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Imago BioSciences
Protocol #: IMG-7289-CTP-101

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

Statistical Analysis Plan

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This plan conforms to all International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, including E3 (Structure and Content of Clinical Study Reports) and E9 (Statistical Principles for Clinical Trials).

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I. Introduction

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Imago Biosciences, Inc. Protocol IMG-7289-CTP-101 [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]. The purpose of this plan is to provide specific guidelines from which the analysis will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR).

A. Background

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 patient 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.

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).

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 patient 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.

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.

The protocol for Study IMG-7289-CTP-101 describes the general approach to analysis of data from the study. This analysis plan describes additional detail needed to complete such an analysis.

B. Protocol and Amendment History

This Statistical Analysis Plan (SAP) is based on Amendment 2 of the Protocol.

Version	Approval Date	Salient Changes, if any*
Protocol	05 April 2016	
Amendment 1	29 June 2016	

Amendment 2	19 January 2017	
Amendment 3	29Aug2017	(1) Change "The adequacy of dose and duration in producing a pharmacodynamic effect" from a secondary to a primary objective (2) Include additional combination therapy sub-cohorts in dose-finding phase (3) Remove Cohort 2 and add combination therapy cohorts in the duration-finding phase (4) Add Stable and Progressive Disease Response Criteria for AML patients (5) Remove Medical Events of Interest (MEOIs) categories (6) Increase the number of patients

* Changes expected to require accommodation in analysis plan.

This SAP will govern the analysis of data from this study. The plan may be modified until database lock. Any deviations from the analysis plan, including any after the time of treatment database lock, will be documented as such in the study report.

II. Protocol Hypothesis and Objectives

A. Hypothesis

The protocol (Section 4.1) lists the following 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.

B. Primary

The protocol (Section 4.2) lists the following primary objectives:

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

C. Secondary

The protocol (Section 4.2) lists the following secondary objectives:

- 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

III. Study Endpoints

A. Primary

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 Protocol 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. CCI

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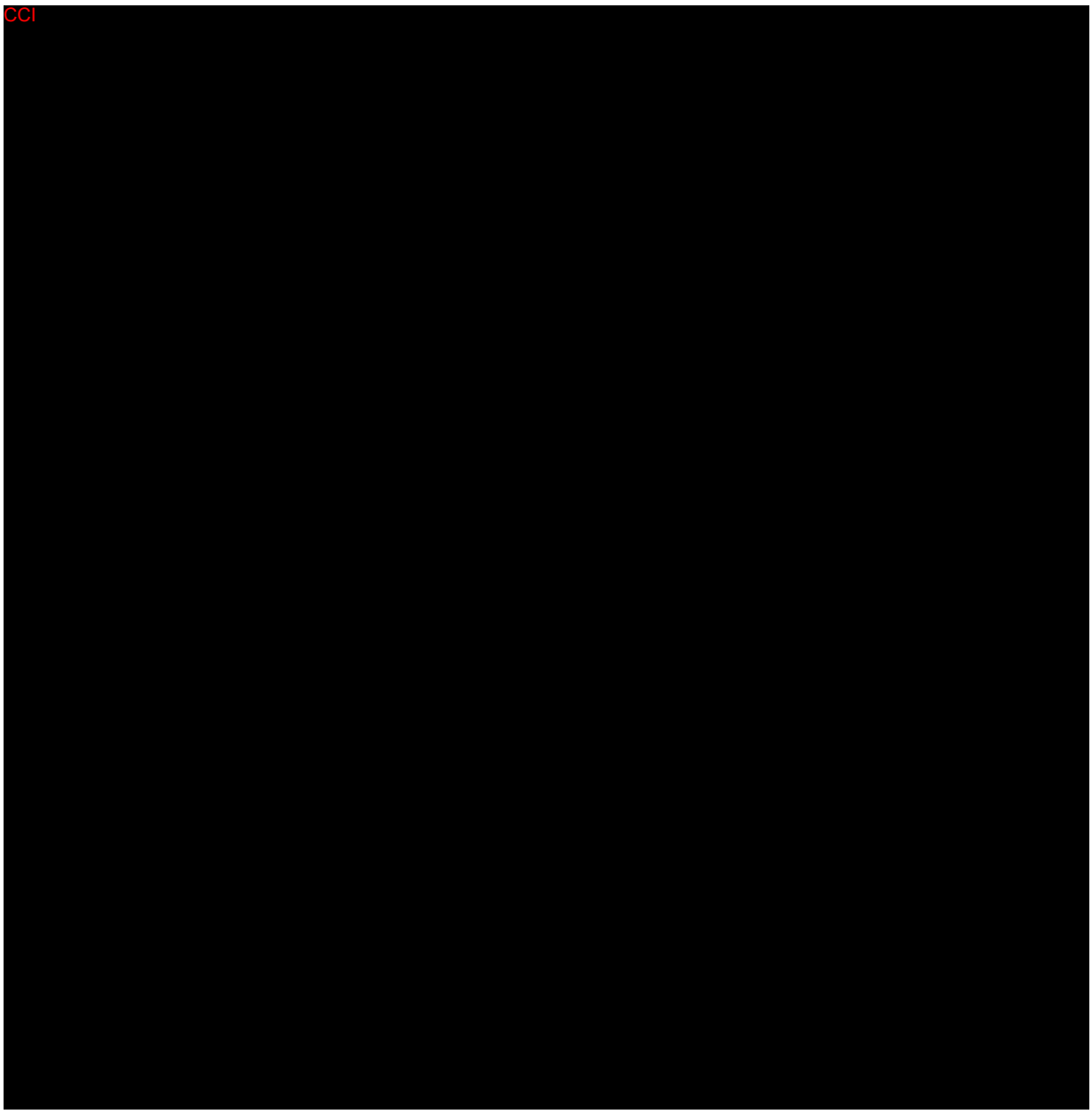


IV. Study Design

A. Design Overview

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.

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 Protocol 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 sub-cohort/cohort with a minimum of 3 patients 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 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, 1ω in accordance with Protocol Section 7.2.2.1, following DSMC reviews as detailed in Protocol Section 8.1 and the rules outlined in Protocol 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 Protocol 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 Protocol Section 7.2.2.3, following DSMC reviews as detailed in Protocol Section 8.1 and the rules outlined in Protocol 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.

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 Protocol 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 Protocol 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 Protocol Table 14 and Protocol 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 Protocol Section 9. Additionally, a by-cohort schema of assessments is included in Protocol Section 16.1, Schedule of Assessments.

B. Study Population

The patient population will consist of men and women age 18 or older who have been diagnosed with either high-risk Acute Myeloid Leukaemia or Myelodysplastic Syndrome. Eligible patients who have signed informed consent must not have had prior treatments within a specified period of time and must have meet pre-specified laboratory values for selected parameters, in addition to multiple other required eligibility criteria.

C. Sample Size Predictions

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. Approximately 40 patients with high risk AML/MDS patients will be enrolled and treated in this study.

D. Treatment Randomization

This is not a randomized study.

E. Assessment Schedule

The study assessments depend upon the cohort and the recommendations of the DSMC. Further description is available in the Protocol Sections 9 and 16.1.

V. Interventions

A. Clinical Trial Material

CCI [redacted] CCI [redacted] IMG-7289 will be supplied in capsules of multiple strengths. These strengths, based on IMG-7289 free base, i.e. the active substance, may include: 5 mg, 10 mg, 25 mg, and 50 mg. Additional strengths may be added over the duration of the study.

ATRA will be supplied as oval, soft gelatin capsules; one half of each capsule is opaque orange-yellow and the other half opaque reddish brown. One capsule strength will be provided: 10 mg. In addition to ATRA, the capsule contents are beeswax-yellow, soya oil-hydrogenated and soya oil. The capsule shell contains gelatin, glycerol, Karion 83, titanium dioxide, iron oxide yellow CI177492 and iron oxide red CI77491.

The protocol provides additional product details in Protocol Section 7.

B. Study Procedures

Patients will undergo procedures described in Protocol Section 9 to assess the study drug safety, pharmacodynamics, and pharmacokinetics in order to achieve the study objectives.

VI. General Analytical Considerations

The statistical analyses will be reported using summary tables, figures, and data listings. Unless otherwise noted, all statistical testing will be two-sided with significance being $p < 0.05$. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentage of patients in corresponding categories. As appropriate and where specified, continuous and categorical variables will be evaluated using the Student t-test, ANOVA, Wilcoxon rank sum, Fisher's exact, or χ^2 tests. As appropriate and where specified, summary tables will be presented by cohort, and may also include a "Total" or "All Patients" summary.

The analyses described in this plan are considered *a priori*, in that they have been defined prior to database lock. If any post-hoc analyses are performed they will be defined and reported in the CSR.

All analyses will be performed using SAS statistical analysis software (SAS, SAS/GRAPH and SAS/STAT; version 9.3 or higher of SAS for Windows [SAS Institute Inc; Cary, NC, USA]).

A. Data Sources

All data are collected *via* electronic case report forms (eCRFs) through remote data entry. Section 13.7 of the protocol describes data quality assurance.

B. Definition of Baseline

For analysis purposes, baseline is defined as the last assessment prior to the first dose of study drug. Cycle 1 Day 1 is the first day a patient receives study drug. For most measurements, baseline assessments will be taken pre-dose on Cycle 1 Day 1. If pre-dose assessments on Day 1 are not available, the most recent prior assessment closest to Day 1 may be substituted in some cases, and unless otherwise specified. For local laboratory data, baseline data will be obtained during the screening period (Days -28 to 1). All other baseline data will be collected on Days -21 to 1.

C. Missing Data

For safety and tolerability, missing data, including those not obtained because of death, will be the last value carried forward.

If CTCAE Grade is missing, the event is assumed to be 'Severe' (grade 3). If AE relatedness is missing, the event is assumed to be 'possibly' related.

Otherwise, missing data will not be replaced with imputed values. When relevant, sections below will address how missing data will be handled for the particular analyses.

D. Display and Imputation Methods for Missing Dates

Every effort will be made to query missing dates. However, partial dates are allowed on the eCRF for Adverse Event (AE) onset and resolution dates (only month and year are required), Concomitant Medication (CM) start and stop dates (only year is required), and Prior and Concurrent Cancer Chemotherapy (PCTHX) start and stop dates (only year is required).

Per protocol, Adverse Events (AEs) are captured in the eCRF commencing with the first dose of IMG-7289 through to the End of Study Visit (scheduled for approximately 28 days post last IMG-7289 dose). For records with missing AE onset day, the following procedure will be employed for use in determining whether the AE is treatment-emergent:

- AE onset dates with missing day will be assumed to occur on the first day of the non-missing month, except for AEs occurring in the first month of dosing, in which case the date will be the first day of dosing.

Additionally, if for some reason the start date of an AE is partially or completely missing and the end date of the AE does not indicate that the AE occurred prior to the first dose of IMG-7289, then the determination of treatment-emergent status will be based on the following:

- If the start date is completely missing, then the AE is treatment-emergent.
- If the start year is the same as the year of the first dose of study drug and the start month is the same or after the month of the first dose of study drug, then the AE is treatment-emergent.
- If the start year is after the year of the first dose of study drug, then the AE is treatment emergent.

For records with a missing CM or PCTHX start and/or stop day or month, the following procedure will be employed for use in determining whether the therapy (i.e., medication or chemotherapy) is prior or concomitant/concurrent:

- Therapy start dates with a missing day and non-missing month will be assumed to occur on the *first* day of the non-missing month, except for therapies occurring in the first month of dosing, in which case the date will be the first day of dosing.
- Therapy start dates with a missing day and month will be assumed to occur on the *first* day of the non-missing year (i.e., January 1), except for medications occurring in the first year of dosing, in which case the date will be the first day of dosing.
- Therapies that are not marked as ongoing, and have a stop date with a missing day and non-missing month will be assumed to occur on the *last* day of the non-missing month.

- Therapies that are not marked as ongoing, and have a stop date with a missing day and month will be assumed to occur on the *last* day of the non-missing year (i.e. December 31).

For the listings, AE, CM and PCTHX dates will be listed as collected in the eCRF. All other data will be reported as they are collected. No imputation methods will be used to replace missing data unless otherwise stated in this document.

Partial transfusion start dates are not permitted, and thus assumptions should not be needed to determine if the transfusion was prior to the first dose of IMG-7289.

E. Multiple Study Centers

There will be no adjustment for multiple study centers in the analysis.

F. Covariate Adjustment in Primary Analysis

There will be no adjustment in the analysis for covariates.

G. Sample Size Reassessment

No sample size reassessment is planned for this study.

H. Interim Analyses or Timing of Analyses

The 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 Protocol Section 8 for details pertaining to DSMC reviews, and management of study toxicities.

I. Multiple Comparisons

No control for the effect of multiple comparisons is planned.

J. Analysis Populations

Two analysis populations will be defined for use with various analyses.

1. Safety Population

All enrolled patients who received at least one dose of IMG-7289 will be included in the Safety population.

2. Efficacy Population

All enrolled patients who received at least one dose of IMG-7289 and have disease assessment at baseline (Bone Marrow Aspirate/Biopsy and Haematology). Patients having no post-baseline response assessment will be defined as NE (Not Evaluable).

K. Data Display Characteristics

Data displays produced for this study will include three types—summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. In general, there will be one set of data displays encompassing patients in both the dose-finding phase and duration-finding phases. Summary tables will include columns for each cohort, and the ordering of these cohorts will be defined in the tables, listings, and figures (TLF) shells document. Summary tables will be produced as specified in the following sections. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes.

Data listings will simply list the data that are either recorded on the CRF or derived for each patient. In general, they will be ordered by cohort, site, patient number, and time of assessment, unless otherwise specified in the display shell. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within patient. Data listings will not display patient initials.

Summary tables will display summary statistics calculated for each cohort, and for all patients combined, unless described otherwise in the following sections, or in the display shells. For most summary tables, the cohorts will be presented in a column, and the summary statistics of interest will be presented in rows.

Descriptive statistics (arithmetic mean, standard deviation (SD), sample size, median, minimum, maximum, and number) will be calculated for quantitative safety data as well as for the differences to baseline, when appropriate. In addition, shift tables for laboratory values with respect to normal range (low, normal, high) will be summarized; and overall laboratory and ECG result shift from baseline (Normal, Abnormal clinically significant (CS), and Abnormal non-clinically significant (NSC) will be summarized.

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.

VII. Patient Accountability

A. Patient Characteristics

Demography. Data collected about the following patient characteristics at the screening/baseline visit will be listed and summarized for the safety population:

- Disease diagnosis (i.e., AML or MDS)
- Age. Age will be calculated as the number of years elapsed between birth date and the date of informed consent, adjusted for whether the birthday has passed as of the day of the screening visit. (This corresponds to the typical calculation of age a person would use in conversation.)
- Sex at birth
- Ethnicity
- Race
- Height
- Weight
- Body Mass Index (BMI)

AML Baseline Disease History. Baseline history will be summarized and listed.

- AML type
- Genetic Classification
- WHO Classification
- ECOG Performance Status

MDS Baseline Disease History. Baseline history will be summarized and listed.

- MDS type
- WHO Classification
- IPSS-R Risk
- IPSS Risk

Medical History. Medical Histories will be listed.

Prior Disease Treatment. Data from prior disease treatments will be summarized and listed:

- Prior Radiation Therapy
- Prior Cancer Related Surgeries/Procedures
- Prior Transplants
- Prior Cancer Chemotherapy

B. Disposition

Disposition. Patient disposition data will be summarized for the Safety Population by cohort. Summaries will include: the numbers of patients enrolled, the number of patients in each analysis population, and the number of patients that either completed

the study or prematurely withdrew from study participation. Treatment completion will be indicated by the response "Yes" (they completed their initially allowed cycles) on the End of Treatment form. Any other non-missing response on this form will be counted as a premature withdrawal.

Premature withdrawals from treatment in each cohort group will be further characterized as the number of patients who ended treatment of IMG-7289 prematurely and the number of patients who ended treatment of ATRA prematurely for each of the reasons listed in the eCRF End of Treatment (EOT) form and in the corresponding summary display shell.

Premature withdrawals from the study in each cohort group will be characterized as the number of patients who permanently discontinued from the study for each of the reasons listed in the eCRF Study Discontinuation (EOS) form and in the corresponding summary display shell.

C. Protocol Deviations

Protocol deviations and waivers will be provided in a listing.

VIII. Efficacy Analysis

A. Response

The primary objective, 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 with responses documented according to revised/modified International Working Group (IWG) Response Criteria – Cheson *et al.* 2003 for AML and Cheson *et al*. 2006 for MDS as described in Protocol Section 16.2. Response is to be assessed each time a bone marrow aspirate or biopsy is performed, with the exception of baseline. All available response data will be listed. The visit overall response per patient, as determined by the Investigator, and recorded on the eCRF, will be listed and summarized for each cohort, using the Efficacy Population.

The best response of each AML patient will be programmatically selected based on the following order: Complete Remission (CR), CR w/Incomplete Recovery (CRi), Morphologic Leukaemia-Free State (MLFS), Partial Remission (PR), Cytogenetic CR (CRc), Molecular CR (CRm), Stable Disease (SD), Resistant Disease (RD), Relapse (Rel), Progressive Disease (PD), Death from Indeterminate Cause (DInd), Death in Aplasia (DiA), and Not Evaluable. The best response of each MDS patient will be programmatically selected based on the following order: Complete Remission (CR), Partial Remission (PR), Marrow CR (CRm), Cytogenetic Response (CyR), Stable Disease (SD), Relapse After CR or PR (Rel), Disease Progression (DP), Failure: Disease Progression (FDP), Survival (Sur), Failure: Death During Treatment (FDDT), and Not Evaluable.

Objective response in AML includes Complete remission (CR), CR with incomplete recovery (CRi), Morphologic leukamia-free state, Partial remission (PR), Cytogenetic CR (CRc), and Molecular CR (CRm) and Stable Disease (SD); while objective response in MDS includes Complete remission (CR), Partial remission (PR), Marrow CR, or Cytogenetic response (CyR) and Stable Disease (SD). Objective response rate (ORR) is the proportion of responders with AML or MDS. ORR and its Fisher exact 95% confidence interval will be presented.

Additionally, the Kaplan-Meier method will be used to analyze event-free survival (EFS) and overall survival (OS); Summaries will present the number (%) of subjects with events, the number (%) of subjects without events (censored), the median (95% CI) survival, and the probability of 6-month survival. OS is defined as the time interval between treatment start date and death date, and OS will be censored at the last date known alive. EFS is defined as the time interval between the date of treatment start and date of resistance, relapse, progression, or death. For subjects that do not have an event, EFS will be censored at the date of last tumor assessment prior to any concurrent cancer chemotherapy and transfusion.

IX. Safety Analysis

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, laboratory values and ECGs as detailed below, using the Safety Population.

A. Adverse Events

The AEs reported on the eCRFs will be coded using the latest version of MedDRA available to the sponsor at the time of study initiation (up-versioning will not occur), associating lower-level terms with preferred terms and system organ classes (SOC) by the primary hierarchy. The tables will display counts and percentages of subjects who reported at least one AE in each system organ class represented in the AE data. Within each system organ class, the tables will display the counts and percentages of subjects reporting at least one AE, as designated by the preferred terms.

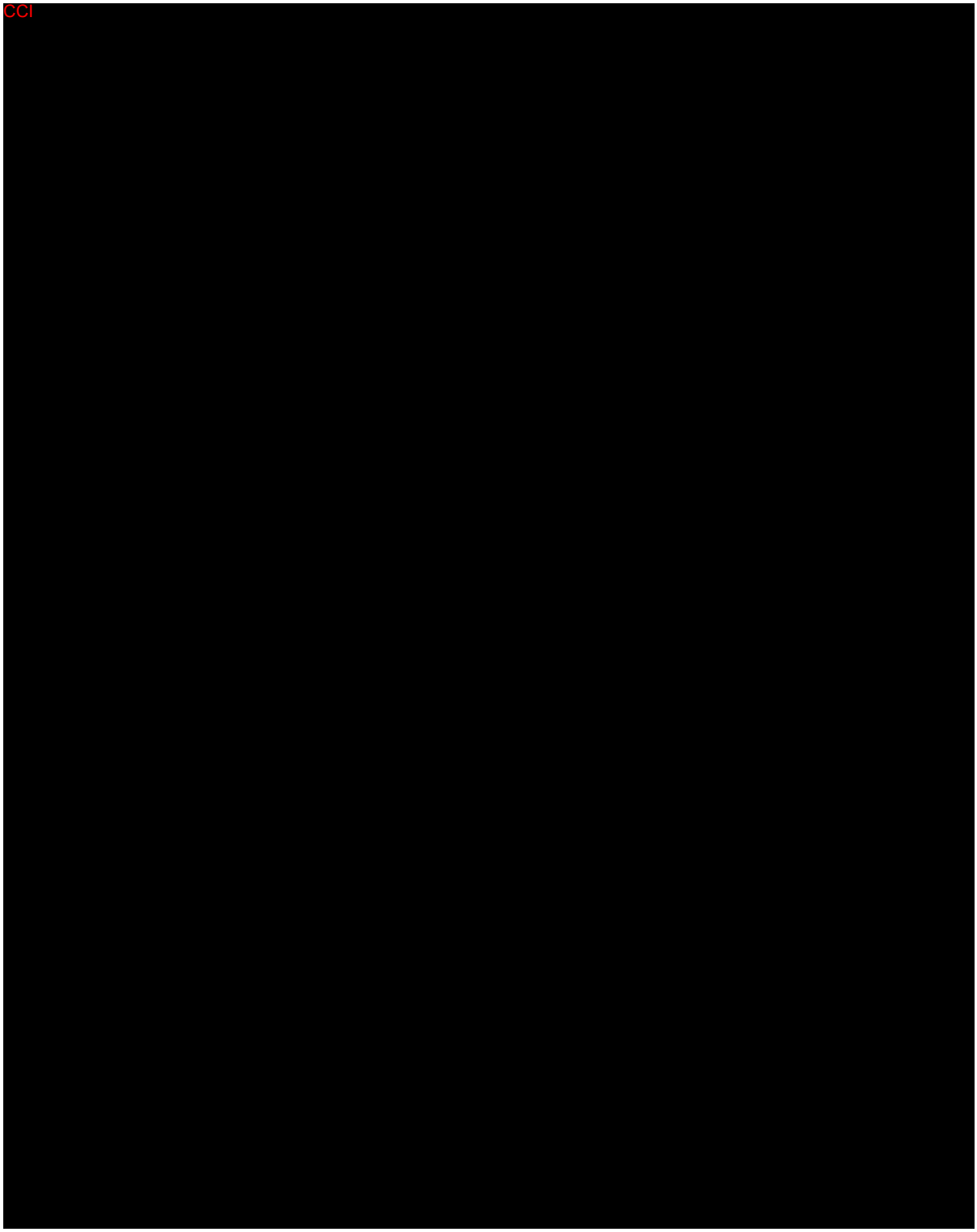
In any given category (e.g., SOC or preferred term) a patient will be counted only once. If a patient has the same AE on multiple occasions, only the highest toxicity grade will be used. Similarly, only the most related event will be used. Percentages will be based on the number of patients in the subgroup of patients being tabulated and not the number of events. Summaries that are displayed by system organ class and preferred terms will be ordered by descending order of incidence of system organ class and preferred term within each system organ class.

Treatment-emergent adverse events will be summarized. Only those events with an onset date on or after the date on which IMG-7289 was first dispensed, and within 28 days of last IMG-7289 treatment are to be recorded on the AE eCRF; therefore, all reported AEs are expected to be treatment-emergent. However, if eCRF completion

guidelines change, or are not followed adequately, treatment-emergent events will be identified programmatically per the above definition, using imputed start date.

Severity of AEs will be reported using the NCI CTCAE grades (v4.03) where Grade 1 is Mild, Grade 2 is Moderate, Grade 3 is Severe, Grade 4 is Life-Threatening, and Grade 5 is Fatal.

CCI



CCI [redacted]

B. Other Safety Parameters

Changes in vital signs, laboratory values and ECGs will also be evaluated and assessed. Information on the timing of these assessments is presented in Protocol 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
- ECGs

Laboratory values will be listed and summarized at each assessment. Numerical laboratory results will be summarized with the actual values, change from baseline (CFB), percent CFB by visit. P-value for test to assess maximum and minimum change from baseline within each cohort will be calculated using paired t-test.

Shift tables for laboratory values with respect to normal range (low, normal, high) and CTCAE toxicity grade, compared to baseline, will be summarized by visit. Overall laboratory result shift from baseline (Normal, Abnormal clinically significant (CS), and Abnormal non-clinically significant (NSC)) will be summarized.

ECG parameters and vital sign assessments will be summarized with the actual values, change from baseline, and percent change from baseline by visit. P-value for test to assess maximum and minimum change from baseline within each cohort will be calculated using paired t-test. Additionally, overall ECG result shift from baseline (Normal, Abnormal clinically significant (CS), and Abnormal non-clinically significant (NSC)) will be summarized.

Physical exam data will be listed.

X. Additional Analysis

The additional analyses outlined here will be performed using the Safety Population.

A. Pharmacodynamics

Pharmacodynamics (PD) obtained from serial blood, bone marrow, and urine sampling at specified time points will be listed and summarized. CCI [redacted]

CCI [redacted]

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CCI The assessment value, change from baseline and percentage change from baseline of these parameters will be summarized by each treatment cohort and visit. P-value for test to assess maximum and minimum change from baseline within each cohort will be calculated using paired t-test.

Additionally, maximum change from baseline, maximum percentage change from baseline, minimum change from baseline, and minimum percentage change from baseline for these parameters will be analyzed in the dose-finding cohorts separately. The treatment effect among different cohorts will be analyzed with Kruskal-Wallis tests.

B. Exposure

Exposure to IMG-7289 and ATRA will be summarized separately (i.e., by drug). Exposure will be summarized as the number of doses each patient received, as well as number of missed doses, along with the reasons for the missed doses (if feasible). Average number of cycles and total amount of time on study drug (duration of dosing in weeks) will also be summarized. Total cumulative dose, dose intensity (mg/-week, calculated as [total cumulative dose (mg-) / duration of dosing (weeks)]), and relative dose intensity (% of planned, calculated as [total cumulative dose / total planned dose] *100) will also be derived and summarized with descriptive statistics for IMG-7289 and ATRA separately.

Dose adjustments (increases and decreases), interruptions, and permanent drug withdrawals, along with corresponding reasons for each, will be summarized by study drug (IMG-7289 and ATRA).

Study drug accountability by dosage strength will be summarized based on the number of capsules of study drug (IMG-7289 or ATRA) dispensed and the number of capsules returned.

All exposure data will also be listed by cohort and patient.

C. Prior and Concomitant Medications

Prior medication is defined as any medication with a stop date prior to the date of first dose of IMG-7289. Concomitant medications are defined as medications or therapies with a start date on or after the first dose of IMG-7289. Medications may be flagged as both prior and concomitant if the start date is prior to the date of the first dose of IMG-7289 and the medication continued after the first dose of IMG-7289. The medications will be coded using the most updated version of WHO Drug at the time of study initiation (up-versioning will not occur) and will be listed by cohort and by patient. The number (%) of patients using prior, prior and concomitant, and concomitant medications will be summarized.

D. Prior and Concomitant Transfusions

Prior transfusions are defined as those with a transfusion start date from the 15 days prior to Screening up to the first IMG-7289 dose. Concomitant transfusions are defined as those with a transfusion start date on or after the date of the first IMG-7289 dose.

Prior and concomitant transfusions will be listed and summarized.

E. Prior and Concurrent Cancer Chemotherapy

Prior chemotherapy, which is ended before the first IMG-7289 dose, will be summarized with other prior treatment or therapy. Prior and concurrent chemotherapy will be listed by cohort and by patient.

XI. Pharmacokinetic Analyses

Pharmacokinetic data are not within the scope of this SAP. Analysis details are provided in the protocol and in a separate Pharmacokinetic Analysis Plan.

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