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Author(s) : PPD , Senior Biostatistician
PPD , Biostatistician II

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I confirm that I have reviewed this document and agree with the content.

APPROVALS	
Syneos Health	
PPD Authoring Biostatistician	*Electronically signed by:* PPD *Reason: I am the author* *Date: Dec 21, 2020 17:03 EST* **Date** (dd-Mmm-yyyy)
PPD Senior Biostatistician	
PPD Senior Reviewing Biostatistician	*Electronically signed by:* PPD *Reason: I am the approver* *Date: Dec 21, 2020 16:01 CST* **Date** (dd-Mmm-yyyy)
PPD Senior Biostatistician	
Imago BioScience, Inc	
PPD Senior VP of Clinical Operations	21-Dec-2020 **Date** (dd-Mmm-yyyy)

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1. Introduction

This Phase 2 multi-center, open-label study will evaluate the safety, efficacy and pharmacodynamics of IMG-7289, an irreversible inhibitor of the enzyme lysine-specific demethylase 1 (LSD1) when administered orally once daily in patients with essential thrombocythemia (ET). ET is an indolent hematologic cancer characterized by reduced quality of life, thrombocytosis, elevated cytokines, and increased rates of thrombosis and bleeding that can evolve to myelofibrosis and/or acute myeloid leukemia. LSD1 is an enzyme that regulates the maturation of megakaryocytes from progenitor cells, as well as the function of mature megakaryocytes. In ET, acquired mutations in hematopoietic stem cells cause JAK/STAT activation, which results in an over-abundance of activated megakaryocytes that in turn produce an excess of platelets, growth factors, and inflammatory cytokines.

2. Study Objectives

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

2.1 Primary Objectives

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

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[redacted]

3. Study Design

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

The therapeutic goal for the treatment of ET is to inhibit the activity of LSD1 in hematopoietic cells for only a fraction of the 24-hour dosing cycle, sufficient to reduce the production of platelets, whose over-production characterizes this condition. Considerations leading to the choice of a safe starting dose include chronic toxicology studies in conjunction with the clinical experience of the patients who have received IMG-7289 to date. Using all of the information available in conjunction with the therapeutic goal for the treatment of ET, an IMG-7289 starting dose of 0.6 mg/kg QD has been selected.

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

This study consists of 2 treatment periods: The Initial Treatment Period (ITP), followed by the Additional Treatment Period (ATP). In the ITP, patients will be treated daily for 169 days. In the ATP, which is iterative, treatment may continue for an additional 169 days in those patients deriving clinical benefit (defined as not meeting “progressive disease” criteria as per Appendix 16.5 in the Protocol) and safely tolerating IMG-7289; as determined by the Principal Investigator (PI).

All patients will undergo follow-up period visits, including an End-of-Treatment (EoT) visit on the day of last dose or as soon as possible thereafter, a pre-End-of-Study (EoS) visit approximately 7 days post last dose, and an End-of-Study (EoS) visit approximately 14 days post last dose. Patients that do not enter the ATP, or discontinue early, will undergo follow-up beginning with an EoT visit.

Patients will be followed closely throughout the study for both adverse events (AEs) and signs of toxicity by frequent monitoring of clinical signs and symptoms as well as safety laboratory parameters. Efficacy and pharmacodynamic effects will be closely monitored by frequent hematology assessments of peripheral blood, and requisite bone marrow aspirates and biopsies. Throughout dosing, transfusions may be administered if needed in accordance with standard institutional guidelines.

3.1 Initial Treatment Period (ITP)

Through the use of dose titration, the dose of IMG-7289 will be adjusted in each patient to that dose that provides sufficient exposure to safely inhibit thrombopoiesis for a fraction of the dosing cycle (designated as the D_{pi}). Treatment will begin on Day 1 at the IMG-7289 D_s of 0.6 mg/kg QD for all patients, with dose-titration contigent on the comparison of hematology values from the prior visit. **Up-titrations** may begin on ITP Day 28 and occur no more frequently than every 4 weeks from the previous up- or down-titration. **Down-titrations** can be made at any time in the best interest of the patient. Up-titrations will be made in increments of 0.2 mg/kg/d, and down-titrations in decrements of 0.1 or 0.15 mg/kg/d, as summarized in tabular form in Table 1.

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

3.2 Additional Treatment Period (ATP) for Qualifying Patients Only

In the ATP, treatment may continue for an additional 169 days in those patients deriving clinical benefit, as determined by the PI. For the purposes of clarity and efficiency, rather than continuing to present chronological days/weeks, visits are presented as 'ATP Day 1', followed by, 'ATP Days 29, 57, 85', etc. Qualifying patients will 're-start' IMG-7289 on ATP Day 1, with dose titration continuing as per the Titration and Re-challenge Rules (Table 1); there should be no interruption in dosing (Day 169 = Day 1 of the next ATP). Additional dose-titration may occur in consultation with the Medical Monitor.

Qualifying patients will return for study assessments monthly (ATP Days 1, 29, 57, 85, 113, 141 and 169). It is anticipated that patients continuing in the ATP will have already achieved a stable dose, with every other week visits no longer necessary. For safety purposes, every other week visits may continue at the

PI's discretion, if necessary. On Day 169 of every other ATP (i.e., ATP 2, 4, etc.), the equivalent of yearly, patients will undergo bone marrow sampling. At the Day 169 visit, a 'qualification' assessment will be made to determine whether the patient is continuing to derive clinical benefit. Such patients thereby qualify for re-entry into the ATP, which is iterative; patients may continue to receive IMG-7289 for as long as they continue to qualify. Patients not deriving clinical benefit will discontinue IMG-7289 and undergo EoT, pre-EoS, and EoS visits.

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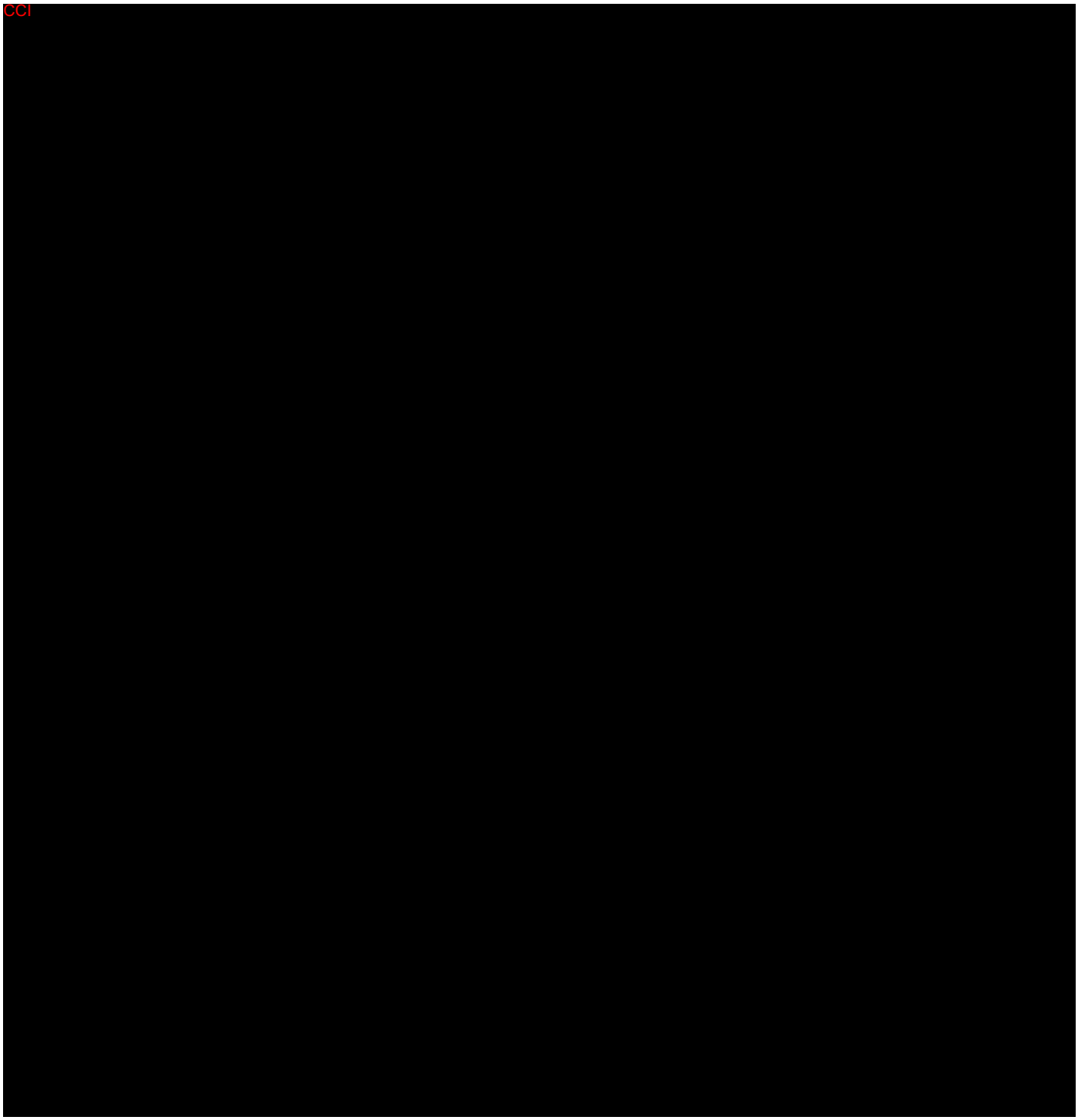

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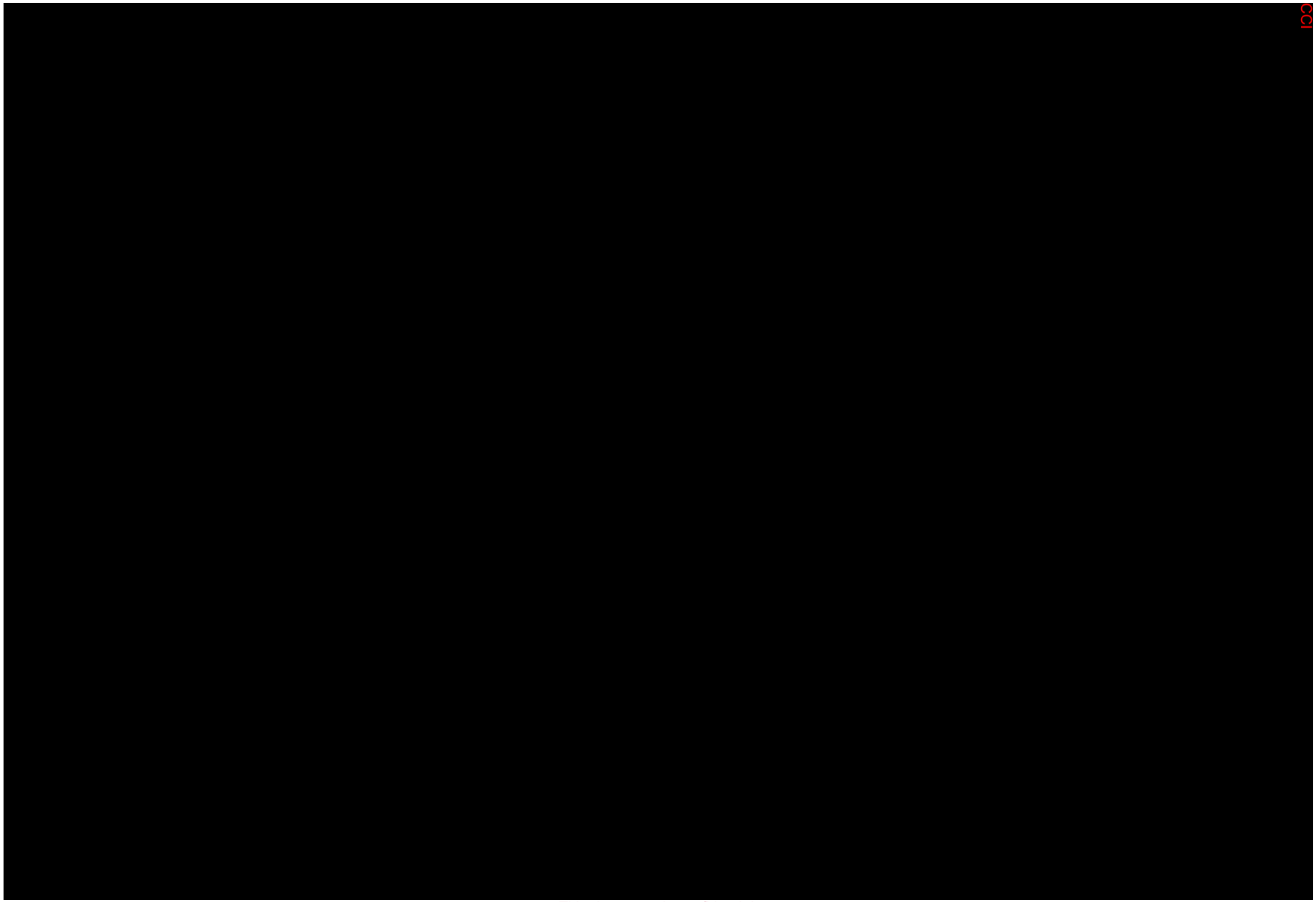

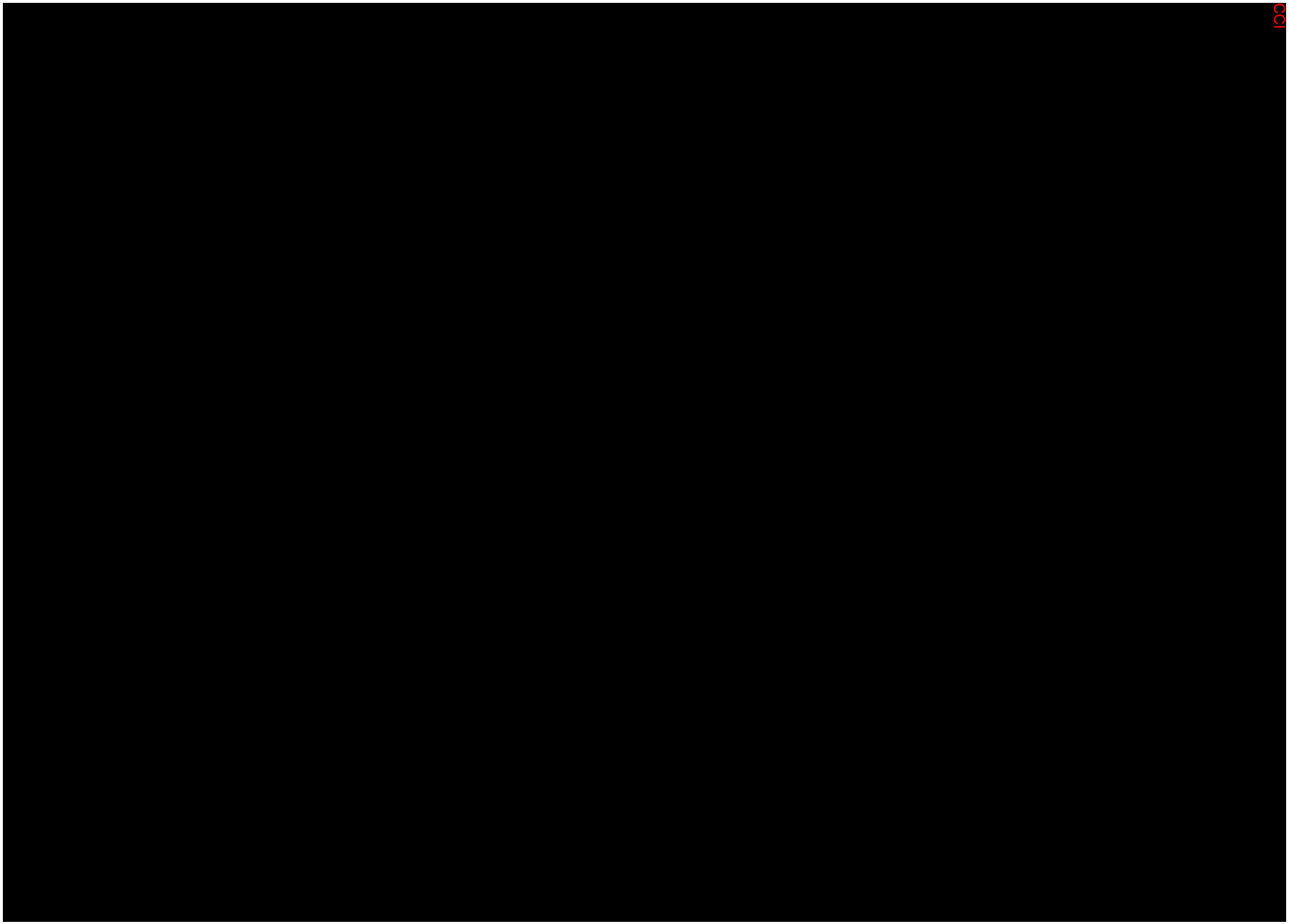

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5. Analysis Populations

The following subject populations (i.e., analysis sets) will be evaluated and used for presentation of the data.

5.1 Safety Population

The Safety Population will include all subjects who are enrolled in the study and receive at least 1 dose of study medication. Subjects will be analyzed according to treatment received in the study. The Safety Population will be used for all analyses of demographics, baseline characteristics, safety endpoints, and for subject disposition at the end of treatment. The Safety Population will be used for all data listings, with the exception of subject disposition at the end of study.

5.2 Modified Intent-to-Treat (mITT) Population

The mITT Population will include all subjects who are enrolled in the study, receive at least 1 dose of study medication, and who have a non-missing baseline and at least 1 non-missing post-baseline efficacy assessment. Subjects will be analyzed according to treatment received in the study. The mITT Population will be used for all analyses of efficacy and pharmacodynamic endpoints.

CCI

6. Statistical Methodology

6.1 Statistical and Analytical Issues

6.1.1 Statistical Methods

Tabulations will be produced for appropriate demographic, baseline, safety, pharmacodynamic, and efficacy parameters. CCI [redacted]

By-subject data listings will be produced for data collected throughout the study. CCI [redacted]

Statistical analyses will be carried out by using SAS Version 9.4 or higher. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the Clinical Study Report (CSR).

Adverse events will be graded by the Investigator based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5, and will be coded for summarization using the Medical Dictionary for Regulatory Activities (MedDRA® Version 23.0 or later). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (Global B3 March 2020 version or later).

6.1.1.1 Dose and Study Part

Many analyses will be presented by treatment period (ITP and ATP). Analyses on the ITP, ATP and overall will be presented.

Data listings will be presented overall.

Details regarding the presentation of the individual analyses will be described in the relevant sections of this SAP.

6.1.1.2 Visit Windows

All data will be tabulated per the evaluation visit as recorded on the eCRF, even if the assessment is outside of the visit window. Unless otherwise stated in the analysis sections below, unscheduled visits and data collected at suspected relapse will be included in data listings only.

6.1.2 Handling of Dropouts and Missing Data

6.1.2.1 Last Observation Carried Forward

For the following endpoints, both as-observed analyses and imputed analyses will be performed. Missing data, including those not obtained because of death, will be imputed using the last observation carried forward (LOCF) method, up until the end of the given treatment period:

- MPN-SAF Total Symptom Score: CCI [redacted]
- Quality of Life (QoL): CCI [redacted]
- Spleen size by physical examination

CCI [redacted]

CCI [redacted]

CCI [redacted]

6.1.3 Pooling of Investigative Sites

No by-site analyses are planned.

6.1.4 Determination of Sample Size

This study is designed to make an assessment of the safety, tolerability, and efficacy of IMG-7289 for the treatment of essential thrombocythemia. This is a single-arm trial with a primary endpoint that is a proportion variable (proportion of subjects who achieve a reduction in the platelet count to ≤400 k/μL in the absence of new thromboembolic events). The test of significance is a 1-sided test at the alpha=0.025 level of significance (equivalent to a 2-sided test at the alpha=0.05 level of significance).CCI [redacted]

CCI [redacted]

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

6.2 Subject Characteristics

6.2.1 Subject Disposition

Subject disposition at EoS will be summarized for all subjects and presented overall. CCI

[redacted]

CCI

[redacted]

6.2.3 Background and Demographic Characteristics

Demographics and baseline characteristics will be summarized overall on the Safety Population. CCI [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Unless otherwise stated, percentages will be calculated based on the number of subjects in the Safety Population.

CCI [redacted]

6.2.4 Treatment Exposure and Compliance

Study drug exposure will be presented cumulatively by treatment period, summarizing overall for both the ITP and ATP. The number of days dosed will be summarized by treatment period using both continuous CCI [redacted] n addition, the total cumulative dose (mg) received and the duration of exposure will be summarized by treatment period and overall. CCI [redacted]

Study drug compliance will be presented for each scheduled study visit, presented by treatment period. CCI [redacted]

- [redacted]
- [redacted]

CCI [redacted]

6.2.5 Prior and Concomitant Medications

Prior medication will be defined as any medication with a start date prior to the date of first dose of study drug. Concomitant medication is defined as any medication that is ongoing or has a stop date on or after the first dose date of study drug. Medications can be classified in both categories if the start date is prior to the date of the first dose of study treatment and the medication continued after the first dose of study treatment.

CCI [redacted]

Prior and concomitant medications will be coded using the WHO Drug Dictionary, and subject incidence will be tabulated by Anatomic Therapeutic Class (ATC) and preferred term (PT) on the Safety Population. CCI [redacted] Summaries will be presented overall for prior and concomitant medications separately.

CCI [redacted]

CCI [redacted]

6.2.6 Medical and Surgical History (Non-Cancer Related)

Medical and surgical history (non-cancer related) will be coded using MedDRA and listed only on the Safety Population. CCI [redacted]

6.2.7 Disease History and Treatment

Descriptive statistics of disease history characteristics will be presented overall on the Safety Population CCI [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

CCI [redacted]

6.3 Efficacy Analysis

All efficacy analyses will be performed using the mITT Population. CCI [redacted] Summaries will be presented overall for the ITP and ATP, unless otherwise noted below.

6.3.1 Primary Efficacy Analysis

The primary efficacy objective for this study is to evaluate the reduction of platelet counts to ≤ 400 k/μL (400 x 10^9/L) in the absence of new thromboembolic events. The reduction of platelet counts will be evaluated and assessed based on local laboratory measurements of platelet counts from Day 1 to each visit where platelets are measured CCI [redacted]

The primary efficacy endpoint is the proportion of subjects who achieve a reduction of platelet counts to ≤ 400 k/μL (400 x 10^9/L) in the absence of new thromboembolic events. This endpoint will be analyzed using an exact 1-sample binomial test. The proportions and corresponding 95% confidence intervals (CIs) based on the Clopper-Pearson method will be presented for each post-baseline study visit on the mITT Population. 2-sided *p*-values will be calculated for the Day 169 visit to test the null hypothesis assuming that the test statistic follows an exact binomial distribution.

The null hypothesis tested for the primary efficacy endpoint is that the true response rate is 5%, where the response rate is defined as the proportion of subjects who achieve a reduction of platelet counts to ≤ 400 k/μL (400 x 10^9/L) in the absence of new thromboembolic events. The corresponding alternative hypothesis is that the true response rate is not 5%. The primary efficacy endpoint will be achieved if the null hypothesis is rejected at the 0.05 alpha level in favor of a higher (> 5%) response rate.

CCI [redacted]

CCI [redacted]

6.3.2 ECOG Performance Status

CCI [redacted]

[redacted] The frequency distribution of ECOG performance status at baseline (Screening) and the changes from baseline will be presented for each visit by treatment period.

CCI [redacted]

CCI [redacted]

6.4 Safety Analysis

For this study, the primary objectives involve safety and tolerability. The safety and tolerability of IMG-7289 will be assessed by the analysis of adverse events (AEs), as well as changes in physical examinations, vital signs and laboratory values as detailed below. All safety analyses will be performed using the Safety Population. Summaries will be presented overall for the ITP and ATP, unless otherwise noted below. All CCI [redacted]

6.4.1 Adverse Events

CCI [redacted] AEs will be assessed post-first dose until 14 days post-last dose (Note for UK: Non-serious AEs will be assessed post-first dose, and SAEs post-consent, until 14 days post-last dose). Adverse events will be graded according to the NCI CTCAE Version 5, coded using the MedDRA coding system, and displayed in tables and data listings by system organ class (SOC) and preferred term (PT).

Analyses of AEs will be performed for those events that are considered treatment-emergent. A treatment-emergent AE (TEAE) is defined as any AE occurring or worsening after the first dose of study drug on Day 1 through the end of the study CCI [redacted]

An overall TEAE incidence summary table will be produced and presented by treatment period, CCI [redacted]

- [redacted]

CCI [redacted]

Tabulations by SOC and PT will be produced for all TEAEs, TEAEs related to study drug, serious TEAEs, serious TEAEs related to study drug, TEAEs classified as DLTs (applicable for ITP only), TEAEs leading to study drug withdrawal, TEAEs leading to study discontinuation, TEAEs leading to death, and TEAEs by maximum severity.

CCI [redacted]

AE analyses by SOC and PT will be presented by treatment period.

No formal hypothesis-testing analysis of AE incidence rates will be performed. CCI [redacted]

CCI [redacted]

CCI [redacted]

Physical examination findings will be summarized on the Safety Population by means of a shift table from baseline (Screening/Day 1 pre-dose) until EoS/Early Termination for each body system. Summaries will be presented by treatment period CCI [redacted]

CCI [redacted]

6.4.3 Vital Signs

The actual value and change from baseline (Screening/Day 1 pre-dose) to each post-baseline visit until EoS/Early Termination will be descriptively summarized by visit on the Safety Population. CCI [redacted]. Summaries will be presented by treatment period and sorted by study visit.

CCI [redacted]

6.4.4 Laboratory Parameters

The absolute values and change from baseline (Screening/Day 1 pre-dose) to each post-baseline visit until EoS/Early Termination for each laboratory parameter CCI [redacted] will be descriptively summarized on the Safety Population. Summaries will be presented by treatment period CCI [redacted].

All laboratory values will be categorized according to their normal ranges, where normal ranges exist. Shift tables from baseline will present the frequency counts and percentages of subjects CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

CCI

[redacted]

6.4.6 Pharmacodynamic Analysis

All pharmacodynamic analyses will be performed using the mITT Population. Summaries will be presented overall for the ITP and ATP. CCI [redacted].

CCI

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CCI

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[redacted]

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[redacted]

CCI

[redacted]

6.7 Data Monitoring Committee

To ensure patient safety, in accordance with a SAB Monitoring Plan (SABMP), a SAB will perform reviews at least quarterly of safety parameters and pharmacodynamic markers to draw conclusions around the safety and pharmacodynamic effect of IMG 7289. The SAB will also review patient dose titrations and may recommend adjustments.

6.8 Changes to Methods Planned in the Protocol

There are no changes in the planned methods in the SAP from those outlined in the protocol.

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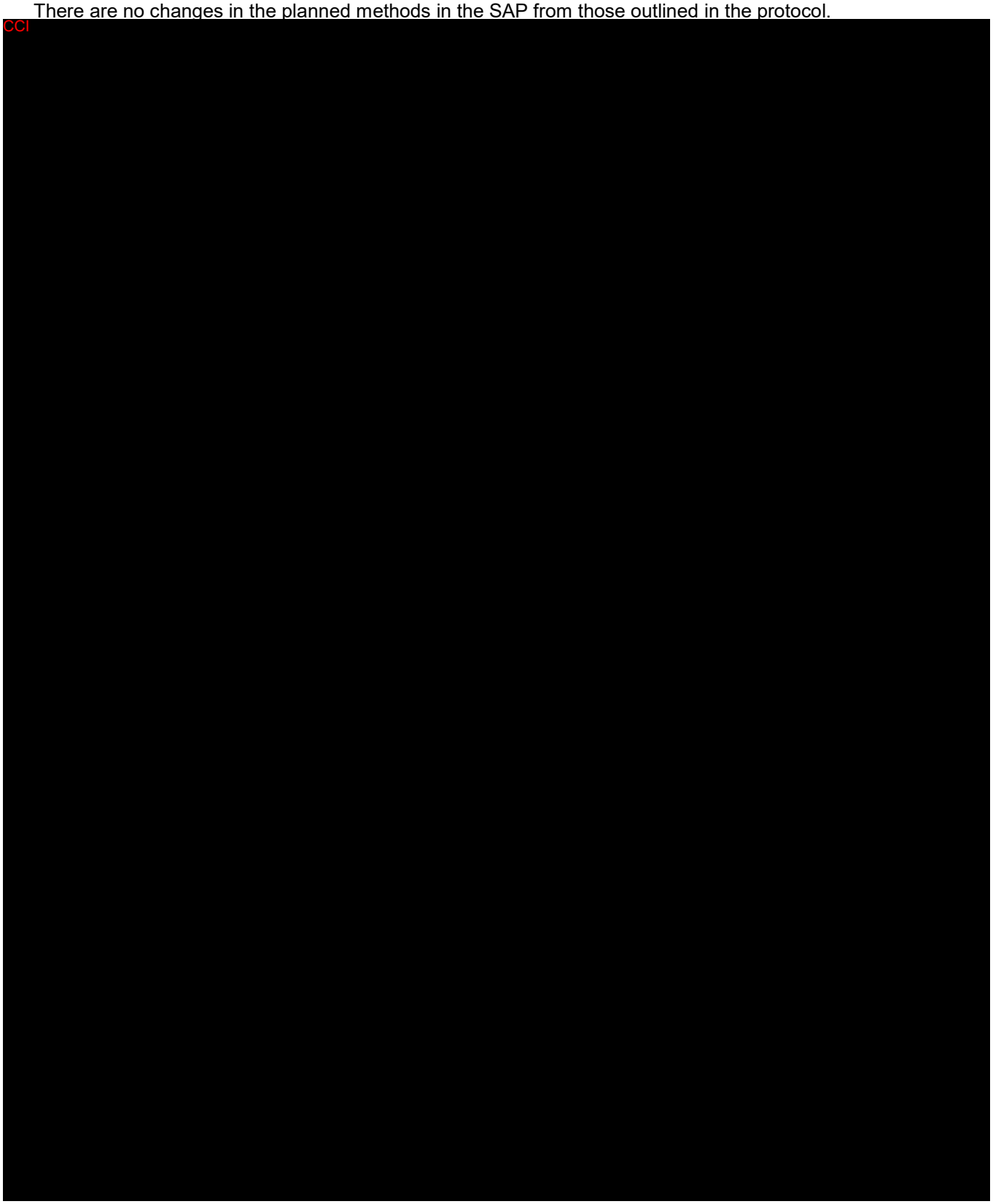

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8. References

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