x multiple of the last cohort's dose, followed by further sub-cohorts with dose escalation continuing in such increments until the DSMC determines that no further dose escalation is anticipated$^{\Psi}$. Upon such confirmation, the combination therapy sub-cohorts will commence.

$^{\Psi}$The DSMC may revisit dose escalation after having progressed to combination therapy.

If the DSMC determines a specific IMG-7289 dose is associated with greater therapeutic benefit, patients who have fully completed their initially allowed IMG-7289 treatment cycles and are at a different dose will be titrated to the more optimal dose at the start of their next cycle.

The table below summarizes the IMG-7289 alone component of the dose-finding phase by sub-cohort, dose, dosing duration, rest period and the number of initially allowed cycles.

Table 1: IMG-7289 Alone Dose-Finding Sub-cohorts, Including Doses for Escalation

Sub-cohort	IMG-7289 Dose (free base)	IMG-7289 Cycle		No. of Initial IMG-7289 Cycles**
		Dosing Duration	Rest Period*	
1a	**0.75 mg/kg/d = D_s**	**7 days**	**7 days**	**4**
1b	1.5 mg/kg/d			
1c	3 mg/kg/d			
1dΦ	6 or 10 mg/kg/d			
1e***	10 mg/kg/d			

*The duration of the rest period may be adjusted based on an assessment by the DSMC that either a specific patient or an entire sub-cohort could benefit from an extended rest period. This decision could be taken if there is no clear indication of the restoration of normal haematopoiesis in the 7 day period or on analysis of the pharmacokinetic parameters in the earlier sub-cohorts suggest the rest period duration requires adjusting; for example, if the half-life of IMG-7289 is unexpectedly long. Investigators will be notified of any such change.

**Additional cycles may be allowed, contingent on clinical benefit/patient response.

ΦThe dose to be used in Sub-cohort 1d, either 6 mg/kg/d or 10 mg/kg/d, will be determined by the DSMC based on review of safety and pharmacodynamics data from earlier dose-finding sub-cohorts.

***If 10 mg/kg/d was not studied in Sub-cohort 1d, and if deemed appropriate by the DSMC, then 10 mg/kg/d will be studied in Sub-cohort 1e. If deemed appropriate by the DSMC, then additional sub-cohorts beyond Sub-cohort 1e will commence with up-titration of dosing continuing in such increments until the D_p is identified.

The IMG-7289 administered in combination with ATRA component of the dose-finding phase is summarized below.

Sub-cohort 1χ: Dosing will begin on Day 1 with IMG-7289 (dose to be determined by DSMC) dosed for 7 days on followed by 7 days off, in combination with ATRA 45 mg/m^2 per day dosed for 7 days on followed by 7 days off.

Additional combination therapy sub-cohorts may follow (i.e., 1ω, 1ν, etc.) as the DSMC continues to review data on an ongoing basis.

If the DSMC determines combination therapy should proceed, then additional sub-cohorts will commence.

Sub-cohort 1ω: Dosing will begin on Day 1 with IMG-7289 (dose to be determined by the DSMC) dosed for 7 days on followed by 7 days off, in combination with ATRA 45 mg/m^2 per day dosed for 21 days♀ on followed by 7 days off.

♀Patient's enrolled in Sub-cohort 1χ will continue their current treatment regimen until completion of their initially allowed treatment cycles and pending DSMC review of the sentinel patient in Sub-cohort 1ω, after which transition to the new (21 day ATRA) regimen may occur at the start of the next cycle.

If the DSMC determines that combination therapy offers greater therapeutic benefit as compared to single agent IMG-7289 therapy, then patients who have fully completed their initially allowed IMG-7289 treatment cycles and are receiving a different treatment regimen (i.e., IMG-7289 alone) will be transitioned to combination therapy at the start of their next cycle.

The table below summarizes the IMG-7289 in combination component of the dose-finding phase by sub-cohort, dose, dosing duration, rest period, and number of initially allowed IMG-7289 cycles.

Table 2: Combination Therapy Component of the Dose-finding Cohort

Sub-cohort	IMG-7289 Dose (free base)	IMG-7289 Cycle		No. of Initial IMG-7289 Cycles**
		Dosing Duration	Rest Period*	
1χ	**TBD¥**	**7** days on	**7** days off	4
	Administered in combination with			
	ATRA§ 45 mg/m²/d for **7** days♀ on followed by 7 days off			
1ω§	**TBD¥**	**7** days on	**7** days off	4
	Administered in combination with			
	ATRA§ 45 mg/m²/d for **21** days on followed by **7** days off			

*The duration of the rest period may be adjusted based on an assessment by the DSMC that either a specific patient or an entire cohort could benefit from an extended rest period. This decision could be taken if there is no clear indication of the restoration of normal haematopoiesis in the 7 day period or analysis of the pharmacokinetic parameters in the earlier sub-cohorts suggest the rest period duration requires adjusting; for example, if the half-life of IMG-7289 is unexpectedly long. Investigators will be notified of any such change.
**Additional cycles may be allowed, contingent on clinical benefit/patient response.
¥The IMG-7289 dose for administration with ATRA will be determined by the DSMC based on ongoing review of safety and pharmacodynamic data.
§The ATRA dose may be reduced or the dosing and/or rest period duration adjusted by the DSMC based on ongoing review of safety and pharmacodynamic data.
§If deemed appropriate by the DSMC, then additional sub-cohorts beyond 1ω will commence.
♀Patient's enrolled in Sub-cohort 1χ will continue their current treatment regimen until completion of their initially allowed treatment cycles and pending DSMC review of the sentinel patient in Sub-cohort 1ω, after which transition to the new (21 day ATRA) regimen may occur at the start of the next cycle.

Upon DSMC confirmation that no further dose-finding sub-cohorts are anticipated, and safety permitting (the DSMC must have determined it safe to extend the duration of IMG-7289 treatment), the study will progress to assess the effect of IMG-7289 dosing duration.

7.2.2.2 Provisional Sub-cohorts; Unacceptable Dose Limiting Toxicity is Demonstrated at the D_s

Although unlikely, it is possible that unacceptable toxicity may be seen at the D_s; the D_s could also be the maximum tolerated dose. To address this possibility, and though not anticipated, the below contingencies are in place in the event that the DSMC determines that the starting dose is too high. Upon such determination, the enrollment of additional cohorts at lower doses will be necessary. All procedures and rules (i.e., sentinel patient, DSMC reviews, number of DLTs, progression to duration finding cohorts, etc.) remain applicable to these additional lower dose cohorts throughout the study.

Sub-cohort 1z will enroll the standard 3 patients at 0.375 mg/kg/d. If unacceptable toxicity occurs (DLT in 2 out of 3 patients), then Sub-cohort 1y will enroll 3 patients at the reduced dose of 0.1875 mg/kg/d.

Table 3: Provisional Sub-cohorts to Initiate if Unacceptable Toxicity is Demonstrated at the D_s

Sub-cohort	IMG-7289 Dose (free base)	IMG-7289 Cycle		No. of Initial IMG-7289 Cycles**
		Dosing Duration	Rest Period*	
1y	0.1875 mg/kg/d	**7 days**	**7 days**	**4**
1z	0.375 mg/kg/d			
1a	**0.75 mg/kg/d = D_s**			

*The duration of the rest period may be adjusted based on an assessment by the DSMC that either a specific patient or an entire sub-cohort could benefit from an extended rest period. This decision could be taken if there is no clear indication of the restoration of normal haematopoiesis in the 7 day period or on analysis of the pharmacokinetic parameters in the earlier sub-cohorts suggest the rest period duration requires adjusting; for example, if the half-life of IMG-7289 is unexpectedly long. Investigators will be notified of any such change.

**Additional cycles may be allowed, contingent on clinical benefit/patient response.

7.2.2.3 Dosing and Duration of Treatment During the Duration-finding Phase

The rationale for the IMG-7289 dosing schedule can found in Section 3.6.2. The duration-finding cohorts (Cohorts 3, 3χ, 4 and 4χ) will be dosed at the IMG-7289 D_p (determined by the DSMC) for either 14 or 21 days, with or without ATRA. The D_p may change as data from earlier sub-cohorts becomes available and different durations continue to be evaluated; the length of dosing will be extended by cohort as described below and summarized in **Table 4**. The number of initially allowed IMG-7289 cycles differs by cohort, as does the duration of IMG-7289 dosing. The duration-finding cohorts are outlined below.

It is anticipated that duration extension will proceed in cohorts in accordance with the below, following DSMC reviews as detailed in Section 8.1 and in accordance with the rules outlined Section 8.2.2. Of note, there are two potential duration-extension pathways for the duration-finding cohorts which will be determined at the discretion of the DSMC.

Cohort 3: Dosing of IMG-7289 at the D_p will begin on Day 1 for a duration of 14 days.

Cohort 3χ: The above IMG-7289 regimen in combination with ATRA 45 mg/m^2 per day for 14 days.

Cohorts 3 and 3χ patients will initially be allowed to receive **2 cycles** of IMG-7289, provided they continue to tolerate IMG-7289 (with or without ATRA).

If the DSMC determines that duration extension should proceed, then additional cohorts will be dosed with extending durations; possible cohorts are outlined below.

Cohort 4: Dosing of IMG-7289 will begin on Day 1 for a duration of 21 days.

Cohort 4χ: The above IMG-7289 regimen in combination with ATRA 45 mg/m^2 per day for 21 days.

Cohort 4 and 4χ patients will initially be allowed to receive **1 cycle** of IMG-7289.

If the DSMC determines that a specific dosing duration is associated with greater therapeutic benefit, then patients who have fully completed their initially allowed IMG-7289 treatment cycles and are at a different dosing duration will be transitioned to the more optimal dosing duration at the start of their next cycle.

The table below summarizes the duration-finding phase by cohort, dosing duration, treatment regimen, rest period and number initially allowed IMG-7289 treatment cycles.

Table 4*:* Duration-finding Cohorts, Including Durations for Extension

Cohort	IMG-7289 Dose (free base)	IMG-7289 Cycle		No. of Initial IMG-7289 Cycles**
		Dosing Duration	Rest period*	
3	D_p¥	**14** days	**7** days	2
3χ	The Cohort 3 IMG-7289 regimen, administered in combination with ATRA§ 45 mg/m²/d for **14** days on followed by **7** days off			
4	D_p¥	**21** days	**7** days	1
4χ	The Cohort 4 IMG-7289 regimen, administered with ATRA§ 45 mg/m²/d for **21** days on followed by **7** days off			

*The duration of the rest period may be adjusted based on an assessment by the DSMC that either a specific patient or an entire cohort could benefit from an extended rest period. This decision could be taken if there is no clear indication of the restoration of normal haematopoiesis in the 7 day period or analysis of the pharmacokinetic parameters in Cohort 1 suggest the rest period duration requires adjusting. Investigators will be notified of any such change.

**Additional cycles may be allowed, contingent on clinical benefit/patient response.

¥The IMG-7289 dose for administration will be determined by the DSMC based on ongoing review of safety and pharmacodynamic data.

§The ATRA dose may be reduced or the dosing and/or rest period duration adjusted by the DSMC based ongoing review of safety and pharmacodynamic data.

Additional Cycles: Upon completion of the number of initially allowed IMG-7289 cycles per cohort, patients deriving clinical benefit and safely tolerating IMG-7289, as determined by the Principal Investigator, may continue to receive IMG-7289 beyond the number of initially allowed IMG-7289 treatment cycles, specifically: 4 cycles of 7 days IMG-7289 dosing for Cohort 1 patients; 2 cycles of 14 days IMG-7289 dosing for Cohort 3/3χ patients; and, 1 cycle of 21 days IMG-7289 dosing for Cohort 4/4χ patients. Additional dose titration, treatment regimen or dosing duration changes may occur in consultation with the Medical Monitor, until disease progression or unacceptable toxicity ensues. During the additional cycle period, the rest period may be extended from the 7 day standard to a maximum of 56 days but only after: 1) the patient has received a minimum of 28 IMG-7289 doses; and, 2) consultation with or recommendation by the DSMC. Such recommendation may be made for a variety of reasons including evidence of tumour reduction, marked hypocellularity in the marrow consistent with myelosuppression, or to enable the return of normal haematopoiesis. For protocol purposes, a rest period extending beyond the 7 day standard will be referred to as the extended rest period (see Section 9.10).

Patients who either fail to demonstrate stable disease, demonstrate progressive disease after achieving partial remission or stable disease, or who relapse after achieving CR, CRi or PR (see **Table 14** and **Table 15**) are the equivalent of treatment failures and will discontinue study drug and enter the follow-up period.

7.2.3 Administration

Appropriately trained personnel of the study site will provide instruction pertaining to study drug administration and supervise the administration of the study drug on any day that it is taken in the clinic. With the exception of the Day 1 visits, and other visits where either PK or samples for C_{min} drug concentrations will be collected, it is not required that study drug 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.

Initial IMG-7289 dosing will be based on the patient's weight on Day 1. If during the course of the study, the patient's weight differs from the weight used for Day 1 by more than 10%, the amount of IMG-7289 dispensed should be corrected per the dose chart provided to sites. Initial ATRA dosing will be based on the patient's body surface area calculated from height at Screening and weight on Day 1. In cases where using weight measured on Day 1 is impractical for pharmacy dispensing, a weight taken as close to Day 1 as possible, e.g., Screening Visit or Baseline Visit may be used as long as the source data is clear on which weight has been used.

7.2.3.1 IMG-7289 Administration

Patients should be instructed to:

- Take their IMG-7289 in the morning once daily, at approximately the same time (suggest that patient select their dosing time with consideration given to fasting requirements) for the requisite dosing duration
- Swallow their IMG-7289 capsules whole, with a glass of water
- Take IMG-7289 on an empty stomach (fast for 1 hour prior to and 30 minutes after dose)

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

7.2.3.2 ATRA Administration

Patients should be instructed to:

- Take their ATRA twice daily, split into two equal doses for the requisite dosing duration
- Take their ATRA doses during or immediately after a meal, at about the same time each day
- Swallow their ATRA capsules whole, with a glass of water
- Take their second dose of ATRA approximately 12 hours after their first dose

7.2.4 Missed Doses

Patients who miss more than 2 consecutive doses may be removed from the study at the discretion of the Sponsor.

7.2.4.1 Missed IMG-7289 Doses

Patients who do not take their IMG-7289 dose at the usual required time should take it immediately upon noting that it was not taken; the patient should not take the dose more than 12 hours after the usual dosing time. If a patient misses a dose, they should not take two doses the following day, but should notify their study coordinator and continue with their normal daily dose the following day.

7.2.4.2 Missed ATRA Doses

Patients who do not take their ATRA dose at the usual required time should take it immediately upon noting that it was not taken; however, if it is within 3 hours of their next scheduled dose time, the patient should not take the dose. If a patient misses a dose, they should not take double the dose at the next dosing time, but should notify their study coordinator and continue with their twice daily dosing the following day.

8 DATA SAFETY MONITORING COMMITTEE (DSMC) REVIEWS AND MANAGEMENT OF STUDY TOXICITIES

8.1 Data Safety Monitoring Committee (DSMC) Reviews

Safety will be monitored throughout the study in accordance with a Data Safety Monitoring Plan (DSMP) by a DSMC constituted by, at a minimum: the Imago BioSciences Principal Medical Monitor, a Principal Investigator and an Independent designee, an AML clinical trials specialist with extensive clinical experience. To ensure a quorum of 3 members at all meetings, an alternate DSMC member will also routinely attend Safety Reviews, and participate when needed.

During all phases, the DSMC will review safety parameters, pharmacodynamic (PD) markers and pharmacokinetic (PK) parameters to form conclusions around the safety and pharmacodynamic effect of differing doses, treatment regimens and dosing durations. DSMC reviews are critical, as neither a new dose-finding sub-cohort, nor a duration-finding cohort may commence without DSMC review and recommendation to do so. The DSMC will assess: the safety of each dose and dosing duration, with and without ATRA. The DSMC will also assess: any clinically significant biochemistry trends; the impact of each dose on normal myeloid haematopoiesis; the PD impact of each dose on malignant cells, and whether further cohorts/sub-cohorts in each respective phase are appropriate.

Data from each cohort/sub-cohort will be reviewed by the DSMC after a minimum of 3 patients in a cohort/sub-cohort have completed Cycle 1 and prior to dosing the next cohort/sub-cohort. Safety data to be evaluated, may include: clinical laboratory results, ECGs [ECGs required in the first 9 patients only as there have been no non-clinical cardiovascular findings; if clinically meaningful trends in ECGs are noted, then the DSMC will make a recommendation as to the appropriate action to be taken (i.e., cardiologist consult, additional ECG requirements, etc.]; physical examination and vital sign measurements; and AEs/DLTs/Medical Events of Interest (MEOIs). A combination of PD and PK markers will be evaluated, as available, and may include: peripheral white blood cell count; peripheral blast count; reticulocyte count; platelet count; bone marrow blast count; expected changes in immunophenotype; changes in VAF, changes in cytokine profiles; and, changes in PSA (males only). These metrics will be evaluated in the context of PK parameters such as changes in

the clearance of IMG-7289 (with and without ATRA) based on drug concentrations at C_{min}, C_{max} and AUC, as available.

The DSMC is responsible for providing recommendations regarding the conduct of the study and guidance to Investigators to ensure the safety and well-being of all participating patients.

To avoid repetition in this section, additional DSMC responsibilities are detailed below:

- Rest period duration (see Section 9.10, Extended Rest Period):
    - During the initially allowed IMG-7289 treatment cycles, the rest period will remain at 7 days in duration, unless assessment is made by the DSMC that there is no clear indication of the restoration of normal haematopoiesis in the 7 day period or analysis of the IMG-7289 PK parameters in earlier sub-cohorts suggest the rest period duration requires adjusting. Consideration of adjustments to the rest period duration will be based on an assessment that either a specific patient or an entire cohort could benefit from an extended rest period.
    - During the additional cycle period, the rest period may be extended from the 7 day standard to a maximum of 56 days, but only after: 1) the patient has received a minimum of 28 IMG-7289 doses; and, 2) consultation with or recommendation by the DSMC. Such recommendation may be made for a variety of reasons including evidence of tumour reduction, marked hypocellularity in the marrow consistent with myelosuppression, or to enable the return of normal haematopoiesis.
- Cohort/sub-cohort progression: In both the dose-finding and duration-finding phases, more than one pathway is available for cohort progression. In these instances, determination will be made by the DSMC on the most appropriate path for progression. Additionally, as DSMC review of data continues throughout the study, the DSMC may a recommend a different cohort progression than is currently outlined in the protocol.
- Doses for use in a cohort/sub-cohort:
    - The DSMC will determine the IMG-7289 dose(s) for use in combination therapy cohorts/sub-cohorts and any duration-finding cohorts. The DSMC may determine (in the presence or absence of DLTs) that use of an IMG-7289 dose not pre-specified in the protocol is appropriate; for example, that a dose-finding sub-cohort of 1 mg/kg/d be studied were the dose of .75 mg/kg/d assessed as potentially too low and 1.5 mg/kg/d potentially too high.
    - As DSMC review continues throughout the study, the DSMC may recommend reducing the ATRA dose and/or adjusting the ATRA dosing duration.
- Transition of patients to a different dose, treatment regimen or dosing duration: Importantly, if a specific dose, treatment regimen or dosing duration is found to be associated with greater therapeutic benefit, patients who have *fully completed* their initially allowed cycles and are receiving a different dose, treatment regimen (i.e., IMG-7289 alone *versus* combination therapy) or dosing duration will be transitioned to the more optimal

dose, treatment regimen or dosing duration at the start of the next cycle. Such transition may occur more than once, as different doses, treatment regimens and dosing durations continue to be evaluated.

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

DSMC reviews during the IMG-7289 alone component of the dose-finding phase are detailed below.

The DSMC will assess the safety of each sentinel patient before the remainder of the sub-cohort is treated. Each dose sub-cohort will be separated by approximately one week to allow for completion and analysis of appropriate safety assessments required for provision to the DSMC. Dose escalation (see Section 7.2.2.1) will proceed in sub-cohorts (i.e., Sub-cohort 1b, 1c) provided that:

1. A minimum of 3 patients from the previous sub-cohort have completed Cycle 1, both the applicable dosing and rest periods
2. The number of patients who experience DLT is within the guidelines (see Section 8.2.2)
3. DSMC review of the previous cohort has determined that:
    a. The dose administered appears safe
    b. Further dose escalation is appropriate

There are two potential dose-escalation pathways for Sub-cohort 1d: 6 and 10 mg/kg/d. The dose to be administered in Sub-cohort 1d will be determined at the discretion of the DSMC. Therefore, upon Cycle 1 completion of a minimum of 3 patients in Sub-cohort 1c, the DSMC will assess the safety and pharmacodynamic effects of the earlier sub-cohorts, and reach consensus on:

1. Whether dose escalation should proceed at all, and if so…
2. Whether the appropriate escalation for Sub-cohort 1d is a doubling or a tripling of the 3 mg/kg/d dose administered in Sub-cohort 1c.

Post DSMC confirmation that no further dose escalation is anticipated, the combination therapy cohort will be enrolled.

DSMC reviews during the IMG-7289 in combination with ATRA component of the dose-finding phase are detailed below.

Combination therapy (see Section 7.2.2.1) will proceed in sub-cohorts (i.e., Sub-cohort 1W, 1V, etc.) provided that:

1. A minimum of 3 patients from the previous sub-cohort have completed Cycle 1, both the applicable dosing and rest periods
2. The number of patients who experience DLT is within the guidelines (Section 8.2.2)
3. DSMC review of the previous sub-cohort has determined that:
    a. The doses administered in combination appear safe
    b. Further combination therapy is appropriate

Upon DSMC confirmation that no further dose-finding sub-cohorts are anticipated, the DSMC will also make a determination of whether it is safe to extend the dosing duration, to determine whether longer durations are associated with greater therapeutic benefit. The study will then progress to assess the effect of IMG-7289 dosing duration.

DSMC reviews during the duration-finding phase are detailed below.

During the duration-finding phase, the DSMC will assess whether the longer duration of IMG-7289 dosing, with and without ATRA, at the D_p is safe and associated with greater therapeutic benefit using a combination of PD and PK markers. Each duration cohort will be separated by approximately one week to allow for completion and analysis of appropriate safety assessments required for provision to the DSMC.

There are two potential duration-extension pathways for the duration-finding cohorts: duration extension with IMG-7289 alone, or IMG-7289 administered in combination with ATRA. Therefore, prior to opening a duration-finding cohort, the DSMC will assess the safety and pharmacodynamic effects of the earlier sub-cohorts, and reach consensus on:

1. Whether it appears safe to extend the duration of IMG-7289 dosing
2. Whether there appears to be greater therapeutic benefit with IMG-7289 dosed in combination with ATRA.

Based on the above assessments, one of the duration-finding cohorts will commence.

The duration of dosing (see Section 7.2.2.3) will be extended in subsequent cohorts provided that:

1. A minimum of 3 patients in the previous cohort have completed Cycle 1, both the applicable dosing and rest periods
2. The number of patients who experience DLT is within the guidelines (see Section 8.2.2)
3. DSMC review of the previous cohort has determined that:
    a. The duration of dosing appears safe
    b. Further duration extension is appropriate

Throughout all phases of the study, if it appears that either a maximally tolerated dose (MTD) or maximally tolerated duration (MTD_u) is reached (see Section 8.2.3), the DSMC will convene to evaluate further dose escalation, combination therapy and/or extended dosing duration.

8.2 Management of Study Toxicities

Adverse event intensity will be evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, published 14 June 2010.

Dose-limiting toxicity and dose escalation and duration extension decision rules are defined in Sections 8.2.1 and 8.2.2 below. Expected IMG-7289 toxicities based on non-clinical studies are reported in the latest available edition of the Investigator's Brochure. Expected ATRA toxicities are reported in the Product Information (PI) document.

8.2.1 IMG-7289 Toxicity Definitions

Haematologic Toxicity: Haematologic values outside of the normal reference range are inherent features of AML and MDS, and are expected effects of many therapeutic attempts to manage these diseases. These effects will not be considered DLTs.

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

The intended dosing plan for high risk AML/MDS patients is predicated on the supposition that LSD1 must be maximally inhibited to achieve the greatest therapeutic benefit. The concentrations of LSD1 inhibitors such as IMG-7289 (free base) used to achieve maximal effects on growth, differentiation and apoptosis *in vitro* with primary patient-derived AML cells as well as AML cell lines are similar to concentrations that *in vivo* inhibit red cell, platelet and granulocyte production. It is therefore expected that high risk AML/MDS patients will require treatment at doses sufficient to induce profound thrombocytopenia and neutropenia. These drug-induced but reversible cytopenias can be managed clinically as needed with platelet and red cell transfusions as well as broad-spectrum antibiotics in the case of febrile neutropenia, as are already standard practices in the routine management of AML/MDS patients receiving intensive SOC chemotherapy.

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

Dose Limiting Toxicity (DLT): DLT is defined as any one of the following AEs that occurs during the first cycle of therapy and is considered by the Investigator to be possibly, probably or definitely related to IMG-7289.

- A clinically significant bleeding event;
- Any Grade 4 or 5 non-haematologic adverse event;

- Any Grade 3 non-haematologic adverse event with failure to recover to Grade 1 within 7 days of drug cessation, with the following exceptions:
    - ≥ Grade 3 nausea, vomiting or diarrhoea that responds to standard medical care
    - ≥ Grade 3 aesthenia lasting less than 14 days
- Any Grade 3 electrolyte abnormality unrelated to the underlying malignancy and persisting greater than 24 hours.

Patients who experience a dose limiting toxicity (DLT) will have their dose adjusted downward if the Medical Monitor and Principal Investigator deem it safe for the patient to continue on IMG-7289. To ensure a minimum of 3 Cycle 1 completers, and contingent on the number of prior DLTs within the sub-cohort/cohort, such patients may be replaced.

Any patient that experiences a DLT that results in discontinuation of IMG-7289 therapy may begin alternative therapy after a one week washout period and if their physician deems this safe and appropriate regarding the resolution of the DLT.

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

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

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Additionally, the DSMC may review safety data and, even in the absence of 2 DLTs, deem that the safe dose has been exceeded. Were this to occur, dose escalation would cease.

Table 5: IMG-7289 Dose Limiting Toxicity and Escalation Decision*

Patients with DLT at a Given Dose	Escalation Decision Rules
0-1 out of 3	Open subsequent sub-cohort/next dose
2 out of 3	Dose escalation will be stopped

*The above instruction applies in kind for combination therapy and duration extension decision making.

8.2.3 IMG-7289 Maximum Tolerated Dose (MTD) and Duration (MTD_u)Φ

The MTD is defined as the highest dose below or at which <2 out of 3 patients experience DLT. If unacceptable toxicity occurs (DLT in 2 out of 3 patients) at the reduced dose of 0.375 mg/kg/d, then the dose will be further reduced to the 0.1875 mg/kg/d dose. In this study, the MTD may not be reached if the highest dose tested is found to be safe (that is, DLT in <2 out of 3 patients).

The above instruction applies in kind for the MTD_u.

ΦMTD and MTD_u definitions also apply to combination therapy sub-cohorts.

8.3 ATRA Toxicity

Decisions on IMG-7289 and ATRA dose interruption, reduction and re-challenge due to observed toxicity will be made by the Investigator in consultation with Medical Monitor and DSMC.

Expected toxicities for ATRA can be found in the Product Information (PI) document.

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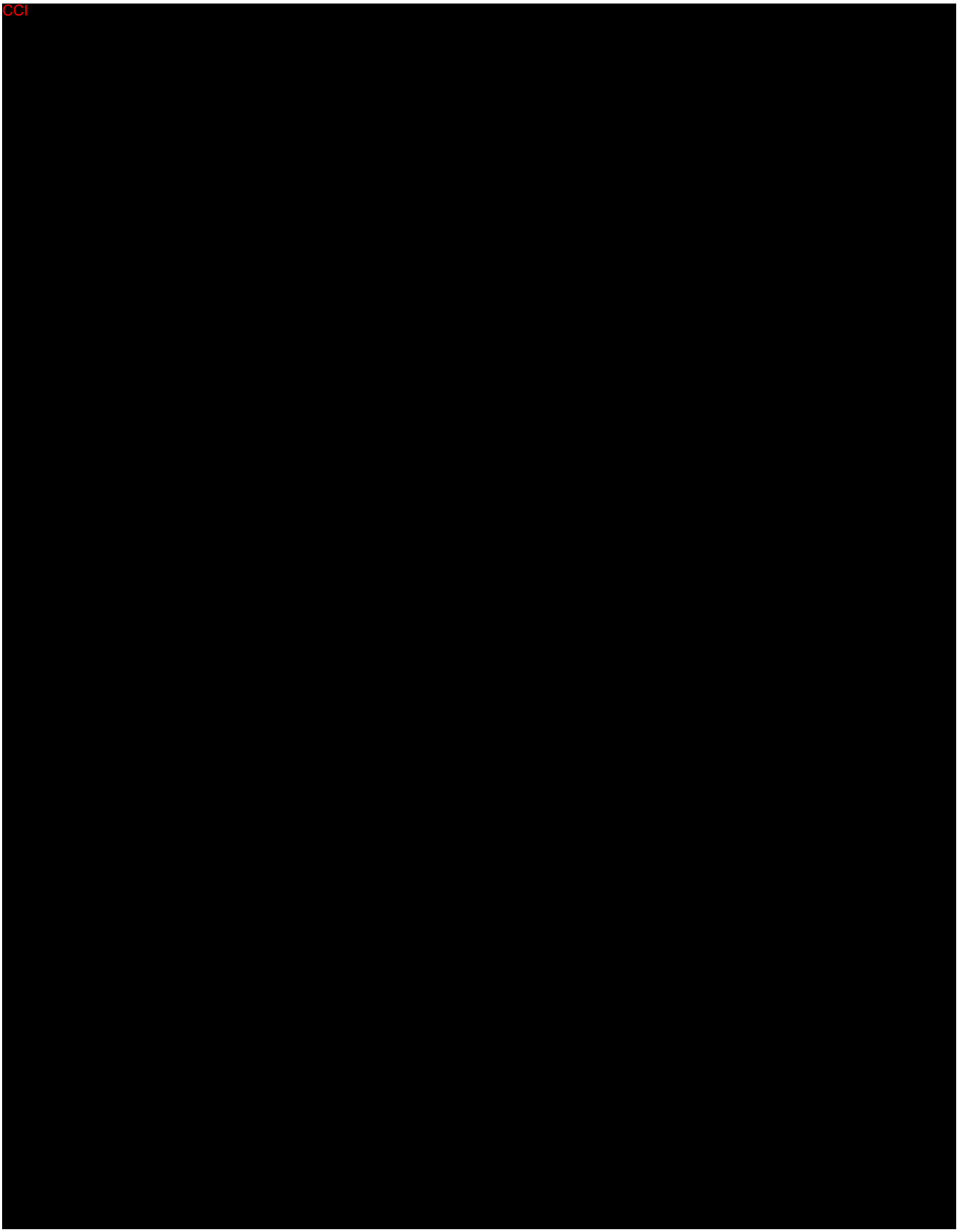
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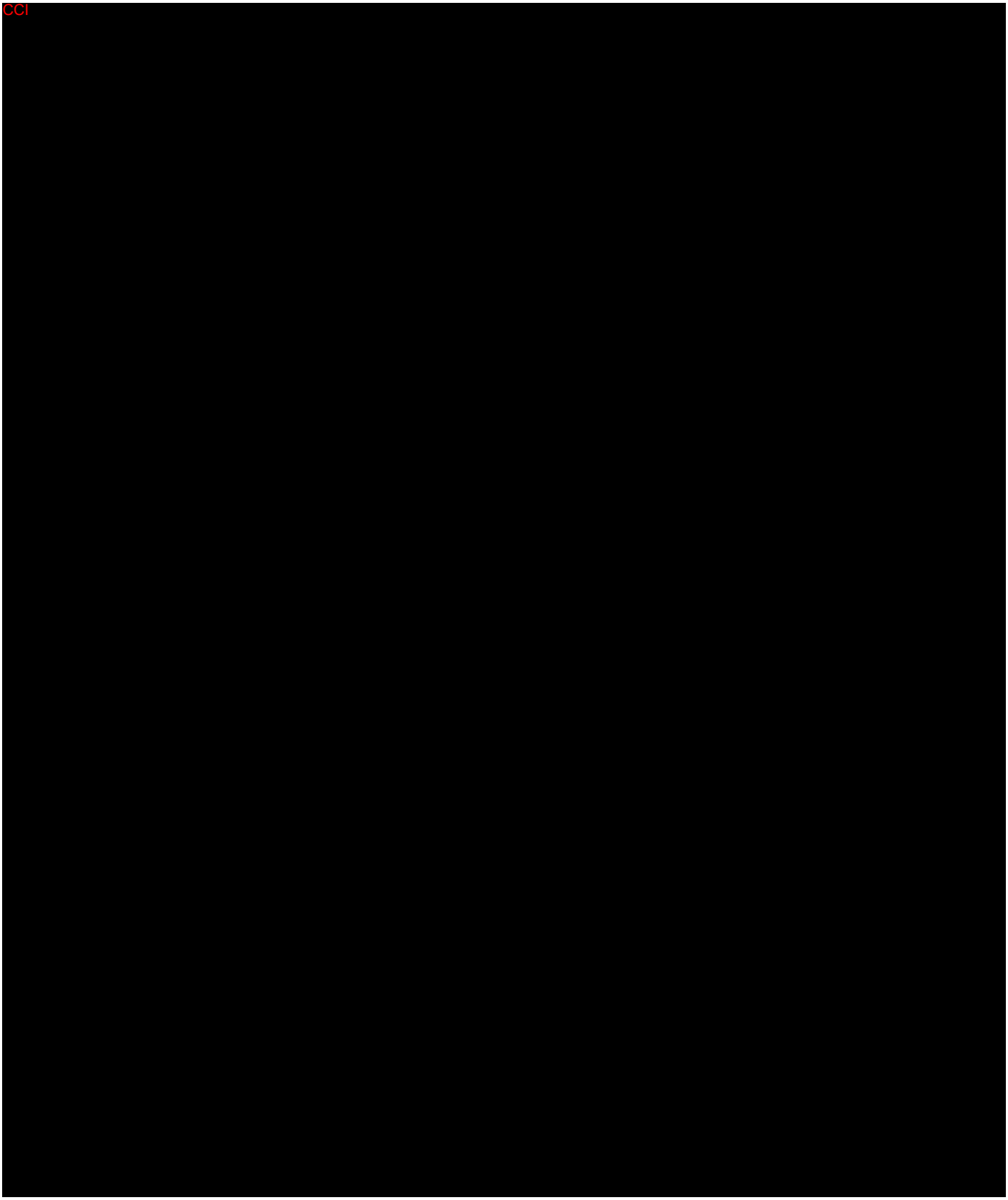

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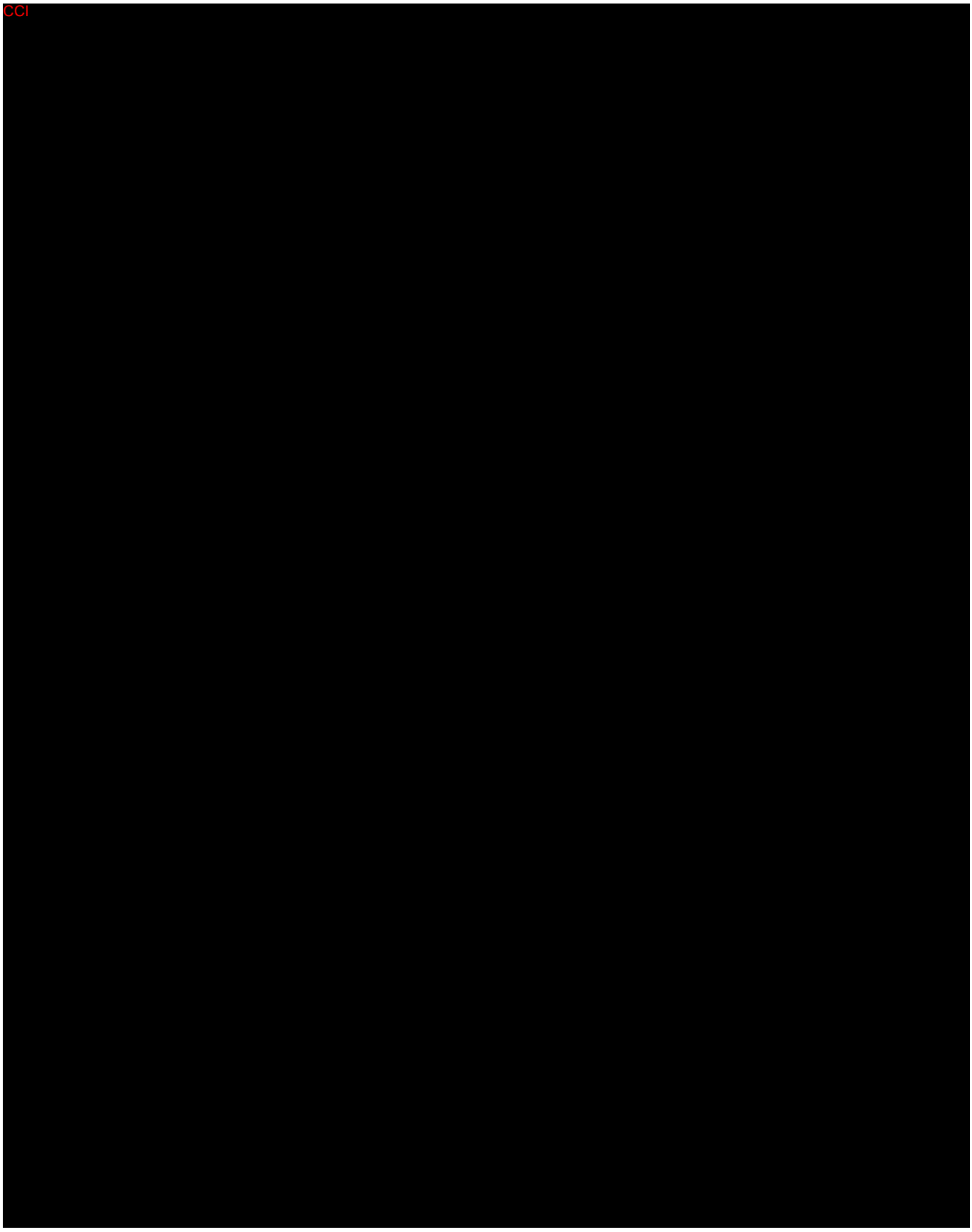
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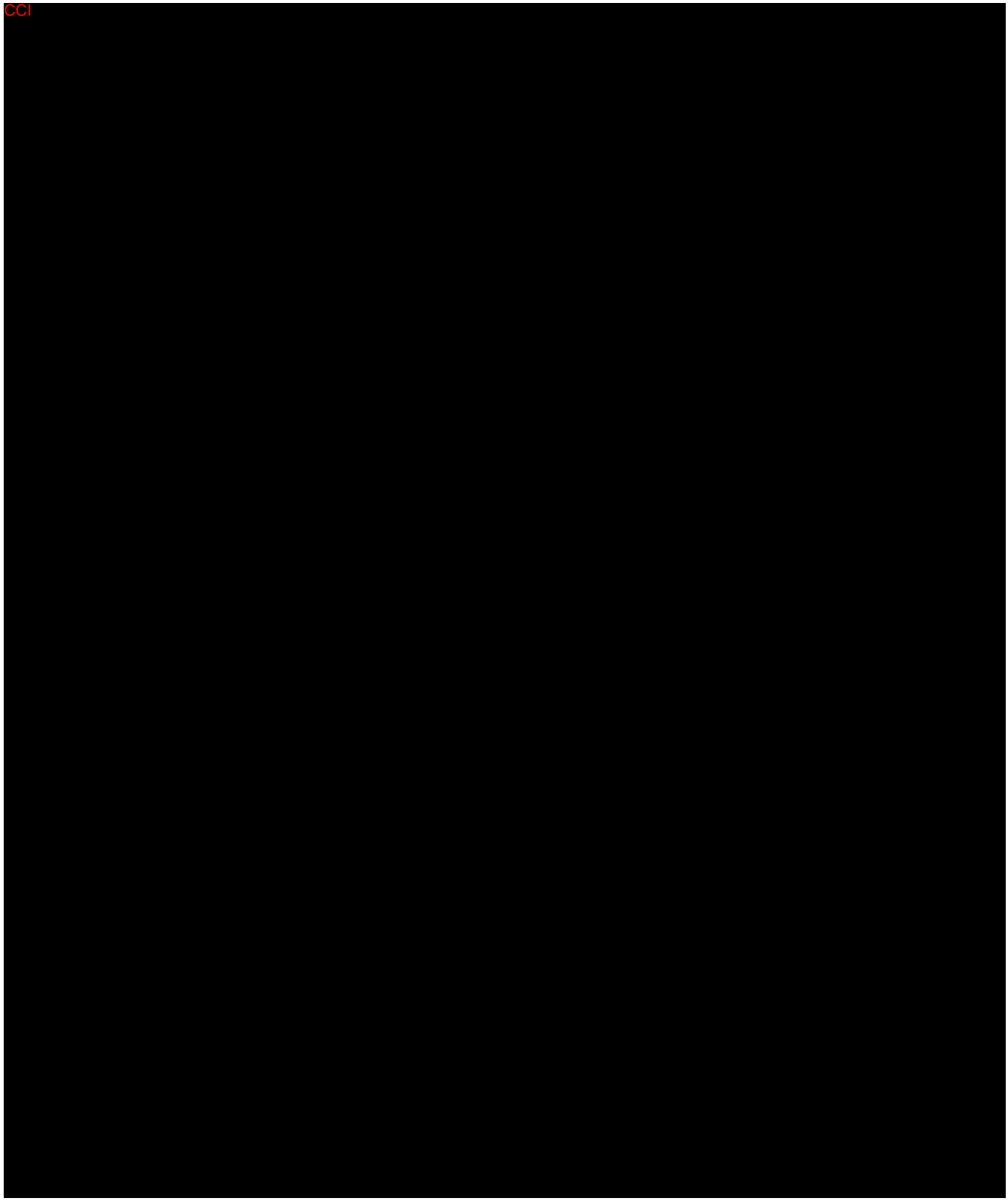
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10 LABORATORY SAMPLING FOR SAFETY, PK AND PD ANALYSIS

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

The amount of blood collected from each patient for safety, PK and PD assessments will vary by Cohort due to differing PK sampling requirements, treatment durations, and DSMC assessment of biochemistry trends as either clinically significant or not clinically significant. The average of the blood volumes, which vary by institution, is provided below for each cohort.

Sub-cohort 1a: Approximately 539 mL blood over ~15 weeks

Sub-cohort 1b*#: Approximately 478 mL blood over ~15 weeks

Cohort 3/3χ#: Approximately 322 mL blood over ~13 weeks

Cohort 4/4χ#: Approximately 267 mL blood over ~11 weeks

The number of bone marrow aspirates and biopsies, and therefore the total volume required, will vary by Cohort due to differing treatment durations, and the number of Cycles allowed. For each sample time-point, approximately 2-3 mL of bone marrow sample is required. Estimates, by cohort, are provided below.

Sub-cohort 1*: 4 samples and approximately 8-12 mL bone marrow over ~15 weeks

Cohort 3/3χ: 3 samples and approximately 6-9 mL bone marrow over ~13 weeks

Cohort 4/4χ: 3 samples and approximately 6-9 mL bone marrow over ~11 weeks

*Applies to all sub-cohorts.

#Figures based on standard biochemistry evaluations; if clinically significant trends are noted by the DSMC, these numbers will increase by Cohort (1, 3/3χ, or 4/4χ respectively), as follows: 63, 49, and 28 mL.

Note: The above blood volume, and bone marrow sampling time-points and volume, includes all Screening assessments and each study visit up to and including the EOS. Not included, however, are any additional cycles that a patient may be allowed to receive if clinical benefit is observed nor the extended rest period.

10.1 Laboratory Measures

Details on the laboratory assessments performed throughout the study are provided below by category of tests (i.e., biochemistry, haematology with manual differential, 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.

10.1.1 Local Laboratory Measures

Biochemistry: Sodium, potassium, magnesium, chloride, bicarbonate, glucose, calculated creatinine clearance (by Cockcroft-Gault method) and/or serum creatinine, uric acid, phosphate, total calcium, anion gap, urea or blood urea nitrogen (BUN), triglyceride, cholesterol, albumin, protein, total bilirubin, conjugated (direct) bilirubin, unconjugated (indirect) bilirubin, gamma

glutamyltransferase (GGT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH). At specified time-points, Prostate Specific Antigen (PSA) will also be measured in males.

Haematology (with manual differential): Haemoglobin, red blood cell count (RBC) (including nucleated RBC), red cell distribution width (RDW), haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), platelets, mean platelet volume (MPV), immature platelet fraction (IPF), white cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, reticulocytes, promyelocytes, myelocytes, blasts and Auer rods. At specified time-points, haemoglobin F (HbF) will also be measured.

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

Urine Pregnancy Test: For WOCBP, a urine pregnancy testing kit will be utilized.

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

Bone marrow sampling: Aspirate and biopsy samples are to be collected as per site procedure. Evaluation, will be performed centrally (see Section 10.1.2); however, any locally available morphology, immunophenotyping, cytogenetic evaluations/ genetic interrogations performed on samples obtained at the same time-point as study samples, will also be reported in the eCRF.

Sample Processing: Imago BioSciences will not provide either a laboratory manual or study supplies for the collection and handling of samples to be analysed locally – with the exception of urine pregnancy test kits for sites that cannot provide these. Local laboratory standard procedures should be followed at each site.

10.1.2 Central Laboratory Measures

Immunophenotyping - peripheral blood: Fluorescence-activated cell sorting or flow cytometry (FACS; FC), will be performed using 4 mL blood per required time-point. Baseline, end of the dosing period, and EOT and EOS visit peripheral blood samples will be routinely analysed; however, samples collected at other time-points may not be analysed unless the bone marrow sample is inadequate for immunophenotyping (note: sample may also be used for genomic testing if bone marrow sample is inadequate). A standardized panel and gating will be used.

Cytokines: A 8.5 mL blood sample, per required time-point, for cytokine profiles may be quantified, via appropriate methods.

Bone marrow: A 2-3 mL bone marrow sample for central analysis must be collected from the first pull, whenever possible, and no later than the third. A 1-2 cm section of trephine bone marrow sample for central analysis must also be collected. Measures to be performed centrally include: immunophenotyping by FACS or FC, genomic analysis, and morphology review using 5 site prepared slides. Fluorescent *in-situ* hybridization may also be performed, cost permitting. A blood film must also be provided for review in conjunction with the marrow sample. For selected

samples, if the marrow sample is inadequate, then immunophenotyping or genomic testing will be performed using peripheral blood.

Genomic Testing: If there is sufficient sample volume, then approximately 1-2 mL bone marrow aspirate will be used for analysis of mutant allele burden over the course of IMG-7289 treatment.; if sample volume is insufficient, then peripheral blood collected for immunophenotyping purposes may be used. At Baseline and EOT, 10 mL blood will be collected for analysis. Genomic sample collection, handling, storage, and analysis will conform to all applicable national guidance and regulations.

Sample Processing: Imago BioSciences will provide a laboratory manual documenting the collection and handling of samples to be analysed centrally. Additional supplies may be provided, dependent on the analyte to be measured and the supplies needed.

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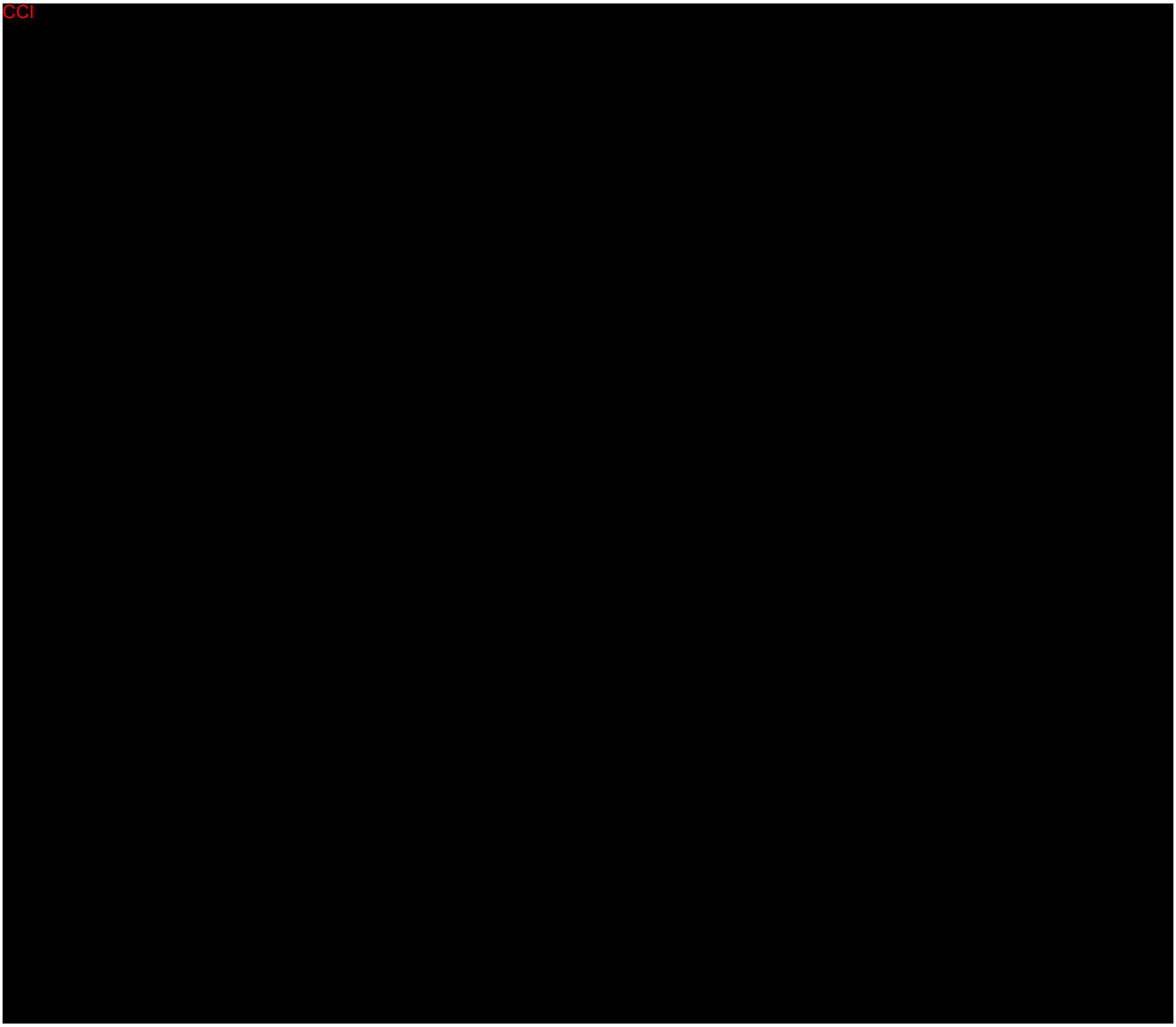

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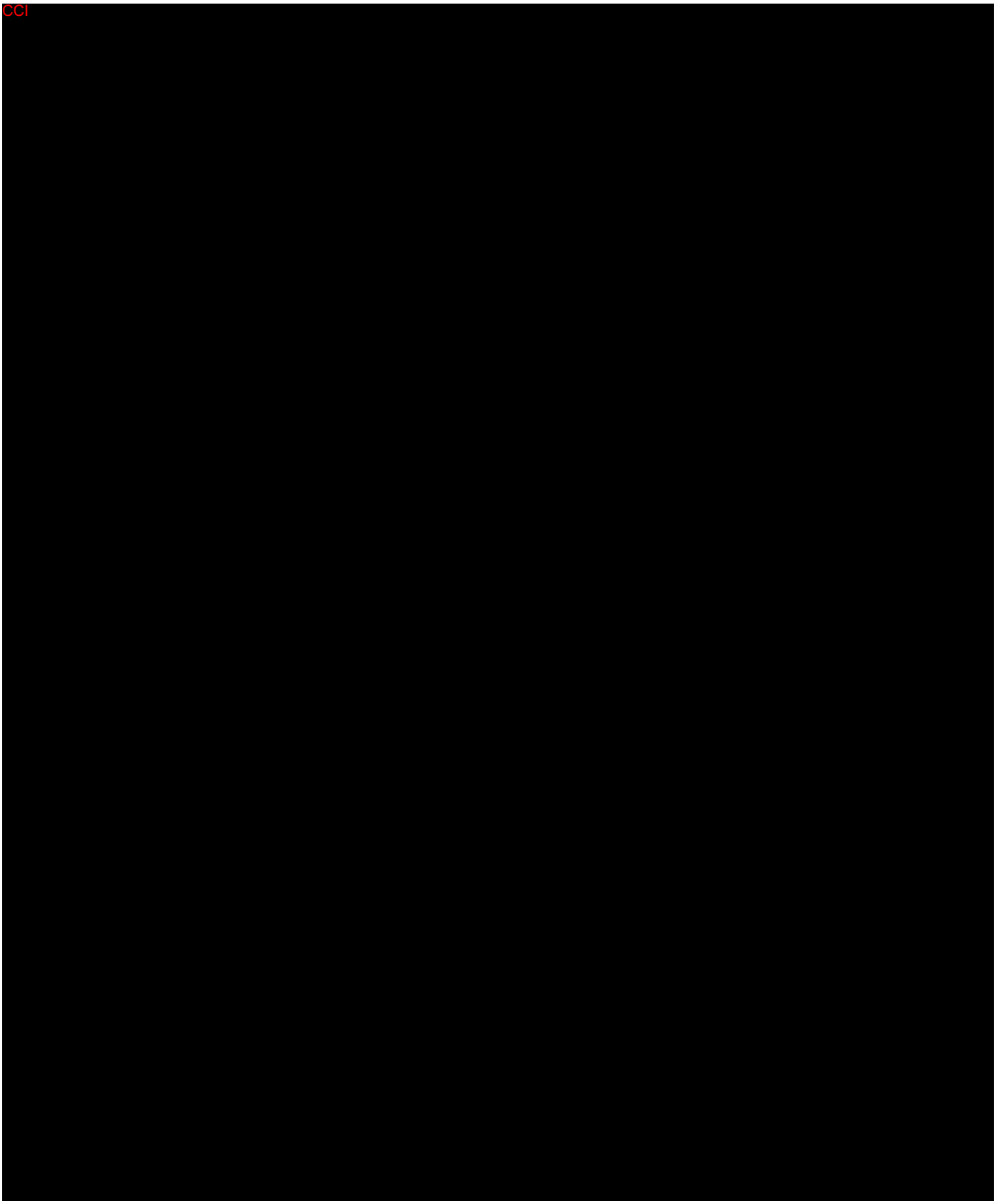

11 SAFETY

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

Once an Investigator determines a patient is a treatment failure (see Section 6.8) or if the patient is withdrawn from treatment early due to a Dose Limiting Toxicity, the patient should discontinue study treatment and undergo all follow-up procedures, beginning with an End of Treatment Visit (see Section 9.12.1).

11.1 Pregnancy

Every effort should be made to prevent pregnancy throughout the entire duration of participation in this study. All patients of reproductive potential involved in the study are required to use effective methods of contraception during the study and for 28 days after the last IMG-7289 dose. Female patients will be instructed to notify the Investigator immediately if they discover they are pregnant; male patients will be instructed to notify the Investigator immediately if they discover that their sexual partner is pregnant. Pregnancy data during the study will be reported in an expedited manner using the Pregnancy Report Form and following the SAE reporting process (see Section 11.2.4). It will be necessary to collect detailed information on the course of any pregnancy occurring in a patient on study, including pregnancies in the partners of male patients, assuming consent to do so is provided. If the outcome and/or a complication of the pregnancy meets serious criteria (i.e., miscarriage or congenital anomaly/birth defect), then it should be reported as an SAE using the SAE/ MEOI Report Form.

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

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

It is well documented that ATRA can cause deformities to the unborn fetus. Patients who are taking the combination therapy will be provided with this information.

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

11.2 Adverse Events

The Investigator is responsible for monitoring the safety of patients who have enrolled in the study and for accurately documenting and reporting information as described in this section. Patients will be instructed to report to the Investigator any AE that they experience. Investigators will ask about the occurrence of AEs at each visit. Investigators are required to document all AEs occurring during the clinical study, commencing with the first dose of IMG-7289 through to the End of Study Visit (scheduled at 28 days post last IMG-7289 dose). Adverse event recording will continue for patients

who discontinue study treatment early but remain in follow-up, until their End of Treatment, Pre-End of Study and End of Study Visits have been completed.

Note: Any medical event which occurs from the time of Informed Consent but prior to dosing with IMG-7289 must still be documented in the patient's medical notes and will be recorded on the appropriate medical history CRF pages.

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

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

Adverse events may include, but are not limited to:

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

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

It is important that Investigators record accurate AE terms on CRFs. Wherever possible, a specific disease or syndrome rather than individual associated signs, symptoms or laboratory parameter will be identified by the Investigator and recorded on the CRF. 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 on the CRF.

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

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

11.2.1 Adverse Event Intensity

Adverse event intensity will be evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, published 14 June 2010. For AEs not included in the NCI CTCAE, the Investigator will be required to assess the intensity of the adverse drug/biologic experience using the following categories and associated guidelines:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 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 on the CRF. Below are guidelines for relationship assessment:

- Unrelated: There was no relationship of the adverse event to the use of the drug or biologic. This may include, but is not limited, to the adverse experience being an expected outcome of a previously existing or concurrent disease, concomitant medication or procedure the subject experienced during their treatment period.
- Remote/Unlikely: Adverse events which are judged probably not related to the drug or biologic.
- Possible: There was no clear relationship of the adverse event to the use of the drug or biologic; however, one cannot definitively conclude that there was no relationship.

- Probable: While a clear relationship to the drug or biologic cannot be established, the event is associated with an expected adverse event (per the current Investigator Brochure or DSMC findings) or there is no other medical condition or intervention which would explain the occurrence of such an experience.
- Definite: The relationship of the use of the drug or biologic to the experience is considered definitively established.

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

11.2.3 Serious Adverse Events

Serious adverse events will be reportable from the time the time of first dose through the End of Study Visit (scheduled for approximately 28 days post last IMG-7289 dose) **or** until the Investigator and Imago BioSciences determine that follow-up is no longer necessary. Serious adverse events that are suspected to be drug related will be reported even if they occur when the patient is no longer on the study.

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

- Death¥
- Life-threatening experience
- Required or prolonged inpatient hospitalisation¥
- Persistent or significant disability/incapacity
- Congenital anomaly
- Important medical events that, based upon appropriate medical judgment, may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

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

Required or prolonged inpatient hospitalisation. The adverse event resulted in an initial inpatient hospitalisation or prolonged an existing hospitalisation of the patient. If a patient is hospitalised as part of the clinical use of the product, a period of normal hospitalisation will be outlined in the protocol or by the judgment of the Investigator. Hospitalisations longer than this period will be prolonged hospitalisations.

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

Congenital Anomaly. The exposure of the patient to the drug or biologic during pregnancy that is

judged to have resulted in the congenital anomaly/birth defect.

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

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

11.2.4 Reporting Serious Adverse Events

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

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

Important: For fatal and life-threatening events, the Sponsor's Medical Responsible Person should be contacted immediately. A death occurring during the study or information related to such occurrence that comes to the attention of the Investigator during the study must be reported immediately to the Sponsor.

Contact numbers will be provided to the site, with a detailed SAE reporting procedure to be included in the Study Reference Manual (SRM), before any patients are consented.

Table 7: Serious Adverse Event Reporting Contact Details

PPD	
Australia Safety (phone/fax) Worldwide Safety (toll - phone/fax)	PPD

Additionally, the Human Research Ethics Committee (HREC)* must be notified in writing of any SAEs that require expedited reporting to Regulatory Authorities. Depending upon regional requirements, it is the responsibility of either the Investigator or Imago BioSciences to notify the HREC. All unexpected SAEs (i.e. not documented in the current version of the Investigator Brochure) that are suspected by the Investigator to be related to the use of the study treatment (deemed possibly, probably or definitely related) will be reported to appropriate regulatory

agencies by Imago BioSciences or their designee as soon as possible and within the timeframes specified in the various regions in which the study is to be conducted.

* If additional countries are engaged outside of Australia, then for purposes of this protocol reference to HREC shall also be deemed reference to any other Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

11.2.5 Medical Events of Interest (MEOIs)

Medical Events of Interest (MEOI) are AEs that do not meet any criteria for an SAE but are nonetheless of particular interest in the context of this study. Medical Events of Interest will be collected for all patients during the study period in an expedited manner using the SAE/MEOI Report Form and following the SAE reporting process (see Section 11.2.4). Although these are non-serious events, the Investigator will be asked to provide detailed initial information and follow-up to the Sponsor. The Sponsor will periodically review the AE data and in some cases may escalate an AE to a MEOI. Examples of MEOI and reporting times include, but are not limited, to the following:

Table 8: Examples of MEOI and Reporting Timelines

MEOI	Reporting Times
Electrocardiogram QT corrected interval prolonged 481 - 500 ms	Within 5 business days

12 ANALYSIS AND STATISTICAL CONSIDERATIONS

12.1 General Considerations

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

12.2 Power

This study is designed to make an assessment of the safety, tolerability, and single-dose pharmacokinetics of the capsule formulation of IMG-7289, with and without ATRA. With the planned minimum number of patients per dose cohort/sub-cohort (N=3), the study is sufficiently powered to determine mean pharmacokinetic parameters. When feasible, more patients will be added to each cohort/sub-cohort.

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, ECG, morphology review, etc.), in order to facilitate consistency of assessments within a patient.

12.4 Study Endpoints

12.4.1 Primary Endpoints

- The safety and tolerability of IMG-7289 with and without ATRA will be assessed by the analysis of adverse events (AEs), as well as changes in physical examinations, vital signs and laboratory values as detailed below.
    - Monitoring of Adverse Events (AEs) including determination of dose limiting toxicities (DLTs), medical events of interest (MEOIs), serious adverse events (SAEs), and AEs. AEs will be assessed in terms of onset, duration, seriousness, severity, and causality, using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03. Deaths and other serious adverse events (SAEs) will also be evaluated and will be collected on a separate case report form (CRF).
    - Changes in physical examinations, vital signs and laboratory values will also be evaluated and assessed. Information on the timing of these assessments is presented in Section 9. The following laboratory tests will be conducted:
        - Complete blood counts (CBC) and differential
        - Coagulation
        - Chemistry panel including LFTs (AST, ALT, INR, total bilirubin, gamma glutamyltransferase (GGT), and albumin)
        - Urinalysis with microscopy
        - Electrocardiograms
- Pharmacokinetic (PK) parameters will be determined using serial blood sampling at specified time points to determine PK effects of IMG-7289 with and without ATRA. Non-compartmental methods of analysis will be used to determine PK parameters following oral dosing of patients in Cycle 1. The following endpoints will be calculated: observed maximum concentration (C_{max}), the time at which C_{max} occurred (T_{max}), the area under the concentration-time curve from time 0 to 24 hours post-dose (AUC_{0-24}), the apparent total clearance of drug after oral administration (CL/F), the apparent volume of distribution during terminal phase after oral administration (V_z/F) the terminal disposition phase half-life ($t_{1/2}$), and the elimination rate constant (k_{el}).
- The adequacy of IMG-7289 dose and duration, with and without ATRA, in producing a pharmacodynamic effect will be determined using serial blood and bone marrow sampling throughout the course of treatment. Responses will be documented according to revised/modified International Working Group (IWG) Response Criteria – Cheson *et al.* 2003 for AML and Cheson *et al.* 2006 for MDS. Measures of response will be assessed by blood counts and simultaneous examination of the bone marrow for percentage of bone marrow blasts, as well as

cytogenetics and molecular studies of bone marrow mononuclear cells.

- Pharmacodynamic (PD) measurements will be obtained from serial blood, bone marrow, and urine sampling at specified time points to describe the PD effects of IMG-7289 with and without ATRA. The following endpoints may be analyzed: CCI

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12.5 Safety and Tolerability Data

Demographics will be tabulated and summarized. Medical and surgical history data at Screening will be listed, as will Physical Examination data (including height and weight) at Screening, and at subsequent visits. All characteristics at Baseline such as age, weight, height, vital signs (resting heart rate, semi-supine systolic/diastolic blood pressure, respiratory rate and temperature), and ECG parameters will be tabulated and summarized.

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

Laboratory values outside the laboratory normal ranges will be summarized and assessed for change from Day 1 and trends indicating a safety signal.

Treatment-emergent adverse events will be coded using the most updated version of Medical Dictionary for Regulatory Activities (MedDRA) available to the Sponsor at the time of study initiation (up-versioning will not occur) and summarized by cohort 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, cohort, severity, and relationship to treatment will be provided.

Concomitant medications will be listed by patient and coded using the most updated version of WHO drug dictionary available to the Sponsor at the time of study initiation (up-versioning will not occur). Medical history will be listed by patient.

Descriptive statistics (arithmetic mean, standard deviation (SD), sample size, CV (coefficient of variation), median, minimum, maximum, and number) will be calculated for quantitative safety data as well as for the differences to baseline, when appropriate. In addition, a shift table describing out of normal range shifts will be provided for clinical laboratory results, and ECG tracings. Chi-square (χ^2), Fisher exact, and Kruskal-Wallis tests may be used to assess the significance of differences in baseline patient characteristics. For safety and tolerability, missing data including those not obtained because of death will be the last value carried forward.

12.6 Pharmacokinetics Data

For the determination of the pharmacokinetic parameters, the concentrations of IMG-7289 will be measured in all patients in Cohort 1, Cycle 1 using a validated assay method. These samples are labeled PK in the protocol. Pharmacokinetic parameters will be tabulated and summarized. The concentration-time profiles for each patient and the mean concentration-time profile will be plotted.

For Cohort 1, Cycles 2, 3 and 4 and all other Cohorts, samples will be collected at the specified times CCI [redacted] for the determination of drug concentrations, which will be used to correlate pharmacodynamic effects with free drug concentrations.

Pharmacokinetic parameters will be calculated for all patients who partake in Cohort 1, intensive PK testing, of the study using standard non-compartmental methods as described below.

The following single dose pharmacokinetic parameters for IMG-7289 will be determined from the time and concentration data:

AUC_{0-24}: The area under the concentration versus time curve will be calculated using the linear trapezoidal rule from the zero time-point to the 24 hour time-point concentration.

C_{max}: The maximum observed concentration will be obtained directly from the concentration time profile.

t_{max}: The time to maximum concentration will be obtained by inspection. If the maximum concentration occurs at more than one time point, the first is chosen.

k_{el}: The terminal elimination rate constant will be obtained from the slope of the line, fitted by linear least squares regression, through the terminal points of the log (base e) concentration-time profiles.

$t_{½}$: The half-life will be calculated by the equation t½ = 0.693/kel.

CL/F: Apparent total clearance of drug after oral administration.

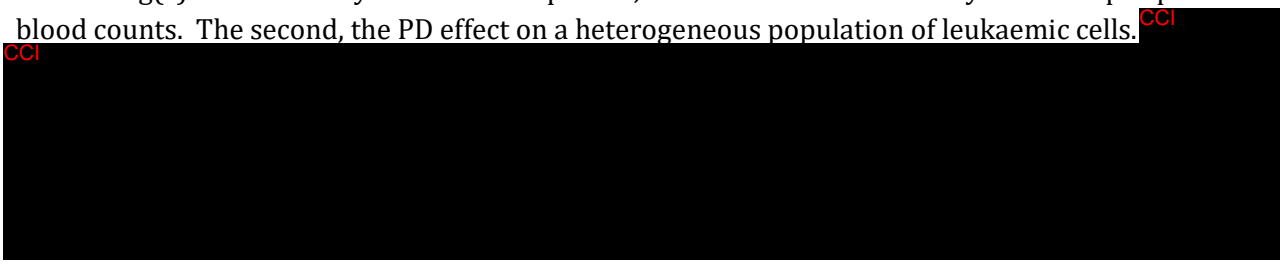
Vz/F: Apparent volume of distribution during terminal phase after oral administration.

Statistical analysis will be performed on the pharmacokinetic parameters using validated statistical software (i.e., WinNonlin, Pharsight Inc.).

Descriptive statistics (mean, standard deviation and coefficient of variation) will be calculated for all pharmacokinetic parameters.

12.7 Pharmacodynamic Data

Measuring the activity IMG-7289 (with or without ATRA) has in producing a pharmacodynamics response (PD) is a secondary objective. There are two PD responses of interest. The first, the effect of the drug(s) on normal myeloid haematopoiesis, which will be measured by standard peripheral blood counts. The second, the PD effect on a heterogeneous population of leukaemic cells. CCI



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

13 STUDY ADMINISTRATION

The names, titles, and addresses of the Investigators and study personnel are listed in the Site Contacts list in a Study Reference Manual for Protocol IMG-7289-CTP-101 and are available from Imago BioSciences.

13.1 Ethical Considerations

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

13.2 Participation Information Sheet/Consent Form (PISCF)

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

The PISCF must be signed by the patient or the patient's legal guardian before his or her participation in the study. A copy of the PISCF must be provided to the patient or the patient's legal guardian. If required by local procedure a second original of the PISCF may be provided to the patient or the patient's legal guardian. 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 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 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 HREC prior to implementing changes in the study.

The Investigator is responsible for keeping the 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 HREC informed of any AEs, according to the HREC policy.

* If additional countries are engaged outside of Australia, then for purposes of this protocol reference to HREC shall also be deemed reference to any other Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

13.4 Study or Site Termination

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

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

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
2. Patient recruitment is unsatisfactory

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

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

13.5 Study Documentation and Record Keeping

13.6 Study Monitoring Requirements

Monitoring and auditing procedures developed by Imago BioSciences will be followed in order to comply with ICH Good Clinical Practice (GCP) guidelines. On-site checking of the CRFs for completeness and clarity, cross checking with source documents, and clarification of administrative matters will be performed. Monitoring visits will consist of site qualification visits, periodic visits during the study period, and site close-out visits.

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

Imago BioSciences or its designee will monitor the study. Monitoring will be done by personal visits from representatives of Imago BioSciences (site monitors) who will review the CRFs and source documents. The site monitors will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, email, telephone, and fax).

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

13.7 Quality Assurance

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

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

13.8 Confidentiality

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

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

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

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

The raw dataset will be available to Imago BioSciences on completion of the study. Imago BioSciences will actively pursue publication of the results. The Lead/Coordinating Investigator will have the right to submit for publication any results arising from the study subject to the terms and

conditions of the Clinical Trial and Confidentiality Disclosure Agreements. The Lead/Coordinating Investigator, with the agreement of Imago BioSciences, will co-ordinate the principal publication of the data arising from the study. Patient names and other personal data relating to an identified or identifiable patient (such as photographs, audio, videotapes, or other factors specific to physical, physiological, mental, economic, cultural, or social identity), may not be disclosed in any publication without prior written authorisation, in compliance with patient privacy law, from Imago BioSciences and the patient.

14 INVESTIGATOR REQUIREMENTS

14.1 Protocol Adherence

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

Modifications to the protocol should not be made without agreement of the Investigators and Imago BioSciences. Changes to the protocol will require written HREC approval / favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The HREC may provide expedited review and approval/favorable opinion for minor change(s) in ongoing trials that have the approval/favorable opinion of the HREC. The Investigator will submit all protocol modifications to the 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 CRF 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, 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 on the CRF 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., ECG tracings, laboratory reports, etc. and signed/dated by appropriately designated investigational site personnel as a true copy of the original.

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

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

14.5 Study Drug Accountability

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

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

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

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

14.6 Disposal of Study Drug

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

14.7 Training of Staff

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

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

14.8 Clinical Study Report

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

14.9 Retention of Records

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

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16 APPENDICES

16.1 Schedule of Assessments (SoA) by Cohort and Cycle

16.1.1 Required General Visits: All Patients, All Cohorts

Visit Name	Screen	Baseline		Suspected Relapse	EOT	Pre-EOS	EOS/Early Termination
Visit Date	Days -28 to -1	Days -21 to 1	Day -1				
Informed Consent	X						
Medical History	X[a]	X					
Inclusion/Exclusion	X						
Complete PE (incl vital signs)	X			X	X		X
Limited PE (incl vital signs)		X				X	
Height	X						
12-lead ECG		X[b]					
Concomitant Medications	◄	———	►	◄	———	———	►
Adverse Event Collection				◄	———	———	►
BM Asp and Biopsy Sample		X[c]		X[ch]	X[c]		X[c]
Phone patient - fasting reminder			X				
LOCAL LAB SAMPLING:							
Haematology with Diff	X	X[i]		X	X	X	X
Coagulation (PT/PTT/INR)	X	X[i]		X	X	X	X
Biochem	X	X[i]		X	X	X	X
Urinalysis with Microscopy	X			X	X	X	X
Urine Pregnancy Test (WOCBP)	X			X	X	X	X
PSA (males)					X		
HbF					X		
CENTRAL LAB SAMPLING:							
Immunophenotyping by FC - PB		X		X[e]	X[e]		X
Immunophenotyping by FC - BM		X		X	X		X
BM Morphology Review		X		X	X		X
Genomic Analysis		X[d]		X[f]	X[f]		X[g]

Asp, aspirate; Biochem, biochemistry; BM, bone marrow; D, day; Diff, differential; ECG, electrocardiogram; EOS, End of Study; EOT, End of Treatment; FC, flow cytometry; HbF, hemoglobin F; incl, including;PB, peripheral blood; PD, pharmacodynamic; PE, physical examination; PK, pharmacokinetic; PSA, prostate-specific antigen; PT, prothrombin time; PTT, partial thromboplastin time; WOCBP, women of child-bearing potential

a Medical history includes documentation of WHO diagnosis criteria, ECOG or IPSS (-R) scores, and transfusions in the previous 15 days

b Performed only in the first 9 patients to receive IMG-7289

c Aspirate is to be obtained from the first pull whenever possible, and no later than the third

d Germline, BM and PB sample required, with BM and PB collected on the same day whenever possible; germline sample(s) can be obtained any time during the screening period including baseline and pre-dose Day 1 (Note:patients that have previously provided a saliva sample under earlier protocol versions will be requested to provide additional germline samples at a future visit)

e PB sample may be used for either immunophenotyping or genomics, if the BM sample is inadequate for analysis purposes

f Only BM sample required for genomic analysis

g BM and PB sample required for genomic analysis

h Unless BM sample has been obtained for study purposes in the last 10 days or is due in the next 3 days are part of the normal study cycles

i If Screening and Baseline performed on the same day, duplicate sampling is not required.

16.1.2 SoA: Cohort 1, Cycle 1

Visit Name	Treatment Period (D = Day)								Rest Period						
Visit Date	Pre- Dose D1	Day							Day						
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Medical History	X														
Verify Patient Eligibility	X														
Complete PE (incl vital signs)	X							X							X
Limited PE (incl vital signs)			X	X		X				X		X			
12-lead ECG		X[a]						X[a]							
Concomitant Medications	←	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Adverse Event Collection		←	—	—	—	—	—	—	—	—	—	—	—	—	→
Phone patient-Time of dose/fasting							X[gh]								
LOCAL LAB SAMPLING:															
Haematology with Diff	X		X	X		X		X		X		X			X
Coagulation (PT/PTT/INR)	X							X							X
Biochem	X			X				X		X		X			X
Urinalysis with Microscopy	X							X							X
Urine Pregnancy Test (WOCBP)	X							X							X
HbF	X							X							X
PSA (males)	X														X
CENTRAL LAB SAMPLING:															
Full PK Sampling	X[b]	X[b]	X[c]					X[dh]	X[eh]	X[eh]		X[eh]			X[eh]
Immunophenotyping by FC - PB								X							
Cytokine Analysis	X							X							X
IMG-7289:															
Dispensing	X														
Dosing		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]							
Accountability/Collect Returns			X	X		X		X							
ATRA (if applicable):															
Dispensing	X							X[k]							
Dosing		X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[ik]	X[ik]	X[ik]	X[ik]	X[ik]	X[ik]	X[ik]
Accountability/Collect Returns			X	X		X		X				X			

Asp, aspirate; Biochem, biochemistry; BM, bone marrow; D, day; Diff, differential; ECG, electrocardiogram; EOS, End of Study; EOT, End of Treatment; FC, flow cytometry; HbF, hemoglobin F; incl, including;PB, peripheral blood; PD, pharmacodynamic; PE, physical examination; PK, pharmacokinetic; PSA, prostate-specific antigen; PT, prothrombin time; PTT, partial thromboplastin time; WOCBP, women of child-bearing potential

a 2 hours post dose (±30 min); performed only in the first 9 patients to receive IMG-7289

b Samples to be collected pre-IMG-7289 dose (within 60 min prior to dosing), and 1, 2 and 3 hours post-IMG-7289 dose (±10 min)

c 24 hours (±1 hour) post Day 1 IMG-7289 dose and pre-IMG-7289 dose Day 2

d Samples to be collected: pre-IMG-7289 dose (within 60 min prior to dosing), 0.5 (±3 min), 1, 2, 3, 4 (±10 min) and 8 hours (±30 min) post IMG-7289 dose

e 24 hours (±1 hour) and approximately 48, 96 and 168 hours post Day 7 IMG-7289 dose

f Patients should take their IMG-7289 in the morning at approximately the same time every day

g Exact time of dose on Day 6 (IMG-7289 and ATRA, if applicable) to be collected from patient and recorded in the source notes; patient should also be reminded to fast prior to Day 7 visit and that Day 7 morning dosing (IMG-7289 and ATRA, if applicable) will occur in the clinic

h Performance of Day 7 through 14 PK sampling may be deferred to Cycle 2, if needed

i Patients should take their ATRA in the morning and the evening at approximately the same time every day

k Patients receiving 21 days continuous dosing with ATRA will continue to dose during the IMG-7289 rest period

16.1.3 SoA: Cohort 1, Cycles 2-4

Visit Name	Treatment Period (D = Day)								Rest Period						
Visit Date	Pre- Dose D1	Day							Day						
		1	2	3	4	5	6	7	8	9	10	11	12	13	14[h]
Complete PE (incl vital signs)	X[b]							X							X
Limited PE (incl vital signs)					X					X		X			
Concomitant Medications	◄	—	—	—	—	—	—	—	—	—	—	—	—	—	►
Adverse Event Collection	◄	—	—	—	—	—	—	—	—	—	—	—	—	—	►
BM Asp and Biopsy Sample															X[ac]
Phone patient-Time of dose/fasting							X[i]								
LOCAL LAB SAMPLING:															
Haematology with Diff	X				X			X		X		X			X
Coagulation (PT/PTT/INR)	X[b]							X							X
Biochem – CS trends noted	X				X					X					
Biochem – standard	X[b]							X							X
Urinalysis with Microscopy	X[b]							X							X
Urine Pregnancy Test (WOCBP)	X[b]							X							X
HbF															X[m]
PSA (males)															X[m]
CENTRAL LAB SAMPLING:															
Drug Concentration Sample	X[d]							X[e]							
Full PK Sampling[k]								X[ek]	X[k]	X[k]		X[k]			X[k]
Immunophenotyping by FC - PB								X							X[cf]
Immunophenotyping by FC - BM															X[c]
BM Morphology Review															X[c]
Genomic Analysis - BM															X[c]
IMG-7289:															
Dispensing	X														
Dosing		X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]							
Accountability/Returns					X			X							
ATRA (if applicable):															
Dispensing	X							X[o]							
Dosing		X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[no]	X[no]	X[no]	X[no]	X[no]	X[no]	X[no]
Accountability/Collect Returns	X[p]				X			X				X[o]			

Asp, aspirate; Biochem, biochemistry; BM, bone marrow; CS, Clinically Significant; D, day; Diff, differential; ECG, electrocardiogram; EOS, End of Study; EOT, End of Treatment; FC, flow cytometry; HbF, hemoglobin F; incl, including; NCS, Not Clinically Significant; PB, Peripheral Blood; PD, pharmacodynamic; PE, physical examination; PK, pharmacokinetic; PSA, Prostate Specific Antigen; PT, prothrombin time; PTT, partial thromboplastin time; WOCBP, women of child-bearing potential

a Samples to be drawn within ± 2 days of the end of rest period but prior to dosing in next cycle. Aspirate is to be obtained from the first pull whenever possible, and no later than the third.

b If test was performed the calendar day prior to Day 1, as part of a previous Cycle, it does not need to be repeated; for physical examination - limited physical examination should be performed instead

c In Cycles 2 and 4 ONLY, BM and associated analyses will be performed

d In Cycle 2 for all patients; also to be collected in Cycle 3 IF Day 7 through 14 PK was deferred to Cycle 2

e 24 hours post Day 6 IMG-7289 dose and prior to next IMG-7289 dose (±1 hour)

f PB sample may be used for either immunophenotyping or genomics, if the BM sample is inadequate for analysis purposes

g Patients should take their IMG-7289 in the morning at approximately the same time every day

h If the patient is completing the study, this visit will be replaced by the EOT visit

i Exact time of dose on Day 6 (IMG-7289 and ATRA, if applicable) to be collected from patient and recorded in the source notes; patient should also be reminded to fast prior to Day 7 visit and that Day 7 morning dosing (IMG-7289 and ATRA, if applicable) will occur in the clinic

k If Cycle 1 Day 7 through14 PK was deferred to Cycle 2

m In Cycle 4 ONLY

n If applicable patients should take their ATRA in the morning and the evening at approximately the same time every day

o In Cycle 3 ONLY, patients receiving 21 days continuous dosing with ATRA will continue to dose and return ATRA during the IMG-7289 rest period

p In Cycles 2 and 4 ONLY, patients receiving 21 days continous dosing with ATRA will return medication from the previous cycle.

16.1.4 SoA: Cohorts 3 and 3χ, Cycle 1

Visit Name	Treatment Period (D = Day)															Rest Period						
Visit Date	Pre- Dose D1	Day														Day						
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Medical History	X																					
Verify Patient Eligibility	X																					
Complete PE (incl vital signs)	X							X							X							X
Limited PE (incl vital signs)				X		X				X		X					X		X			
Concomitant Medications	◄	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	►
Adverse Event Collection		◄	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	►
Phone patient-Time of dose/fasting														X[c]								
LOCAL LAB SAMPLING:																						
Haematology with Diff	X			X		X		X		X		X			X		X		X			X
Coagulation (PT/PTT/INR)	X							X							X							X
Biochem – CS trends noted				X						X							X					
Biochem – standard	X							X							X							X
Urinalysis with Microscopy	X							X							X							X
Urine Pregnancy Test (WOCBP)	X							X							X							X
HbF	X														X							X
PSA (males)	X																					X
CENTRAL LAB SAMPLING:																						
Drug Concentration Sample															X[a]							
Immunophenotyping by FC - PB															X							
Cytokine Analysis	X														X							X
IMG-7289:																						
Dispensing	X							X														
Dosing		X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]							
Accountability/Returns				X		X		X		X		X			X							
ATRA (If applicable):																						
Dispensing	X							X														
Dosing		X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]							
Accountability/Returns				X		X		X		X		X			X							

Asp, aspirate; Biochem, biochemistry; BM, bone marrow; CS, Clinically Significant; D, day; Diff, differential; ECG, electrocardiogram; EOS, End of Study; EOT, End of Treatment; FC, flow cytometry; HbF, hemoglobin F; incl, including; NCS, Not Clinically Significant; PB, Peripheral Blood; PD, pharmacodynamic; PE, physical examination; PK, pharmacokinetic; PSA, prostate-specific antigen; PT, prothrombin time; PTT, partial thromboplastin time; WOCBP, women of child-bearing potential

a 24 hours post Day 13 IMG-7289 dose (±1 hour), pre-IMG-7289 dose Day 14

b Patients should take their IMG-7289 in the morning, at approximately the same time every day

c Exact time of dose on Day 13 (IMG-7289 and ATRA, if applicable) to be collected from patient and recorded in the source notes; patient should also be reminded to fast prior to Day 14 visit and that Day 14 morning dosing (IMG-7289 and ATRA, if applicable) will occur in the clinic

d Patients should take their ATRA in the morning and the evening at approximately the same time every day

16.1.5 SoA: Cohorts 3 and 3χ, Cycle 2

Visit Name	Treatment Period (D = Day)														Rest Period						
Visit Date	Pre- Dose D1	Day													Day						
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21[e]
Complete PE (incl vital signs)	X[b]							X							X							X
Limited PE (incl vital signs)					X						X		X				X		X			
Concomitant Medications	◄	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	►
Adverse Event Collection	◄	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	►
BM Asp and Biopsy Sample																						X[a]
LOCAL LAB SAMPLING:																						
Haematology with Diff	X				X			X			X		X		X		X		X			X
Coagulation (PT/PTT/INR)	X[b]							X							X							X
Biochem – CS trends noted	X				X						X						X					
Biochem – standard	X[b]							X							X							X
Urinalysis with Microscopy	X[b]							X							X							X
Urine Pregnancy Test (WOCBP)	X[b]							X							X							X
HbF																						X
PSA (males)																						X
CENTRAL LAB SAMPLING:																						
Drug Concentration Sample	X																					
Immunophenotyping by FC - PB															X							X[c]
Immunophenotyping by FC - BM																						X
BM Morphology Review																						X
Genomic Analysis - BM																						X
IMG-7289:																						
Dispensing	X							X														
Dosing		X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]							
Accountability/Returns					X			X			X		X		X							
ATRA (If applicable):																						
Dispensing	X							X														
Dosing		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]							
Accountability/Returns					X			X			X		X		X							

Asp, aspirate; Biochem, biochemistry; BM, bone marrow; CS, Clinically Significant; D, day; Diff, differential; ECG, electrocardiogram; EOS, End of Study; EOT, End of Treatment; FC, flow cytometery; HbF, hemoglobin F; incl, including; NCS, Not Clinically Significant; PB, Peripheral Blood; PD, pharmacodynamic; PE, physical examination; PK, pharmacokinetic; PSA, prostate-specific antigen; PT, prothrombin time; PTT, partial thromboplastin time; WOCBP, women of child-bearing potential

a Samples to be drawn within ± 2 days of the end of rest period but prior to dosing in next cycle; Aspirate is to be obtained from the first pull whenever possible, and no later than the third

b If test was performed the calendar day prior to Day 1, as part of a previous Cycle, it does not need to be repeated; for physical examination, limited physical examination should be performed instead

c PB sample may be used for either immunophenotyping or genomics, if the BM sample is inadequate for analysis purposes

d Patients should take their IMG-7289 in the morning, at approximately the same time every day

e If the patient is completing the study, this visit will be replaced by the EOT visit

f Patients should take their ATRA in the morning and the evening at approximately the same time every day

16.1.6 SoA: Cohorts 4 and 4χ, Cycle 1

Visit Name	Treatment Period (D = Day)																					Rest Period						
Visit Date	Pre- Dose D1	Day																				Day						
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28[e]
Medical History	X																												
Verify Patient Eligibility	X																												
Complete PE (incl vital signs)	X							X							X							X							X
Limited PE (incl vital signs)				X		X				X		X						X		X				X		X			
Concomitant Medications	◄	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	►
Adverse Event Collection		◄	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	►
BM Asp and Biopsy Sample																													X[a]
Phone patient-Time of dose/fasting																					X[f]								
LOCAL LAB SAMPLING:																													
Haematology with Diff	X			X		X		X		X		X			X			X		X		X		X		X			X
Coagulation (PT/PTT/INR)	X							X							X							X							X
Biochem – CS trends noted				X						X								X						X					
Biochem – standard	X							X							X							X							X
Urinalysis with Microscopy	X							X							X							X							X
Urine Pregnancy Test (WOCBP)	X							X							X							X							X
HbF	X																					X							X
PSA (males)	X																												X
CENTRAL LAB SAMPLING:																													
Drug Concentration Sample																						X[b]							X
Immunophenotyping by FC - PB																						X							X[c]
Immunophenotyping by FC - BM																													X
Cytokine Analysis	X																					X							X
BM Morphology Review																													X
Genomic Analysis - BM																													X
IMG-7289:																													
Dispensing	X							X							X														
Dosing		X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]							
Accountability/Returns				X		X		X		X		X			X			X		X		X							
ATRA (If applicable):																													
Dispensing	X							X							X														
Dosing		X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]							
Accountability/Returns				X		X		X		X		X			X			X		X		X							

Asp, aspirate; Biochem, biochemistry; BM, bone marrow; CS, Clinically Significant; D, day; Diff, differential; ECG, electrocardiogram; EOS, End of Study; EOT, End of Treatment; FC, flow cytometry; HbF, hemoglobin F; incl, including; NCS, Not Clinically Significant; PB, Peripheral Blood; PD, pharmacodynamic; PE, physical examination; PK, pharmacokinetic; PSA, prostate-specific antigen; PT, prothrombin time; PTT, partial thromboplastin time; WOCBP, women of child-bearing potential

a Samples to be drawn within ± 2 days of the end of rest period but prior to dosing in next cycle; Aspirate is to be obtained from the first pull whenever possible, and no later than the third

b 24 hours post Day 20 IMG-7289 dose (±1 hour), pre-IMG-7289 dose Day 21

c PB sample may be used for either immunophenotyping or genomics, if the BM sample is inadequate for analysis purposes

d Patients should take their IMG-7289 in the morning, at approximately the same time every day

e If the patient is completing the study, this visit will be replaced by the EOT visit

f Exact time of dose on Day 20 (IMG-7289 and ATRA, if applicable) to be collected from patient and recorded in the source notes; patient should also be reminded to fast prior to Day 21 visit and that Day 21 morning dosing (IMG-7289 and ATRA, if applicable) will occur in the clinic

g Patients should take their ATRA in the morning and the evening at approximately the same time every day

16.1.7 SoA: Cohorts 4 and 4χ, First Additional Cycle

Visit Name	Treatment Period (D = Day)																					Rest Period						
Visit Date	Pre- Dose D1	Day																				Day						
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28[e]
Verify Continued Patient Eligibility	X[f]																												
Complete PE (incl vital signs)	X[b]							X								X						X							X
Limited PE (incl vital signs)					X						X			X					X					X		X			
Concomitant Medications	◄																												►
Adverse Event Collection	◄																												►
BM Asp and Biopsy Sample																													X[a]
LOCAL LAB SAMPLING:																													
Haematology with Diff	X				X			X			X			X		X			X			X		X		X			X
Coagulation (PT/PTT/INR)	X[b]							X								X						X							X
Biochem – CS trends noted	X				X						X								X					X					
Biochem – standard	X[b]							X								X						X							X
Urinalysis with Microscopy	X[b]							X								X						X							X
Urine Pregnancy Test (WOCBP)	X[b]							X								X						X							X
CENTRAL LAB SAMPLING:																													
Immunophenotyping by FC - PB																						X							X[c]
Immunophenotyping by FC - BM																													X
BM Morphology Review																													X
Genomic Analysis - BM																													X
IMG-7289:																													
Dispensing	X							X								X													
Dosing		X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]							
Accountability/Returns					X			X			X			X		X			X			X							
ATRA (If applicable):																													
Dispensing	X							X								X													
Dosing		X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]							
Accountability/Returns					X			X			X			X		X			X			X							

Asp, aspirate; Biochem, biochemistry; BM, bone marrow; CS, Clinically Significant; D, day; Diff, differential; ECG, electrocardiogram; EOS, End of Study; EOT, End of Treatment; FC, flow cytometry; HbF, hemoglobin F; incl, including; NCS, Not Clinically Significant; PB, Peripheral Blood; PD, pharmacodynamic; PE, physical examination; PK, pharmacokinetic; PSA, prostate-specific antigen; PT, prothrombin time; PTT, partial thromboplastin time; WOCBP, women of child-bearing potential

a Samples to be drawn within ± 2 days of the end of rest period but prior to dosing in next cycle; Aspirate is to be obtained from the first pull whenever possible, and no later than the third

b If test was performed the calendar day prior to Day 1, as part of a previous Cycle, it does not need to be repeated; for physical examination, limited physical examination should be performed instead

c PB sample may be used for either immunophenotyping or genomics, if the BM sample is inadequate for analysis purposes

d Patients should take their IMG-7289 in the morning, at approximately the same time every day

e If the patient is completing the study, this visit will be replaced by the EOT visit

f Post completion of Cycle 1, verification of continued patient eligibility includes confirming the patient qualifies for additional cycles (based on PI assessment of safety and clinical benefit)

g Patients should take their ATRA in the morning and the evening at approximately the same time every day

16.1.8 SoA: All Cohorts, All Additional Cycles

Visit Name	Treatment Period (D = Day)																					Rest Period						
Visit Date	Pre- Dose D1	Day																				Day						
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	R1	R2	R3	R4	R5	R6	R7[f]
Verify Continued Patient Eligibility	X[g]																											
Complete PE (incl vital signs)	X[b]							X							X							X							X
Concomitant Medications	←																													→
Adverse Event Collection	←																													→
BM Asp and Biopsy Sample																														X[ad]
LOCAL LAB SAMPLING:																														
Haematology with Diff	X				X			X			X				X				X			X		X		X			X
Coagulation (PT/PTT/INR)	X[b]							X							X							X							X
Biochem – CS trends noted	X				X						X								X					X					
Biochem – standard	X[b]							X							X							X							X
Urinalysis with Microscopy	X[b]							X							X							X							X
Urine Pregnancy Test (WOCBP)	X[b]							X							X							X							X
HbF																														X[d]
PSA (males)																														X[d]
CENTRAL LAB SAMPLING:																														
Immunophenotyping by FC - PB																														X[de]
Immunophenotyping by FC - BM																														X[d]
BM Morphology Review																														X[d]
Genomic Analysis - BM																														X[d]
IMG-7289:																														
Dispensing	X							X							X														
Dosing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Accountability/Returns								X			X				X				X			X							
ATRA (If applicable):																														
Dispensing	X							X							X														
Dosing		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Accountability/Returns	X[h]							X			X				X				X			X							

Asp, aspirate; Biochem, biochemistry; BM, bone marrow; CS, Clinically Significant; D, day; Diff, differential; ECG, electrocardiogram; EOS, End of Study; EOT, End of Treatment; FC, flow cytometry; HbF, hemoglobin F; incl, including; NCS, Not Clinically Significant; PB, Peripheral Blood; PD, pharmacodynamic; PE, physical examination; PK, pharmacokinetic; PSA, prostate-specific antigen; PT, prothrombin time; PTT, partial thromboplastin time; WOCBP, women of child-bearing potential

a Samples to be drawn within ± 2 days of the end of rest period but prior to dosing in next cycle; Aspirate is to be obtained from the first pull whenever possible, and no later than the third

b If test was performed the calendar day prior to Day 1, as part of a previous Cycle, it does not need to be repeated; for physical examination, limited physical examination should be performed instead

c Only to be performed in the FIRST additional Cycle

d Only to be performed EVERY OTHER Cycle

e PB sample may be used for either immunophenotyping or genomics, if the BM sample is inadequate for analysis purposes

f If the patient is completing the study, this visit will be replaced by the EOT visit

g Verification of continued patient eligibility includes confirming the patient qualifies for each additional cycle (based on PI assessment of safety and clinical benefit)

h Patients receiving 21 days continuous dosing with ATRA, with IMG-7289 in 7 on/7 off cycles will continue to dose during the IMG-7289 rest period in every other cycle. ATRA will be returned on Day 1 of the alternate cycle.

16.1.9 Extended Rest Period

Visit Name	Abbreviated Visit[a]	Standard Visits	
Visit Date	**RD 9, 11, 16, 18, 23, 25, 31, 38, 45, 52**	**RD 14, 21, 35, 42, 49**	**RD 28, 56**
Concomitant Medications	←	—	→
Adverse Event Collection	←	—	→
Complete Physical Examination		X	X
BM Asp and Biopsy Sample			X[b]
LOCAL LAB SAMPLING:			
Haematology with Diff	X	X	X
Coagulation (PT/PTT/INR)		X	X
Biochem		X	X
Urinalysis with Microscopy		X	X
Urine Pregnancy Test (WOCBP)		X	X
CENTRAL LAB SAMPLING:			
Immunophenotyping by FC - PB			X[c]
Immunophenotyping by FC - BM			X[b]
BM Morphology Review			X[d]
Genomic Analysis			X[bcd]

Asp, aspirate; Biochem, biochemistry; BM, bone marrow; Diff, differential; FC, flow cytometry; PB, peripheral blood; PT, prothrombin time; PTT, partial thromboplastin time; RD, rest day; WOCBP, women of child-bearing potential

a Conducted as appropriate based on the duration of the extended rest period

b Aspirate is to be obtained from the first pull whenever possible, and no later than the third

c PB sample may be used for either immunophenotyping or genomics, if the BM sample is inadequate for analysis purposes

d BM and PB sample required for genomic analysis

16.2 Diagnostic Classifications, Prognostic Scores, and Response Criteria

Table 9: 2016 WHO Classification System for AML and Related Precursor Neoplasms, and Acute Leukaemias of Ambiguous Lineage (Arber *et al.*, 2016)

Acute myeloid leukaemia with recurrent genetic abnormalities	-AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* -AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* -APL with *PML-RARA** -AML with t(9;11)(p21.3;q23.3); *MLLT3-KM2A*† -AML with t(6;9)(p23;q34.1); *DEK-NUP214* -AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM* -AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1* *-Provisional entity: AML with BCR-ABL1* -AML with mutated NPM1 -AML with biallelic mutations CEBPA *-Provisional entity: AML with mutated RUNX1*
Acute myeloid leukaemia with myelodysplasia-related changes‡	
Therapy-related myeloid neoplasms§	
Acute myeloid leukaemia, not otherwise specified (NOS)	-Acute myeloid leukaemia with minimal differentiation -Acute myeloid leukaemia without maturation -Acute myeloid leukaemia with maturation -Acute myelomonocytic leukaemia -Acute monoblastic/monocytic leukaemia -Pure erythroid leukaemia -Acute megakaryoblastic leukaemia -Acute basophilic leukaemia -Acute panmyelosis with myelofibrosis
Myeloid sarcoma	
Myeloid proliferations related to Down syndrome	-Transient abnormal myelopoiesis (TAM) -Myeloid leukaemia associated with Down syndrome

Acute leukaemias of ambiguous lineage	-Acute undifferentiated leukaemia -Mixed phenotype acute leukaemia with t(9;22)(q34.1;q11.2); *BCR-ABL1*‖ -Mixed phenotype acute leukaemia with t(v;11q23); *KMT2A* rearranged -Mixed phenotype acute leukaemia, B/myeloid, NOS -Mixed phenotype acute leukaemia, T/myeloid, NOS

For a diagnosis of AML, a marrow blast count of ≥ 20% is required, except for AML with the recurrent genetic abnormalities t(15;17), t(8;21), inv(16) or t(16;16) and some cases of erythroleukaemia.

*Other recurring translocations involving *RARA* should be reported accordingly: for example, AML with t(11;17)(q23;q12); *ZBTB16-RARA*; AML with t(11;17)(q13;q12); *NUMA1-RARA*; AML with t(5;17)(q35;q12); *NPM1-RARA*; or AML with *STAT5BRARA* (the latter having a normal chromosome 17 on conventional cytogenetic analysis).

†Other translocations involving *MLL* should be reported accordingly: for example, AML with t(6;11)(q27;q23); *MLLT4-MLL*; AML with t(11;19)(q23;p13.3); *MLL-MLLT1*; AML with t(11;19)(q23;p13.1); *MLL-ELL*; AML with t(10;11)(p12;q23); *MLLT10-MLL*.

‡More than 20% blood or marrow blasts *AND* any of the following: previous history of myelodysplastic syndrome (MDS), or myelodysplastic/ myeloproliferative neoplasm (MDS/MPN); myelodysplasia-related cytogenetic abnormality (see below); multilineage dysplasia; *AND* absence of both prior cytotoxic therapy for unrelated disease and aforementioned recurring genetic abnormalities; cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes are:

- Complex karyotype (defined as 3 or more chromosomal abnormalities).
- Unbalanced changes: -7 or del(7q); -5 or del(5q); i(17q) or t(17p); -13 or del(13q); del(11q); del(12p) or t(12p); del(9q); idic(X)(q13).
- Balanced changes: t(11;16)(q23;p13.3); t(3;21)(q26.2;q22.1); t(1;3)(p36.3; q21.1); t(2;11)(p21;q23); t(5;12)(q33;p12); t(5;7)(q33;q11.2); t(5;17)(q33;p13); t(5;10)(q33;q21); t(3;5)(q25;q34).

§Cytotoxic agents implicated in therapy-related haematologic neoplasms: alkylating agents; ionizing radiation therapy; topoisomerase II inhibitors; others.

‖*BCR-ABL1*–positive leukaemia may present as mixed phenotype acute leukaemia, but should be treated as *BCR-ABL1*–positive acute lymphoblastic leukaemia.

Table 10: Eastern Cooperative Group Performance Status for AML Patients

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

Table 11: 2016 WHO Classification System for Myelodysplastic Syndromes (Arber *et al.*, 2016)

Disease	Dysplastic lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	Blood Findings	Bone Marrow Findings	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%†	<1% blasts no Auer rods	<5% blasts no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15%/<5%†	<1% blasts no Auer rods	<5% blasts no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)						
MDS-RS and single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15%/≥5%†	<1% blasts no Auer rods	<5% blasts no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS and multilineage dysplasia (MDS-RS-MLD)	2 or 3	1-3	≥15%/≥5%†	<1% blasts no Auer rods	<5% blasts no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	<1% blasts no Auer rods	<5% blasts no Auer rods	del(5q) alone or with 1 additional abnormality except -7 or del(7q)
MDS with excess blasts (MDS-EB)						
MDS with excess blasts-1 (MDS-EB-1)	0-3	1-3	None or any	2-4% blasts no Auer rods	5-9% blasts no Auer rods	Any
MDS with excess blasts-2 (MDS-EB-2)	0-3	1-3	None or any	5-19% blasts or Auer rods	10-19% blasts or Auer rods	Any
MDS, unclassified (MDS-U)						
With 1% blasts	1-3	1-3	None or any	=1% blasts‡ no Auer rods	<5% blasts no Auer rods	Any
With single lineage dysplasia and pancytopenia	1	3	None or any	<1% blasts no Auer rods	<5% blasts no Auer rods	Any
Based on defining cytogenetic abnormality	0	1-3	<15%§	<1% blasts no Auer rods	<5% blasts no Auer rods	MDS-defining abnormality
Provisional entity: Refractory cytopenia of childhood	1-3	1-3	None	<2% blasts	<5% blasts	Any

*Cytopenias defined as: haemoglobin, <10 g/dL; platelet count, <100 x 10^9/L; and absolute neutrophil count, <1.8 x 10^9/L. Rarely, MDS may present with mild anemia or thrombocytopenia above these levels. PB monocytes must be <1 x 10^9/L

† If *SF3B1* mutation is present.

‡One percent PB blasts must be recorded on at least 2 separate occasions.

§Cases with $15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as MDS-RS-SLD.

Table 12: International Prognostic Scoring System (IPSS) and Risk Categories for Myelodysplastic Syndrome

PROGNOSTIC CHARACTERISTICS	POINTS				
	0	**0.5**	**1**	**1.5**	**2**
Cytogenetic risk category[a]	Good	Intermediate	Poor		
Blasts in bone marrow	<5%	5-10%		11-20%	21–30%
Cytopenias[b]	0 or 1	2 or 3			

[a]Good: normal, –Y, del(5q), or del(20q) as single abnormalities; Intermediate: abnormalities other than good or poor; Poor: complex, 3 or more abnormalities, abnormal chromosome 7.

[b]Each of the following cytopenia counts as a value of 1: haemoglobin < 10 g/dl; absolute neutrophil count (ANC) < $1{,}500\times10^9$/L; platelet count less than $100{,}000\times10^9$/L

IPSS Risk Category	Score
Low	0
Intermediate-1	0.5-1.0
Intermediate-2	1.5-2.0
High	> 2.0

Table 13: Revised International Prognostic Scoring System (IPSS-R) and Risk Categories for Myelodysplastic Syndromes

PROGNOSTIC CHARACTERISTICS	POINTS						
	0	0.5	1	1.5	2	3	4
Cytogenetic risk category[a]	Very good		Good		Intermediate	Poor	Very poor
Blasts in bone marrow, %	≤2		>2%–5%		5%–10%	>10%	
Haemoglobin, g/dl	≥10		8–<10	<8			
Platelet count, $\times10^9$/l	≥100	50–<100	<50				
Absolute neutrophil count, $\times10^9$/l	≥0.8	<0.8					

[a]Very good: –Y and del(11q) as single abnormalities; good: normal, del(5q), del(12p) and del(20q) as single abnormalities, double abnormalities including del(5q); intermediate: del(7q), +8, +19, i(17q) and any other single abnormalities, any other double abnormalities; poor: −7 and inv(3)/t(3q)/del(3q) as single abnormalities, double abnormalities including −7/del(7q), complex (3 abnormalities); very poor; >3 abnormalities.

IPSS-R Risk Category	Score
Very low	≤1.5
Low	>1.5–3
Intermediate	>3–4.5
High	>4.5–6
Very high	> 6

Table 14 Response criteria in AML

Category	Definition
Complete remission (CR)*	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count > 1.0 x 10^9/L (1000/μL); platelet count > 100 x 10^9/L (100 000/μL); independence of red cell transfusions
CR with incomplete recovery (CRi)	All CR criteria except for residual neutropenia (< 1.0 x 10^9/L [1000/μL]) or thrombocytopenia (< 100 x 10^9/L [100 000/μL])
Morphologic leukaemia-free state (MLFS)	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no haematologic recovery required
Partial remission (PR)	Relevant in the setting of phase 1 and 2 clinical trials only; all haematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Cytogenetic CR (CRc)	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR (CRm)	A reduction in the frequency to below 0.01% in one or more alleles of AML-associated genes known to be somatically mutated in the patient
Stable Disease (SD)	Failure to achieve a response (CR, CRi, MLFS, PR, CRc or CRm) but not meeting Progressive Disease criteria for a period of more than 8 weeks.
Progressive Disease (PD)	Patient previously had partial remission or stable disease. For those with 5% to 66% bone marrow blasts at nadir, a >50% increase in bone marrow blast count percentage from the nadir and percentage is ≥20%; and for those with ≥67% bone marrow blasts at nadir, a doubling of the nadir absolute peripheral blood blast count with a final absolute peripheral blood blast count >10 x 10^9/L.
Treatment failure	
Resistant disease (RD)	Failure to achieve CR or CRi (general practice; phase 2/3 trials), or failure to achieve CR, CRi, or PR (phase 1 trials); only includes patients surviving ≥ 7 days following completion of initial treatment, with evidence of persistent leukaemia by blood and/or bone marrow examination
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukaemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or < 7 days following its completion; or deaths occurring ≥ 7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Relapse¶	Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extramedullary disease

Definitions of response criteria are based primarily on those given by Cheson et al. 2003. Stable and Progressive Disease included for analysis purposes.

*All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukaemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.
¶In cases with low blast percentages (5-10%), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of haematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

Table 15: Response Criteria for MDS

Category	Response Criteria (responses must last at least 4 weeks)
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines* Persistent dysplasia will be noted*† Peripheral blood‡ Hgb ≥ 11 g/dL Platelets ≥ 100 x 10^9/L Neutrophils ≥ 1.0 x 10^9/L† Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment† Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete: Disappearance of the chromosomal abnormality without appearance of new ones Partial: At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts 5%-10% blasts: ≥ 50% increase to > 10% blasts 10%-20% blasts: ≥ 50% increase to > 20% blasts 20%-30% blasts: ≥ 50% increase to > 30% blasts Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥ 2 g/dL Transfusion dependence

Category	Response Criteria (responses must last at least 4 weeks)
Survival	Endpoints: Overall: death from any cause Event free: failure or death from any cause PFS: disease progression or death from MDS DFS: time to relapse Cause-specific death: death related to MDS

To convert haemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
MDS indicates myelodysplastic syndromes; Hgb, haemoglobin; CR, complete remission; HI, haematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukaemia; PFS, progression-free survival; DFS, disease-free survival.
*Dysplastic changes should consider the normal range of dysplastic changes (modification).
†Modification to IWG response criteria.
‡Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.