STATISTICAL ANALYSIS PLAN

A RANDOMIZED, OPEN LABEL, PHASE 2 STUDY OF THE SELECTIVE INHIBITOR OF NUCLEAR EXPORT (SINE) SELINEXOR (KPT-330) VERSUS SPECIFIED PHYSICIAN'S CHOICE IN PATIENTS ≥ 60 YEARS OLD WITH RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA (AML) WHO ARE INELIGIBLE FOR INTENSIVE CHEMOTHERAPY AND/OR TRANSPLANTATION

SOPRA Study: Selinexor (KPT-330) in Older Patients with Relapsed AML

PROTOCOL KCP-330-008

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Protocol Version and Date:	Amendment 5: 04 August 2015, Version 5.0 Amendment 4.1: 09 July 2015, Version 4.1 (Germany specific) Amendment 4: 24 April 2015, Version 4.0 Amendment 3: 25 November 2014, Version 3.0 Amendment 2: 30 September 2014, Version 2.1 (United Kingdom specific) Amendment 1: 03 July 2014, Version 2.0 Original: 21 January 2014, Version 1.0
Name of Test Drug:	Selinexor (KPT-330)
Phase:	Phase 2
Methodology:	Randomized, Open-label, Multicenter
Sponsor:	Karyopharm Therapeutics Inc. 85 Wells Ave. Newton MA 02459 Tel: +1-617-658-0557 Fax: +1-504-975-4833
Sponsor Representative:	PPI PPI
Analysis Plan Date:	30 September 2016
Analysis Plan Version:	Version 1.0

APPROVAL SIGNATURE PAGE

Protocol Title: A Randomized, Open Label, Phase 2 Study of the Selective Inhibitor of Nuclear Export (SINE) Selinexor (KPT-330) versus Specified Physician's Choice in Patients ≥ 60 Years Old with Relapsed/Refractory Acute Myeloid Leukemia (AML) Who are Ineligible for Intensive Chemotherapy and/or Transplantation

SOPRA Study: Selinexor (KPT-330) in Older Patients with Relapsed AML

Sponsor: Karyopharm Therapeutics Inc.
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Protocol Number: KCP-330-008

Document Date / Version: 30 September 2016 / Version 1.0

Reviewing Statistician:

PPI

PPI to Karyopharm Therapeutics

Signature: PPI _____

Date: _____

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the statistical consultant.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

PPI

Karyopharm Therapeutics Inc.

Signature: PPI _____

Date: PPI _____

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AML	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
ATC	Anatomic Therapeutic Class
BSA	Body surface area
BSC	Best supportive care
CI	Confidence interval
CMH	Cochrane-Mantel-Haenszel
CR	Complete remission
CRi	Complete remission with incomplete hematologic recovery
CRO	Contract research organization
CRp	Complete remission with incomplete platelet recovery
CRR	Complete remission rate
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DFS	Disease free survival
DOR	Duration of overall response
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EQ-5D-5L	European Quality of Life Five Dimension Five Level Scale
EWB	Emotional well-being
FACT-G	Functional Assessment of Cancer Therapy
FACT-Leukemia	Functional Assessment of Cancer Therapy – Leukemia
FWB	Functional well-being
HR	Hazard ratio
ICH	International Conference on Harmonisation
IN	Inevaluable
INR	International normalization ratio
ITT	Intent-to-treat
IWG	International Working Group
KM	Kaplan-Meier
LD-AraC	Low-dose Cytidine Arabinoside
mCRR	Modified complete remission rate

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic leukemia-free state
MMRM	Mixed-model repeated-measures analysis of variance
ORR	Overall response rate
OS	Overall survival
PC	Physician's choice
PD	Disease progression
PDn	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-protocol
PR	Partial remission
PWB	Physical well-being
QoL	Quality of life
RBC	Red Blood Cell
Rel Day	Relative study day
RTSM	Randomization and trial supply management
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SCT	Stem cell transplantation
SD	Stable disease
SI	International System of Units
SINE	Selective Inhibitor of Nuclear Export
SOC	System Organ Class
Std Dev	Standard deviation
SWB	Social/family well-being
TEAE	Treatment-emergent adverse event
TOI	Trial Outcomes Index
WBC	White Blood Cell (count)
WHO	World Health Organization
XPO1	Exportin 1

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults, accounting for over 80% of all acute leukemias in individuals aged > 18 years (Thein 2013). AML is predominantly a disease of older adults, with a median age at diagnosis of over 65 years (Motyckova 2011). For the growing number of older patients with AML where intensive chemotherapy is associated with unacceptable mortality, therapeutic options are severely limited and median overall survival (OS) is < 1 year (Yanada 2012). Single agent 'low-dose' cytidine arabinoside (LD-AraC) is the only agent to show a clear reduction in mortality in this population of AML patients. Despite some increases in response rates, no other agent has shown a clear improvement in OS in this population, where both efficacy and low rates of side effects are critical (Burnett 2013).

Selinexor is a first in class Selective Inhibitor of Nuclear Export (SINE) that specifically blocks the karyopherin protein Exportin 1 (XPO1, also called CRM1). Selinexor (oral) has shown single-agent, durable, anti-cancer activity in patients with multiple relapsed or refractory hematologic and solid tumor malignancies in initial Phase 1 dose escalation studies. Elderly patients (median age 68 years) with heavily pretreated AML whose life expectancy is very short were included in the initial phase 1 studies, and durable complete remission (CR), complete remission with incomplete hematologic recovery (CRi), partial remission (PR) and stable disease (SD) were observed in these patients. With standard supportive care for selinexor-induced anorexia and fatigue, long-term tolerability has been adequate with no acute toxicities or major organ damage, even in patients > 70 years of age. Therefore, oral selinexor may represent a novel treatment for AML in this difficult-to-treat population.

This randomized, open label study has been designed to assess whether oral, single agent selinexor can improve OS in patients with relapsed or refractory AML who are not candidates for intensive chemotherapy or stem cell transplantation (SCT).

Further information about the preclinical and clinical characteristics of selinexor may be found in the Investigator's Brochure.

1.1.2. Study Objectives

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data in order to answer the study objective(s). Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.1.3. Primary Objective

The primary objective of the study is to determine OS of selinexor as compared to physician's choice (PC) in patients ≥ 60 years old with relapsed/refractory AML that requires treatment and are ineligible for intensive chemotherapy and/or transplantation.

1.1.4. Secondary Objectives

The secondary objects of the study are to:

- Determine the proportion of patients whose OS is at least 3 months (OS3.0)
- Determine the complete remission rate (CRR) per the International Working Group (IWG) criteria (Cheson 2003), including CR, and median disease free survival (DFS) for patients who achieve CR
- Determine the modified CRR (mCRR), including CR or CRi (including complete remission with incomplete platelet recovery [CRp]), and median DFS for patients who achieve CR or CRi (including CRp)
- Determine the overall response rate (ORR) and duration of overall response (DOR), including CR, CRi, morphologic leukemia-free state (MLFS), and PR
- Determine the disease control rate (DCR) defined as ORR + SD for ≥ 4 weeks, and duration of DCR
- Assess the general safety and tolerability of selinexor (KPT-330), as compared to PC, as well as incidence of common and expected adverse events (AEs)
- Assess quality of life (QoL) and patient reported outcomes (Functional Assessment of Cancer Therapy [FACT] - Leukemia, European Quality of Life Five Dimension Five Level Scale [EQ-5D-5L])

1.2. Study Design

1.2.1. Synopsis of Study Design

This is a randomized, multicenter, open-label, Phase 2 study of the SINE compound selinexor given orally versus restricted physician choice (i.e., one of three potential salvage therapy combinations).

Patients who have relapsed or refractory AML (except Acute Promyelocytic Leukemia: APL, AML M3), after at least one prior AML therapy (must have included an adequate trial of a hypomethylating agent with at least 2 cycles), are ≥ 60 years old, have never been transplant eligible, are currently deemed unfit for intensive chemotherapy, have poor prognosis (intermediate or adverse risk) cytogenetics, and meet the inclusion and exclusion criteria will be randomized to receive either oral selinexor or PC (one of three potential salvage therapy combinations: best supportive care [BSC] alone, BSC + low dose AraC, or BSC + hypomethylating agent) until disease progression, death, or intolerance has occurred.

Due to a possible increase in sepsis related serious adverse events (SAEs) for selinexor (dose equivalent to ~55 mg/m^2, 8 sepsis events) versus PC (2 sepsis events) that was detected during an annual review of clinical safety data (29 July 2015), the selinexor dose was reduced to a 60 mg flat dose (equivalent to ~35mg/m^2). Clinical safety data supporting the 60 mg fixed dose are provided in Protocol Section 4.3.1.1. As a result, 2 separate cohorts will be randomized in a 2:1 allocation within strata to either selinexor or PC.

1) Protocol Versions < 5.0: As of 18 November 2015, approximately 141 patients have been randomized under Protocol Versions < 5.0 to either selinexor ~55 mg/m^2 or PC. Enrollment will continue under Protocol Version 4.0 at each site until Protocol Version 5.0 is approved by the local IRB, and patients randomized to the selinexor arm will be prescribed the updated fixed dose of 60 mg. Patients in this cohort are randomized in a 2:1 ratio to selinexor or PC, stratified by two stratification factors: (1) duration of their first CR on prior therapy, > 1 year versus ≤ 1 year or never achieved CR; (2) age < 70 years versus age ≥ 70 years.
2) Protocol Version 5.0: Under Protocol Version 5.0, approximately 171 additional patients will be randomized to either 60 mg of selinexor (fixed dose) or PC. Patients will be randomized in a 2:1 ratio, stratified by three stratification factors: (1) duration of their first CR on prior therapy, > 6 months versus ≤ 6 months or never achieved CR; (2) number of prior therapies, 1 versus > 1; (3) peripheral leukemic blast counts ≥ 10,000/μL versus < 10,000/μL.

The targeted sample size is 300 patients overall.

Test Product, Dose, and Mode of Administration:

Under Protocol Versions < 5.0, selinexor is administered orally twice weekly (i.e. Monday and Wednesday, Tuesday and Thursday, or Wednesday and Friday) at a dose of 60-120 mg based on body surface area (BSA) as described in Table 1.1, (~55 mg/m^2)

Table 1.1 Selinexor Dose (mg) Based on BSA

BSA (m^2)	Dose (mg)
< 1.4	60
≥ 1.4 and < 1.8	80
≥ 1.8 and < 2.2	100
≥ 2.2	120

Under Protocol Version 5.0, selinexor will be administered orally twice weekly (i.e. Monday and Wednesday, Tuesday and Thursday, or Wednesday and Friday) at a fixed dose of 60 mg (equivalent to ~35 mg/m^2). As of 29 July 2015, all patients who were randomized to selinexor (~55 mg/m^2) under previous protocol versions were switched to the 60 mg fixed dose.

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted as described in Protocol Section 12.3.

Reference Therapy, Dose, and Mode of Administration:

For patients randomized to the PC treatment group, one of the following three salvage therapy combinations will be selected by the treating physician:

1) BSC alone: blood product transfusions, antimicrobials, growth factors as needed, and hydroxyurea
2) BSC + low dose AraC: 20 mg twice daily by subcutaneous (SC) injection daily on Days 1-10/14 days (20/28 doses) to be repeated at 28 to 42 day intervals

3) BSC + hypomethylating agent: azacitidine 75 mg/m^2 by SC injection daily on Days 1-7 or Days 1-5, 8-9 (7 doses) to be repeated at ≥28 day intervals, *or* decitabine (20 mg/m^2 IV over 1 hour daily on Days 1-5 or Days 1-10 to be repeated at ≥28 day intervals)

Treatment with selinexor or PC will continue until the Investigator removes a patient from study treatment for the reasons specified in Section 1.2.3.2 (Protocol Section 11.2). As OS is the primary endpoint of this study, crossover onto selinexor from the PC treatment group is not permitted. Patients can receive appropriate anti-leukemia therapy following discontinuation of study treatment.

Concomitant Medications:

Patients may continue their baseline medication(s) while on-study. Patients will receive concomitant medications to treat symptoms, AEs, and intercurrent illnesses that are medically necessary as standard care. Medications to treat concomitant diseases like diabetes, hypertension, etc., are allowed, as is concurrent therapy with glucocorticoids and hydroxyurea. Patients are instructed to minimize the use of products containing acetaminophen (paracetamol) on the days of selinexor dosing.

In order to minimize nausea, unless contraindicated, all patients must receive 5-HT3 antagonists (ondansetron 8 mg or equivalent) before the first dose of selinexor and continued two - three times a day as needed. In addition, aggressive use of other supportive care including anti-nausea/anti-emetic therapy, appetite stimulants, acid suppression (proton pump inhibitors and/or H2-blockers) and other treatments is strongly recommended.

Concurrent therapy with any other approved or investigative anticancer therapeutic is not allowed in either treatment group, neither is any other investigational agent. Use of any immunosuppressive agents during the study must be confirmed by the Medical Monitor. Use of concomitant medications and treatments is further described in Protocol Sections 12.3.2 and 12.3.3.

1.2.2. Randomization Methodology

Study treatment will be administered in a non-blinded, open-label manner. Randomization will be performed centrally using a randomization and trial supply management (RTSM) system, and patients will be randomized with a 2:1 allocation to receive selinexor or PC.

Prior to Protocol Version 5.0, the randomization will be stratified using two stratification factors: (1) duration of their first CR on prior therapy, ≤ 1 year (including no CR on prior therapy) versus > 1 year; (2) age < 70 versus age ≥ 70 years.

Under Protocol Version 5.0, the randomization will be stratified using three stratification factors: (1) duration of their first CR on prior therapy, ≤ 6 months (including no CR on prior therapy) versus > 6 months; (2) number of prior therapies, 1 versus > 1; (3) peripheral leukemic blast counts ≥10,000/μL versus <10,000/μL.

The randomization process will maintain the 2:1 allocation between treatment groups within each of the stratification categories. The total number of patients enrolled within a randomization stratum will not be restricted overall or by site.

Any patient randomized into this trial cannot be re-randomized for any reason (i.e. a patient will only be randomized once).

1.2.3. Stopping Rules

1.2.3.1. Discontinuation of the Study

The study may be discontinued at the sole discretion of the sponsor for any reason, including medical or ethical reasons affecting the continued performance of the study, or difficulties in the recruitment of patients. The results of the interim analyses, to take place after approximately one-quarter and one-half the required number of OS events have occurred, may result in a statistical conclusion of futility, and this would be taken into consideration in the decision to potentially stop the trial.

1.2.3.2. Discontinuation of Individual Patients

An Investigator may remove a patient from study treatment at his or her discretion for the following reasons:

- Disease progression defined as an increase in blast counts and absence of hematologic recovery (one or more lineages)
- Unacceptable AEs or failure to tolerate the study treatment
- Patient decides to discontinue study therapy
- Significant deviation from entry criteria (e.g. non-relapsed or non-refractory AML)
- Misuse of study medication (e.g., deliberate overdosing by patient)
- Missed / unscheduled / off-schedule / incomplete / incorrect assessments that result in patients being put at risk
- Any other medically appropriate reason or significant protocol violation, in the opinion of the investigator.

The investigator must determine the primary reason for a patient's discontinuation of study treatment and record this information on the electronic case report form (eCRF). Patients who are prematurely withdrawn from study treatment are not eligible to re-initiate study treatment at a later date.

Patients may decide to discontinue study treatment for any reason. Patients who elect to discontinue study treatment should be encouraged to continue in the study so that follow-up information on disease progression and survival status may be obtained. However, patients may elect to withdraw consent and decline further participation in the trial.

Patients will be followed for survival until the last patient has been followed for 6 months from the end of treatment, disease progression, another withdrawal criterion is met, or until death, whichever occurs first.

1.2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1-2.

Table 1-2 Schedule of Assessments

	Screening		Cycle 1	Cycles 1-3	Cycles 2-5		Cycle ≥ 6	Final Visit	30 Day Safety Follow-up[27]	Survival Follow-up[28]
					Cycle 2-5	Cycle 2 Only				
	Within 14 days prior to start of therapy	Within 7 days prior to start of therapy	Day 1 of each week	Day 4 of each week[25]	Days 1 & Day 15	Day 8 & Day 22	Day 1	≤30 days after last dose		
Visit window [days]			± 1 day	+ 1 day	± 2 days	± 2 days	± 2 days	± 7 days	± 7 days	
Study Visit Number	**Visit 1**	**Visit 2**	**Visits 3, 5, 6, & 7**	**Visit 4 (C1D4)/ Weekly Phone Call**	**Visits 8, 10, 12-17**	**Visits 9 & 11**	**Visits 18+**	**In Clinic**	**Clinic or Phone**	**Phone**
Informed consent[1]	X									
Inclusion and exclusion criteria		X								
Demographics	X									
Medical History[2]	X									
Randomization[3]			X[3]							
Body height and weight[4]		X	X		X		X	X		
BSA[5]		X	X		X		X			
Vital signs[6]		X	X		X	X	X	X		
Physical examination and ECOG[7]		X	X		X		X	X		
Baseline Symptoms	X	X								
Disease risk assessment (Visit 1 or 2)	X									
Ophthalmic exam[8]	X							X		
Oxygen saturation[9]		X	X		X		X	X		
12-lead ECG[10]	X		X		X		X	X		
Urine analysis[11]		X	X		X		X	X		
Hematology (CBC with differential)[12]		X	X		X	X[26]	X	X		
Complete Serum chemistry[13]		X	X			X[26]		X		
Limited Serum chemistry[14]					X		X			
Coagulation test (PT, PTT or TT) [15]		X	X		X		X			
Bone marrow aspirate (assessment of disease status and correlative studies)[16]		X (8-14 days prior to 1st dose if approved by sponsor[16])			X (Day 1 Cycle 2 and as clinically indicated)		X (if clinically indicated)			

	Screening		Cycle 1	Cycles 1-3	Cycles 2-5		Cycle ≥ 6	Final Visit	30 Day Safety Follow-up[27]	Survival Follow-up[28]
					Cycle 2-5	Cycle 2 Only				
	Within 14 days prior to start of therapy	Within 7 days prior to start of therapy	Day 1 of each week	Day 4 of each week[25]	Days 1 & Day 15	Day 8 & Day 22	Day 1	≤30 days after last dose		
Visit window [days]			± 1 day	+ 1 day	± 2 days	± 2 days	± 2 days	± 7 days	± 7 days	
Study Visit Number	**Visit 1**	**Visit 2**	**Visits 3, 5, 6, & 7**	**Visit 4 (C1D4)/ Weekly Phone Call**	**Visits 8, 10, 12-17**	**Visits 9 & 11**	**Visits 18+**	**In Clinic**	**Clinic or Phone**	**Phone**
Chest radiograph[17]	X									
Selinexor dosing in clinic[18]			X		X	X	X			
Blood draws for pharmacokinetic (PK) testing[19]			X		X		X			
CCI										
Blood draw for correlative studies using peripheral blasts[21]		X			X					
FACT-Leu and EQ-5D-5L QoL questionnaires[22]			X (Week 1 Only)		X (Day 1 only)		X	X		
Nutritional consultation[23]			X							
Review of Temperature Diary[24]			X (Weeks 2-4 Only)	X	X	X	X	X		
Adverse events			X	X	X	X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	X		
Collect information regarding antineoplastic therapy after end of selinexor or PC treatment								X	X	X

Note: 28 days per cycle. C= Cycle. D = Day. BSA = Body Surface Area; ECOG = Eastern Cooperative Oncology Group; PT = Prothrombin Time; PTT = Partial Thromboplastin Time; FACT-Leu = Functional Assessment of Cancer Therapy - Leukemia; QoL = Quality of Life.

[1] Prior to the first study-specific measures

[2] Medical history includes baseline symptoms as well as a detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.

[3] Randomization must occur ≤3 calendar days of Cycle 1 Day 1.

[4] Body height will be measured at screening only

[5] Body Surface Area (BSA) calculated by Dubois (Dubois and Dubois, 1916) or Mosteller (Mosteller, 1987) method.

[6] Vital signs: blood pressure, pulse and temperature
[7] Full physical examination for baseline and end of study visit. Physical examinations during the study should be symptom-directed.
[8] Full ophthalmic examination will be conducted on all patients by an optometrist or ophthalmologist at screening, as clinically indicated during the study and at the Final Visit. The full ophthalmic assessment includes:

- *prior to dilation*: best corrected visual acuity and slit lamp examination including tonometry
- *following dilation*: fundoscopy and a slit lamp exam to document lens clarity. If a cataract is seen during the examination for newly enrolling patients or enrolled patients for whom no cataracts have been detected to date, the cataract will be graded using a Grade 1-4 scale (Protocol Appendix 3). However, patients enrolled under a prior version of the protocol who had detectable cataracts graded according to the LOCS III will continue to have their cataracts graded according to LOCS III and will not switch to the Grade 1-4 scale.

[9] Pulse oximetry is performed for patients at rest breathing room air.
[10] ECG on Day 1 of each cycle only
[11] Urine analyses will include appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, and urobilinogen. Microscopy will only be performed if clinically indicated.
[12] Hematology: hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards. Reticulocytes may be done only when clinically indicated
[13] Complete Serum Chemistry for baseline, Cycle 1 Week 1, 2, 3, and 4 and Final Study Visit includes Sodium, Potassium, Chloride, Bicarbonate, Blood Urea Nitrogen (BUN) or Urea, Creatinine, Glucose, Calcium, Phosphate, Magnesium, Alanine Transaminase (ALT), Aspartate Transaminase (AST), Alkaline Phosphatase, Total Bilirubin, Lactic Dehydrogenase (LDH), Total Protein, Albumin, Pancreatic Amylase, Lipase, Creatine Kinase, Thyroid-Stimulating Hormone (TSH), and Uric Acid.
[14] Limited Serum Chemistry for Days 1 and 15 of Cycles 2 through 5 and Day 1 of Cycles ≥ 6 including Sodium, Potassium, Chloride, Bicarbonate, BUN or Urea, Creatinine, Glucose, ALT, AST, Alkaline Phosphatase, Total Bilirubin, TSH, and LDH.
[15] Coagulation test include prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT). Coagulation may also be measured using thromboplastin time (Quick test) if measurement of PT/PTT is not feasible.
[16] Disease status will be measured by bone marrow aspirate (or biopsy if aspirate is not adequate) at Screening and on Day 1 of Cycle 2, and as clinically indicated to assess treatment response. In certain cases, a bone marrow aspirate/biopsy may be taken up to 14 days of Day 1 of Cycle 1 after consultation with, and approval by, the sponsor. A portion of the bone marrow aspirate at Screening and Cycle 2 Day 1 will be used for correlative studies to include immunophenotyping, cytogenetic and molecular analysis (FLT3 ITD or TKD mutation or NPM1 mutations). If the patient has achieved CR, bone marrow BM aspiration/ biopsies are not required unless clinically indicated. For patients with circulating blasts in peripheral blood, there is no need to perform the bone marrow aspirates and biopsies for Cycles > 2. For patients without circulating blasts that achieved a PR or SD, bone marrow aspiration/ biopsies will be conducted every other cycle until CR/CRi is achieved, or until progression.
[17] Both posteroanterior and lateral films should be obtained for baseline. Note: this test does not need to be repeated if results are available from a test performed 30 days prior to start of therapy. This test serves as a baseline in the event that patients develop any adverse events during the study.
[18] Dosing on Day 1 and 3 of each week of four-week cycle. For doses on non-clinic days, patient will be provided doses to take home, one dose per container.
[19] PK sampling for patients in selinexor arm only. Blood draws (2 mL) for PK analysis will be performed at the following times relative to in-clinic selinexor dose:

- CYCLE 1
  - Day 1: 0 (predose), 1, 2, and 4* hours post-dose (± 10 min for each time point)
  - Day 8: 0 (predose) and 1 hour post-dose (± 10 min)
  - Day 15: 0 (predose) and 1 hour post-dose (± 10 min)
  - Day 22: 0 (predose) and 1 hour post-dose (± 10 min)
- CYCLE ≥ 2
  - Day 1: 0 (predose), 1, and 2* hours post-dose (± 10 min for each time point)

*****If possible, an additional blood sample will be collected just prior to patient discharge from the clinic on Day 1 of Cycles 1 – 5, provided discharge time is at least 1 hour after collection of the previous sample. This sample will be labeled "pre-discharge Day 1;" the time of blood collection will be recorded in the study data.

If a clinic visit to include PK sampling occurs on a non-dosing day, PK sampling for that visit will not be done.

[20] CCI [redacted]

[21] Blood for correlative studies using peripheral blasts will be collected from all patients. 2 × 2.5 mL will be collected during Screening and on Day 1 of Cycle 2 only. For patients in selinexor group, blood should be collected pre-selinexor dose.

[22] Quality of Life (FACT-Leu and EQ-5D-5L) questionnaires will be completed on Day 1 of each treatment cycle and the EOT visit **BEFORE** they undergo any treatment related procedures including study treatment administration.

[23] Selinexor Patients ONLY- It is strongly recommended that patients be given nutritional consultation to discuss any food recommendations and strategies for managing potential nausea and appetite changes experienced with selinexor.

[24] Patient is to take their temperature each morning and record their temperature on the diary card that has been provided. The temperature diary will be reviewed with site personnel during each site visit or phone call.

[25] A visit (Visit 4) at Cycle 1 Day 4 (+ 1 day) is required to monitor adverse events (including infections), to review temperature diaries, to evaluate supportive care medications, and to adjust supportive care as appropriate. Weekly phone calls to the patient may be done in place of visits at Day 4 (+1 day) for all other weeks during Cycles 1-3.

[26] Hematology and complete serum chemistry will be done only if fever and suspected infection are present.

[27] By phone (or a visit, if possible), assess overall medical condition of the patient and status of his/her AML, follow-up on any AEs that were not resolved at the Final Study Visit, and information on any antineoplastic therapies utilized since discontinuation of study treatment.

[28] After treatment discontinuation, a call will be made to the patient (or the patient's family) every 3 months until the End of Study (Protocol Section 11.3) to inquire about the patient's AML status, well-being, and information on any antineoplastic therapies utilized since discontinuation of study treatment.

1.2.5. Efficacy, Pharmacokinetic, CCI and Safety Parameters

1.2.5.1. Efficacy Parameters

The primary efficacy endpoint is OS, defined as the duration from the date of randomization to the date of death.

Secondary efficacy endpoints include:

- Landmark OS of at least 3 months (OS3.0)
- Incidence of CRR including CR with full hematologic recovery, and DFS for patients who achieve CR, defined by IWG criteria
- Incidence of mCRR including CR or CRi (including CRp), and DFS for patients who achieve CR or CRi (including CRp)
- Incidence of ORR and DOR, including CR, CRi, MLFS, and PR
- Incidence of DCR defined as ORR + SD for ≥ 4 weeks, and duration of disease control
- Quality of life and patient reported outcomes (FACT-Leukemia and EQ-5D-5L)

1.2.5.2. Pharmacokinetic and CCI Parameters

Analysis of pharmacokinetic (PK) and CCI parameters will be described in a separate CCI analysis document.

1.2.5.3. Correlative Parameters

Analysis of all correlative study parameters will be described in a separate analysis document.

1.2.5.4. Safety Parameters

Safety evaluations performed during the study include physical examinations, measurement of vital signs, 12-lead electrocardiograms, clinical laboratory evaluations including hematology, serum chemistry, coagulation, and urinalysis, ophthalmologic exam, chest radiograph, and monitoring of AEs and concomitant medications.

1.2.6. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will review the safety of selinexor and to review any SAEs that occur during the study.

The DSMB will be composed of at least two physicians (at least one of whom is an oncologist) and a statistician. The DSMB will be provided with all reports of SAEs regardless of investigator causality assessments.

Following the initial meeting, DSMB meetings will occur on a periodic basis in accordance with the DSMB charter. The chairperson of the DSMB will also be immediately provided with the report of any SAE that is judged as possibly, probably, or definitely attributable to study treatment.

Two interim efficacy analyses will be conducted on the intent-to-treat (ITT) population (see Section 3.12 for further details). The DSMB will be given the results of both interim analyses for review and will provide to Karyopharm the recommendation of stopping the trial for significant efficacy or futility, or continuing the study without modification. In addition to the

interim analyses performed on the ITT population, a review of safety data for all patients (see DSMB charter for details) will also be conducted at each interim analysis.

The charter of the DSMB will specify that this committee is charged with providing periodic reports to Karyopharm that contain recommendations that include, but are not limited to, (a) continuation of the study, and (b) termination of the study.

2. PATIENT POPULATION

2.1. Population Definitions

The following patient populations will be evaluated and used for presentation and analysis of the data:

Intent-to-Treat (ITT) Population: The ITT population will consist of all patients who are randomized to study therapy under Protocol Versions 5.0 and later, regardless of whether or not they receive study treatment. Patients randomized under Protocol Versions < 5.0 will not be included in any analyses of efficacy, due to a change in selinexor dosing and randomization methodology in Protocol Version 5.0. The ITT population will include patients who have discontinued therapy due to toxicity or disease progression and patients who have died from any cause. The ITT population will be used for primary analyses of efficacy, and such analyses will be based on the randomized treatment assignment and strata assignment at the time of randomization.

Modified Intent-to-Treat (mITT) Population: The mITT population will consist of all ITT patients but analyses will be based on randomized treatment assignment and the strata to which patients should have been assigned at the time of randomization rather than the actual strata to which they were assigned. Identification of the strata to which patients should have been assigned will be based on verification of source data prior to database lock. The mITT population will be used for supportive inferences concerning efficacy, however, if there are major differences between the results in this population and those obtained in the ITT population, this will be taken into consideration in the decision to continue to later phase studies, or in the design of further studies.

Per-protocol (PP) Population: The PP population will consist of all patients randomized to study treatment under Protocol Versions 5.0 and later who have received any amount of study treatment and who have no major protocol violations that would compromise the assessment of efficacy. Patients who progress or die are included regardless of duration of time on of study treatment. The PP population will be used for supportive inferences concerning efficacy; however, if there are major differences between the results in this population and those obtained in the ITT population, this will be taken into consideration in the decision to continue to later phase studies, or in the design of further studies.

Safety Population: The Safety population will consist of all patients who have received any amount of study treatment. The Safety population is the primary population for the analysis of safety endpoints, and such analyses will be based on treatment received, even if different from that randomized. Patients enrolled under all protocol versions will be included in the safety population.

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2.2. Protocol Violations

Upon assessment of major protocol violations (e.g., significant eligibility failures, prohibited use of concomitant medications, etc.), the Sponsor may determine to remove a patient's data from

the PP population in an effort to maintain full compliance with study procedures. The Sponsor or designee will be responsible for producing the final protocol violation file (formatted as a Microsoft Excel file); this file will include a description of the protocol violations and clearly identify whether or not the violations warrant exclusion from the PP population. This file will be finalized prior to hard database lock.

All protocol violations will be presented in a data listing.

Relevant Output

Listing 16.2.2.2 Protocol Violations

3. GENERAL STATISTICAL METHODS

3.1. Sample Size Justification

Patients enrolled under protocol versions prior to 5.0 will not be included in the efficacy analyses: therefore, sample size justification will refer to patients to be enrolled under Protocol Versions 5.0 and greater.

The sample size is designed to have 80% power to detect a median OS for patients treated with selinexor of ~5.2 months versus PC of ~3.0 months (hazard ratio [HR] = 0.5769), using a one-sided alpha level of 0.025 and allowing for two interim analyses. The anticipated enrollment period is 12-18 months, and the follow up period for survival is up to 6 months after the end of treatment for the last enrolled patient for the primary analysis. Based on these statistical assumptions, a total of 123 events (deaths) are required for analysis. To achieve these events, a total of approximately 150 patients are required for enrollment. In order to maintain the 2:1 randomization allocation to selinexor:PC and allow for overages to take into account potential drop-out, this number is increased to 169 patients, and rounded up to 171 patients. Therefore, a total of approximately 171 patients with relapsed or refractory AML will be enrolled into the study from approximately 60 sites in North America, Europe and the rest of the world. Patients will be randomized into the selinexor or PC treatment groups in a 2:1 allocation, within each of the 2 × 2 × 2 stratification levels noted in Section 1.2.2. Sample size calculations were performed using East version 5.3 (East 2008).

As described in Protocol Section 4.3.1.1, following a thorough evaluation of patient safety from the first 110 patients enrolled under Protocol Versions < 5.0, a dose reduction for selinexor is being implemented. Under Protocol Versions < 5.0, the selinexor group was prescribed a dose equivalent to ~55 mg/m^2 twice weekly, based on the patient's BSA at baseline. Under Protocol Versions ≥ 5.0, the selinexor group will receive a fixed dose of 60 mg (equivalent to ~35 mg/m^2) twice weekly. Patients enrolled under Protocol Versions < 5.0 will not be included in efficacy analysis. The total sample size of the study is expected to be approximately 300, as approximately 141 patients were enrolled under Protocol Versions < 5.0, and enrollment will continue at each site until Protocol Version 5.0 is approved locally.

Two interim efficacy analyses are planned for patients enrolled under Protocol Version 5.0. The first interim analysis will take place after 31 (25%) OS events have occurred, and will be conducted to assess futility only (non-binding), at a one-sided significance level of 0.8084 (i.e., futility declared if p ≥ 0.8084). The second interim analysis will take place after 62 (50%) OS events, and will allow for a conclusion of significant efficacy at a one-sided significance level of 0.0015 (i.e. superiority claimed if p < 0.0015), and stopping for futility (non-binding) at a one-sided significance level of 0.2957 (i.e., futility declared if p ≥ 0.2957). The final hypothesis test will be performed after 123 OS events are observed with a one-sided significance level of 0.0245. Type I error adjustments were made using the O'Brien-Fleming approach (O'Brien, Fleming 1979).

At the second interim analysis, a sample size re-assessment will be performed if the study is not stopped for futility and significant superiority is not claimed (i.e. if the log-rank test results have a significance level between 0.0015 and 0.2957). To control the type I error rate of the study, the Mehta and Pocock method for sample size re-estimation will be used (Mehta and Pocock 2011). The sample size may be increased in order to ensure a minimum of 80% conditional power, where conditional power is calculated as the probability of a statistically significant result from the stratified log-rank test at the final analysis, conditional on the result at the interim. Boundaries for "unfavorable", "promising" and "favorable" are set based on conditional power

using the adjusted one-sided significance level of 0.0245 for the final analysis (see Table 3-1). If the conditional power at the interim analysis falls below the "unfavorable" boundary, the sample size will not be increased as the conditional power is sufficiently low to indicate clinical benefit is not attained. If the conditional power falls in the "promising" zone the sample size re-assessment will be performed and sample size increased accordingly, subject to a maximum allowable of 1.5 times (50% increase) of the current planned sample size of 171 patients (i.e., a maximum of 255 patients). If the conditional power falls in the "favorable" zone (i.e. conditional power ≥ 80%), the sample size will not be re-estimated or adjusted.

Table 3-1 Sample Size Re-Estimation Boundaries

Boundary	Condition	Action
Unfavorable	Conditional Power < 36%	Sample size will not be re-estimated
Promising	36% ≤ Conditional Power < 80%	Sample size re-assessment will be performed and sample size increased accordingly
Favorable	Conditional Power ≥ 80%	Sample size will not be re-estimated

3.2. General Methods

All data listings that contain an evaluation date will contain a relative study day (Rel Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study treatment (treatment start date) which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. The last day of study treatment (treatment end date) is designated with an "L" (e.g., Day 14L). Post-treatment study days are numbered relative to the last dose and are designated as Day 1P, Day 2P, etc.

The dates of start and end of treatment are identified as follows:

1) Selinexor patients: First and last dose date of selinexor treatment, as recorded on the study drug exposure eCRF.
2) PC patients that are selected to receive the Ara-C or hypomethylating agent: First and last dose date of azacitidine or decitabine as recorded in the study drug exposure eCRF.
3) PC patients that are selected to receive BSC alone: Treatment start date will be date of randomization. Treatment end date will be the date of disease progression or discontinuation from the study as reported on the End of Treatment and End of Study eCRFs.

Formal hypothesis testing methods will be used for efficacy endpoint data, in order to evaluate if selinexor provides statistically significant improvement in efficacy over the control agents (collectively, all 3 PC options) used in this study. No formal hypothesis-testing will be used for other study data, such as demographics and safety data, other than the comparisons described for AEs in Section 4.5.2.

Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented, as well as two-sided 95% confidence intervals (CI), unless otherwise stated. For

continuous variables, the number of patients, mean, median, standard deviation (Std Dev), minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier (KM) methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% CIs, as well as percentage of censored observations and events.

All output will be incorporated into Microsoft Word or Excel files, or Adobe Acrobat PDF files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

3.3. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software Version 9.3, unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 16.0 or later. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version Q12013 or later.

3.4. Baseline Definitions

For all analyses, baseline will be defined as the most recent measurement prior to the first administration of study treatment. For the BSC alone subgroup of PC patients, the treatment start date is designated as the date of randomization.

3.5. Methods of Pooling Data

Patient data from all study centers will be combined for analysis. Patient data from the 3 PC groups will also be combined for analysis. Patient data from the selinexor and PC groups will be presented separately for disposition, demographics and baseline summaries, and analyzed separately for efficacy and safety. Patients enrolled under all protocol versions will be combined for safety analysis, but only patients enrolled under Protocol Version 5.0 or later will be used for the primary efficacy analysis.

3.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned, other than the inclusion of baseline score as a covariate for QoL analyses.

3.7. Multiple Comparisons/Multiplicity

To account for multiple comparisons (an interim analysis with an option to stop for efficacy), Type I error adjustments were made using the O'Brien-Fleming approach (O'Brien, Fleming 1979).

There is a single primary efficacy endpoint for this study. In order to preserve the overall Type I error for the study, secondary efficacy variables will be assessed in hierarchical fashion, as described in Section 4.4.

3.8. Subpopulations

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No additional analyses of patient subgroups are planned; CCI [redacted]

3.9. Withdrawals, Dropouts, Loss to Follow-up

Patients will be free to discontinue treatment or withdraw from the study at any time, for any reason, or they may be withdrawn/ removed if necessary in order to protect their health. Patients who are withdrawn from the study will not be replaced.

3.10. Missing, Unused, and Spurious Data

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the eCRF will be included in data listings that will accompany the CSR.

No imputation of missing efficacy data is planned. For time to event analyses, patients who have no efficacy evaluations will be considered as censored at time 0. For OS, patients will be followed until either lost to follow-up, withdrawal, or death. Patients who are alive at the time of their last assessment will be censored on the date they were last known to be alive, regardless of disease status. For the QoL FACT-Leukemia analysis, missing data will be handled as described in the FACT-Leukemia scoring manual, using the prorating method. If 50% or more of the items for a subscale are missing, the subscale will be considered missing for that visit. If less than 50% of the items are missing, the sum of the subscale will be multiplied by the number of items in the subscale, then divided by the number of items actually answered.

Prorated subscale score = [Sum of item scores] **x** [N of items in subscale] ÷ [N of items answered]

For AEs, missing dates will not be imputed; however, if partial dates are available, they will be used to assess if the AE occurred during the treatment period. Missing severities of AEs will not be imputed and will be considered missing in any tabulations of AE severity. If an AE is missing a response to the question regarding relationship to treatment, the event will be considered to be related.

3.11. Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window. In data listings, the relative day of all dates will be presented.

3.12. Interim Analyses

Two interim analyses will be conducted, as described in Section 3.1.

The statistical analyses of interim efficacy to determine a recommendation to stop the trial for significant efficacy or futility will be performed by a Sponsor-designated statistician and then provided to the DSMB. The recommendation to stop or continue (including possible re-sizing: see Section 3.1) the trial will be provided to the Sponsor by the DSMB, after a review of the interim efficacy results, in conjunction with a review of safety data. Additional operational details are described in Section 9.2 (Appendix 2) and the DSMB charter.

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4. STUDY ANALYSES

Summary tabulations will be provided for disposition, demographic, baseline, efficacy, and safety data as noted in the following sections. All data collected on the eCRF will be provided in by-patient data listings.

The primary presentation of efficacy data will use the treatment group classification of selinexor (60mg) to control, including all 3 PC therapies pooled together. The primary presentation of all non-efficacy data will use a 4 treatment group classification of selinexor at the 2 dose levels of ~55 mg/m^2 (protocol versions prior to version 5.0) and 60 mg (35 mg/m^2) (protocol versions 5.0 and later), physician's choice 1 (protocol versions prior to version 5.0) and physician's choice 2 (protocol versions 5.0 and later), where "physician's choice" is meant to designate all 3 PC therapies together.

The treatment groups will be presented as follows:

- Selinexor 55mg/m^2
- Selinexor 60mg
- Physician's Choice 1
- Physician's Choice 2

Patients enrolled under Protocol Versions < 5.0 after 29 July 2015 who were prescribed the updated dosing regimen of 60 mg at time of randomization will be included in a separate group for presentation of safety data: selinexor 60mg (PV < 5) and selinexor 60mg (PV ≥ 5).

4.1. Patient Disposition

A tabulation of patient disposition will be presented, including the number screened, the number randomized, the number in each analysis population, the number lost to follow-up, the number that withdrew prior to completing the study and reason(s) for withdrawal, the number on treatment at the date of data cut-off, and survival follow-up phase status.

A by-patient listing of study completion information, including the reason for study withdrawal will be presented.

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4.2. Demographic Characteristics

Demographic characteristics will be summarized by treatment group and overall, and will include sex, race, ethnicity (Hispanic origin), age at time of consent, and smoking history. For sex, race, Hispanic origin, and smoking history, the summary statistics will be the number and percentage of patients within each category. For age at time of consent, the mean, standard

deviation, median, minimum, and maximum will be provided for each group and the total sample. No formal hypothesis testing of treatment group differences will be performed.

Demographic data for each patient will be provided in data listings.

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4.3. Baseline Characteristics and Medical History

Baseline characteristics include height, weight, BSA, Eastern Cooperative Oncology Group (ECOG) Performance Status, baseline symptoms and disease risk assessment. If the Dubois and Dubois method for calculating BSA is entered by the site, BSA using the Mosteller method will be derived using the formula: BSA = SQRT([Height(cm)×Weight(kg)]/3600).

Disease History includes duration from initial diagnosis, tumor type, WHO classification, response to previous therapy, and type(s) of prior therapy. Baseline data will be summarized for each treatment group using summary statistics; no formal hypothesis testing of treatment group differences will be performed. Baseline symptoms will be listed only.

Medical history will be summarized by MedDRA System Organ Class and Preferred Term.

Prior treatments will include number and percentage of patients with prior radiation therapy and prior systemic therapy, separated into chemotherapy, biological therapy, or other systemic therapy. One line of prior therapy may include multiple treatments, as long as no disease progression is observed between therapies. Each patient's most recent prior therapy for each type (i.e., radiation therapy, biological therapy, chemotherapy, and other systemic therapy) will be summarized. This summary will include indication, best overall response, whether the treatment was discontinued due to intolerability or serious illness, and whether progression occurred during or after treatment for each therapy type.

Baseline and medical history data for each patient will be provided in data listings.

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4.4. Efficacy Evaluation

Efficacy analyses will be conducted using the ITT population. Supportive analyses of efficacy will be based on the PP population.

4.4.1. Primary Endpoint

Overall survival is the primary efficacy endpoint of this study.

Patients enrolled under Protocol Versions < 5.0 will not be included in the efficacy analyses described below. Efficacy data from these patients will be tabulated separately from the data of patients enrolled under Protocol Versions ≥ 5.0 and no formal statistical hypothesis testing will be performed on the prior efficacy data. Therefore, references to efficacy analysis will be intended for the data collected from patients enrolled under Protocol Versions ≥ 5.0.

For patients meeting the criteria to be included in the ITT or PP populations, OS will be calculated from the date of randomization to the date of death. Patients who are alive at the time of analysis, or who drop out prior to study end, will be censored at the day they were last known to be alive. The statistical significance of the treatment group difference in OS will be based on the stratified log-rank test, with treatment as the group variable, and stratified by the strata included for randomization (duration of first CR on prior therapy [> 6 months versus ≤ 6 months or never achieved CR], number of prior therapies [1 versus > 1], and peripheral leukemic blast counts [≥ 10,000/μL versus < 10,000/μL]). The median duration of OS will be estimated based on the 50th percentile of the KM distribution; additional summary statistics will be presented, including the 25th and 75th percentiles, 95% CIs on the median and other percentiles, proportion of censored data, and proportion of events.

The hazard ratio (HR) and 95% CI for treatment group difference will be estimated from a Cox proportional hazards model stratified by the randomization factors. The adequacy of the model will be evaluated, including an assessment of the proportional hazards assumption. CCI [redacted]

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4.4.2. Secondary Endpoints

In order to preserve the overall Type I error for the study, secondary efficacy variables will be assessed in hierarchical fashion in the following order, as described below:

- OS3.0
- CRR and DFS for CRR
- mCRR and DFS for mCRR
- ORR and DOR
- DCR and duration of DCR
- QoL

The hierarchical assessment will proceed in order, with all statistical tests performed at the one-sided, 0.025 level. All p-values will be reported; however if the prior analysis in the hierarchy was not statistically significant, all remaining analyses will be used to further understand the data and treatment in this population and inform future research, rather than to make inferences based on the treatment differences.

For OS3.0, the proportion of patients surviving at 3 months post-randomization will be determined from the KM estimate at 3 months. The percent of patients alive at 3 months will be presented, with accompanying 95% CI, based on the KM analysis. The comparison between the treatment groups will be based on the log-rank test of equality over strata at 3 months post-randomization.

Complete remission rate will be analyzed as the difference in the proportions of patients with IWG results of CR and will be compared between the treatment groups, accounting for randomization strata, using the Cochrane-Mantel-Haenszel (CMH) chi-square test. Modified CRR will be analyzed as the difference in the proportions of patients with IWG results of CR, CRi, or CRp in a similar manner. The analysis of ORR and DCR will be performed in a similar manner to CRR, using the CMH test.

Analyses of disease free survival (DFS) for CRR and for mCRR will be performed using stratified KM methods where the stratified log-rank test will be used for assessing statistical significance between treatment groups.

Duration of response will be calculated for patients who achieve each response category (CRR, mCRR, and ORR), and duration of disease control will be calculated for all patients. The results of the duration analyses will not be used in the overall hierarchy used to maintain alpha-control, but will be regarded as descriptive adjuncts to the analyses of response rates. Analysis of duration of response and disease control will be performed using stratified KM methods.

- For CRR and mCRR, the duration of response will be based on disease-free survival, defined as the duration from the date when first evidence of complete disease response (complete remission) was achieved based on IWG criteria until disease recurrence or death from any cause. Patients without documented disease recurrence will be censored at the date of last disease assessment.
- For ORR, duration of response will be calculated as the duration from the date when first evidence of overall disease response was achieved until the first date of documented

disease recurrence or progression. Patients without documented disease recurrence or progression will be censored at the date of last disease assessment.

- Duration of disease control will be calculated as the duration from the date of randomization until the first date of documented disease recurrence or progression. Patients without documented disease recurrence or progression will be censored at the date of last disease assessment. Patients without a post-baseline disease assessment will be censored at date of randomization (time 0).

Quality of life will be assessed using the FACT-Leukemia and the EQ-5D-5L assessments.

The FACT-Leukemia combines the General version of the Functional Assessment of Cancer Therapy (FACT-G) with a leukemia-specific subscale (17 items). The subscales for the FACT-G are Physical Well-Being (PWB; 7 items), Social/Family Well-Being (SWB; 7 items), Emotional Well-Being (EWB; 6 items), and Functional Well-Being (FWB; 7 items). The trial outcomes index (TOI; total of 31 items) will be the primary measurement of interest, comprised of the Physical and Functional Well-Being subscales plus the leukemia-specific subscale. Each item is rated on a 5-point Likert scale, ranging from 0 (="Not at all") to 4 (="Very much"), therefore the TOI has a score ranging from 0 to 124. The QoL assessment will be performed at Baseline (prior to first dose of study treatment), Day 1 of each cycle on or after the second, and at the Final visit. The primary QoL endpoint analysis will take place based on changes in the total TOI score from Baseline using mixed-model repeated-measures analysis of variance (MMRM) with treatment, visit, and treatment by visit interaction as factors of interest, Baseline score as a covariate, and the stratification variables as additional fixed factors. The primary inference will be drawn from this model. A secondary analysis of QoL will be performed in a similar manner using the FACT-Leukemia total score (i.e., the total of all subscales). The TOI score, the FACT-Leukemia total score, and all individual subscale total scores will be summarized over time using descriptive statistics.

The EQ-5D-5L consists of assessment of 5 health categories (5 levels each category) and overall health score ("Your Health Today" on 1-100 scale). Change from Baseline in the overall health score (EQ VAS) will be analyzed using a MMRM model, similar to the TOI and FACT-Leukemia total score as described above. All 5 individual category scores will be summarized over time using descriptive statistics.

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4.5. Safety Analyses

Safety analyses will be performed on the Safety Population, including all patients who receive at least one dose of any study medication, regardless of which protocol version they were enrolled under. Summary tables will be presented by treatment group, with the selinexor group presented both overall and separately by patients enrolled under Protocol Versions < 5.0 and patients enrolled under Protocol Versions ≥ 5.0. Similarly, the safety data for the control group patients will be presented both overall and separately by patients enrolled under Protocol Versions < 5.0 and patients enrolled under Protocol Versions ≥ 5.0.

4.5.1. Study Drug Exposure

Study drug exposure will be determined by duration, percent compliance, total drug received, and dose intensity, as described below.

Duration of study drug exposure will be calculated for both selinexor and PC groups as the number of days patients were administered study drug, as determined below, and summarized by treatment group using descriptive statistics. Duration of study drug exposure for each patient will also be provided in a data listing, along with number of cycles administered, where a completed cycle is defined as having received at least 3 weeks of treatment for that cycle.

$$Duration of\ Study Drug Exposure = (Date of\ last dose - Date of\ first dose) + 1$$

For the selinexor group only, percent compliance, total drug received, and dose intensity will be calculated as described below. Percent compliance will be summarized for each patient from date of first dose through the treatment period per the following definition:

$$Percent\ Compliance = \frac{Amount\ of\ drug\ taken\ (mg)}{Amount\ of\ drug\ prescribed\ (mg)} \times 100$$

Total drug received will be calculated by a summation of all doses received. Total drug prescribed will be presented in mg, and calculated by a summation of all doses prescribed, taking into account prescribed dosing reductions or escalations as recorded on the eCRF.

Patient compliance with selinexor will be summarized by treatment group and presented in a by-patient data listing. Percent compliance will be summarized separately for patients who completed the study versus those who withdrew early (i.e. patient decided to discontinue study treatment, patient withdrew consent, or patient was withdrawn from treatment due to protocol violation) so as to distinguish between those patients who were compliant throughout the entirety of the study versus those who were compliant until they withdrew. In the listing, patients who withdrew from the study early will be flagged.

The following exposure data will be summarized for selinexor patients: duration of exposure, number of cycles received, percent compliance, dose intensity (defined as total drug received divided by duration of exposure, presented in mg/week and mg/day for selinexor), number of missed doses, number of dose interruptions, duration of dose interruption, number of dose reductions, and number of dose escalations. Duration of dose interruption will be calculated as the number of days from the most recent dose prior to the interruption until the next dose received.

The following exposure data will be summarized for physician's choice patients: duration of exposure, number of cycles received, number of missed doses, and number of dose reductions.

Dosing information for each patient will be presented in a data listing.

Best Supportive Care will be summarized by treatment group, including number of RBC and platelet transfusions and number and percent of patients receiving dexamethasone and prophylactic medications.

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4.5.2. Adverse Events

Adverse events will be coded using MedDRA and displayed in tables and listings using MedDRA System Organ Class (SOC) and Preferred Term.

Analyses of AEs will be performed for those events that are considered treatment emergent, where treatment-emergent is defined as any AE with onset or worsening of a pre-existing condition on or after the first dose of randomized treatment through 30 days following the last

dose of randomized treatment, or any event considered drug-related by the investigator through the end of the study. For the PC arm, first and last dose of treatment is defined as first or last dose of Ara-C or hypomethylating agent (azacitidine or decitabine). For the BSC alone group, treatment-emergent is defined as any AE with onset or worsening of a pre-existing condition on or after the date of randomization through 30 days following date of disease progression or discontinuation from the study.

Adverse events with partial dates will be assessed using the available date information to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent. No formal hypothesis-testing of AE incidence rates will be performed.

The number and percentage of patients with any treatment-emergent AE (TEAE), further separated by relationship to study drug as assessed by the Investigator and maximum severity, with any TEAE with a Common Terminology Criteria for Adverse Events (CTCAE) severity grade ≥3, with any treatment-emergent SAE, with any treatment-related treatment-emergent SAE, with any TEAE leading to study withdrawal, and with any TEAE leading to death will be presented. In these tabulations, each patient will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

Additional summary tables by SOC and preferred term include all TEAEs, TEAEs assessed by the Investigator as related to treatment, treatment-emergent SAEs, treatment-related treatment-emergent SAEs, non-serious TEAEs, TEAEs with a CTCAE severity grade ≥ 3, TEAEs with a CTCAE severity grade ≥3 by preferred term and severity grade, TEAEs leading to treatment withdrawal. Common TEAEs occurring in ≥10% of the safety population in either treatment group will be presented by preferred term. TEAEs, common TEAEs, and treatment-related TEAEs will also be presented by CTCAE severity grade.

The number and duration of hospitalizations recorded as a result of an adverse event will be summarized. A summary table of TEAEs leading to hospitalization will also be presented by SOC and preferred term.

Formal comparison of safety and tolerability between selinexor and PC will be performed on common AEs (occurring in ≥10% of the safety population in either treatment group) and expected AEs commonly observed in patients receiving selinexor (i.e., anorexia, fatigue, nausea, and thrombopenia) as well as AEs of special interest for this population (i.e., infections). Difference between treatment groups in incidence of common AEs and expected AEs will be assessed using Fisher's exact test. Assessment will be performed separately for patients enrolled under Protocol Version 5.0 (or later) and those enrolled prior to Protocol Version 5.0. For patients enrolled prior to Protocol Version 5.0, assessment will be performed separately by selinexor dose: 55 mg/m^2 or 60 mg.

All AEs (treatment emergent and post-treatment) will be listed in by-patient data listings, classified by treatment, patient, and day on study. In addition, separate by-patient listings will be provided for patient deaths, SAEs, and AEs leading to discontinuation of study drug.

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4.5.3. Laboratory Data

Clinical laboratory values will be expressed using conventional International System of Units (SI) units.

For each treatment group, the actual value and change from Baseline (Day 1, prior to the first administration of study drug) to each on study evaluation will be summarized for each clinical laboratory parameter, including hematology, clinical chemistry, coagulation, and urinalysis. In the event of repeat values, the last non-missing value per study day/time will be used. In the event that Day 1 data are unavailable for a given patient/parameter, the Screening value will substitute as the Baseline value.

Severity of select clinical lab measures will be determined using CTCAE criteria (e.g., those measures that have a corresponding CTCAE grade classification). Shift tables that present

changes from Baseline to worst on-study and Baseline to last on-study values relative to CTCAE classification ranges will be produced.

All laboratory data will be provided in data listings.

A subset listing will be presented for all clinically significant and abnormal laboratory values. Laboratory values with a CTCAE toxicity grade ≥3 will also be presented in a subset listing.

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4.5.4. Vital Signs, Physical Examination, and ECOG Performance Status

The actual value and change from Baseline (Day 1, prior to the first administration of study drug) to each on-study evaluation will be summarized for vital signs, including pulse rate, oxygen saturation, temperature, systolic blood pressure, diastolic blood pressure, weight, and BSA. Shift tables that present changes from baseline to worst on-study and last on-study ECOG performance status values will be produced.

All vital sign measurements, dates of physical examinations, and ECOG performance status scores will be presented in by-patient data listings.

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4.5.5. Electrocardiogram

Electrocardiogram results will be summarized descriptively, including heart rate and PR, QRS, QT, and QTc intervals (calculated by the Fridericia correction formula) intervals. If Bazett correction is entered by the site, the Fridericia corrected QTc interval (QTcF) will be derived using the formula: QT/(RR^(1/3)), where RR = 60/heart rate. Actual values and changes from baseline will be reported for each study visit.

Electrocardiogram data for each patient will be provided in a data listing.

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4.5.6. Ophthalmological Examinations

Ophthalmological examination findings will be summarized descriptively by visit.

All ophthalmological examination findings will be presented in data listings.

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4.5.7. Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary. Results will be tabulated by Anatomic Therapeutic Class (ATC) and Preferred Term.

Concomitant medications will be tabulated by treatment group, where any medications that did not end prior to first dose will be included. If an end date is missing or the medication is ongoing, the medication will be included.

The use of concomitant medications and procedures will be included in a by-patient data listing.

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5. CHANGES TO PLANNED ANALYSES

- Protocol Section 14.1.1 states that no formal hypothesis-testing will be used for other study data, such as demographics and safety data. Sections 1.2.5.4 and 4.5.2 of this document describe formal comparisons of select AEs between treatment groups.
- Section 2.1 of this document updates the definition of PP population described in Protocol Section 14.2.1.2 by removing the requirement that patients need to have received at least 2 months of treatment at least 80% of prescribed study treatment. Further detail is added stating that all patients who receive any amount of study treatment are included, including those who progress or die. CCI [redacted]
- Section 2.1 of this document includes an EE population that is not defied in Protocol Section 14.2.1. CCI [redacted]

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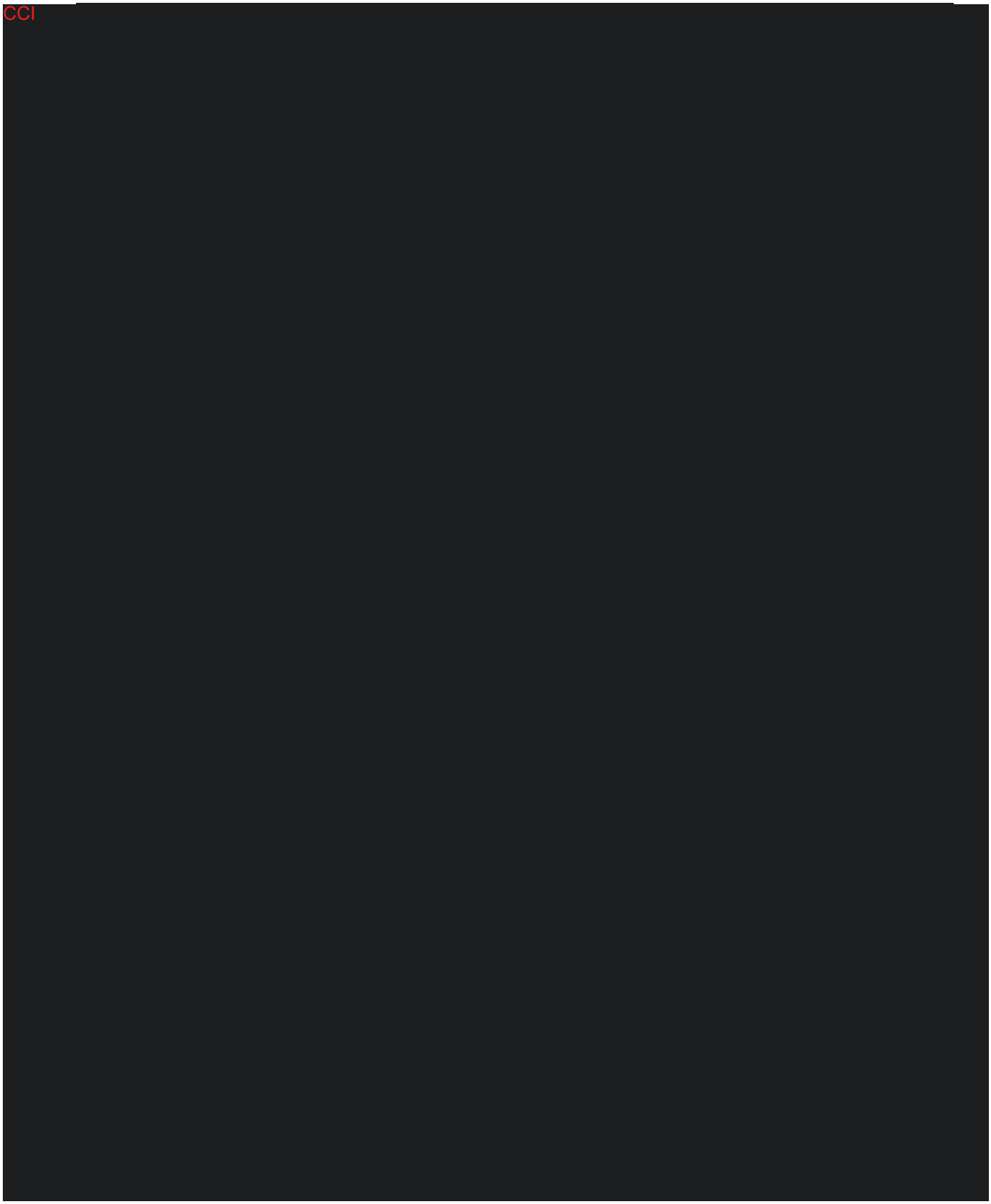

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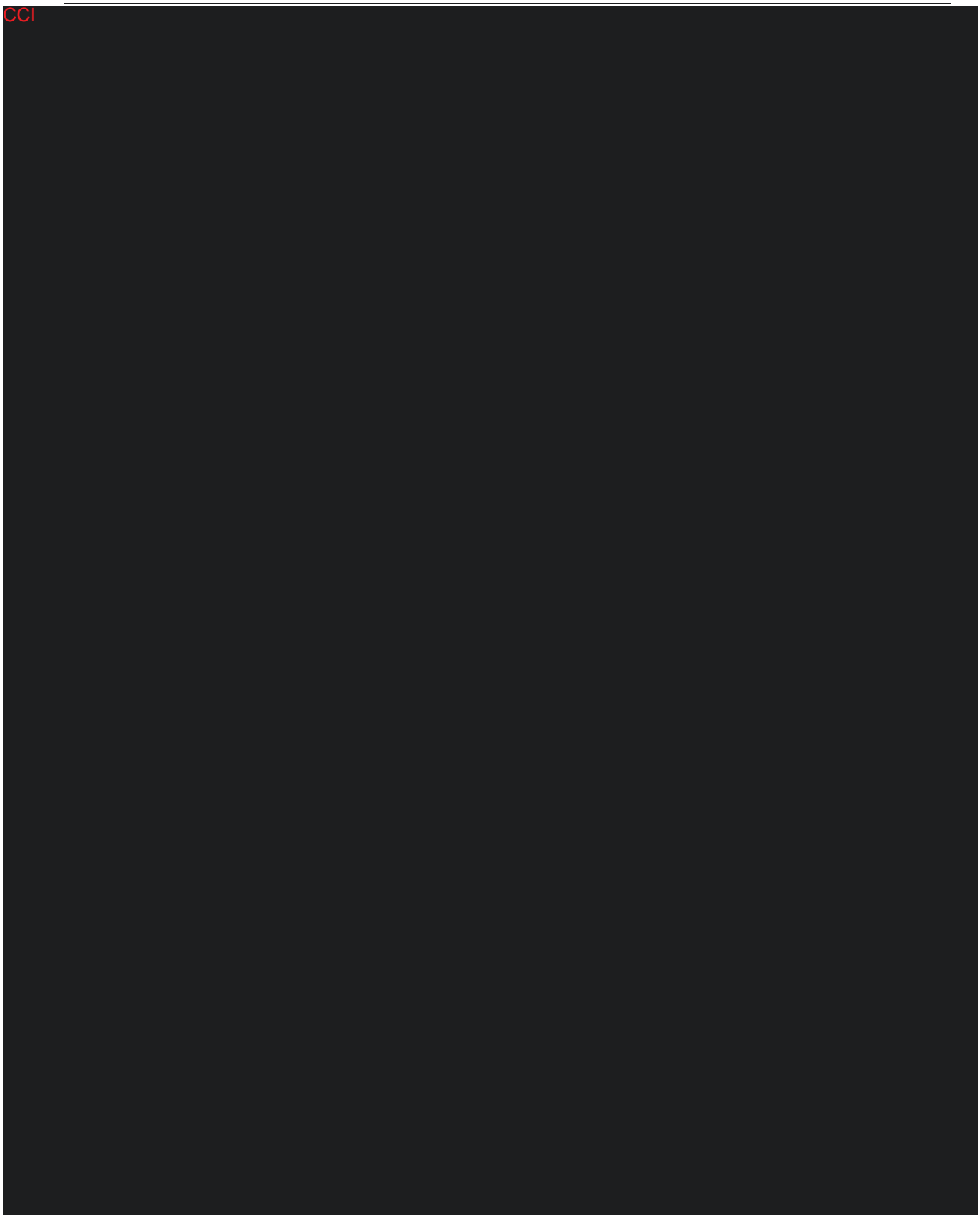

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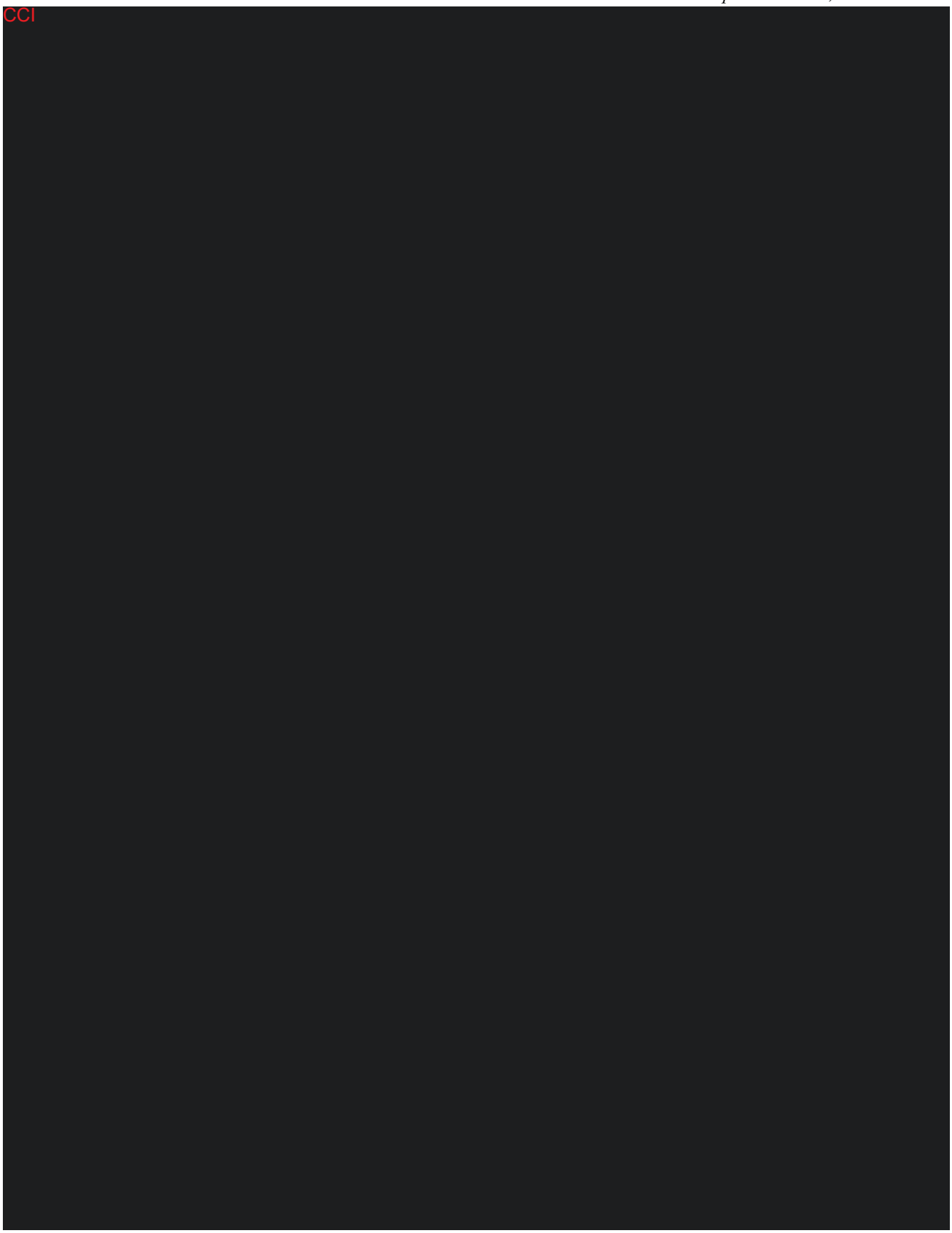

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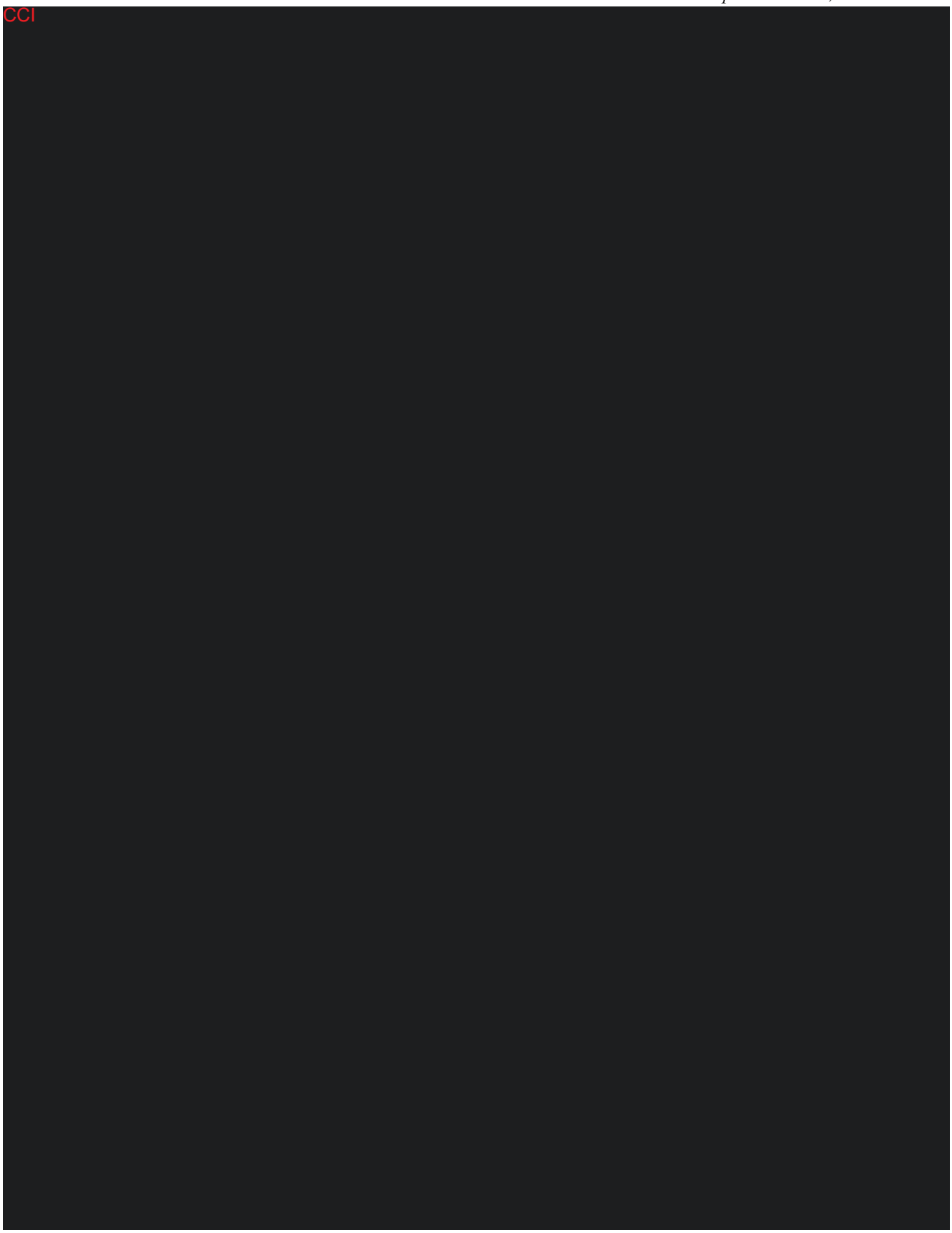

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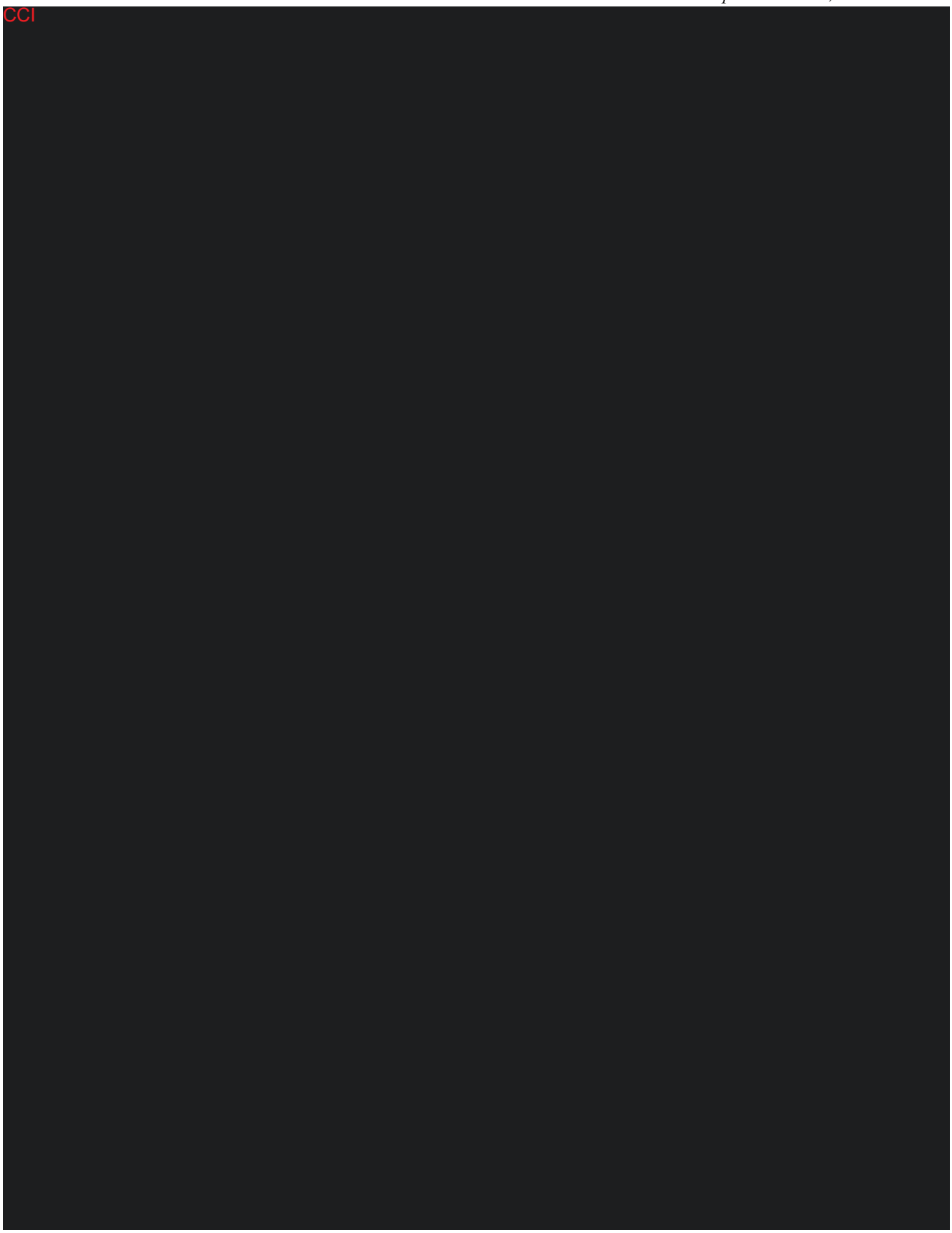

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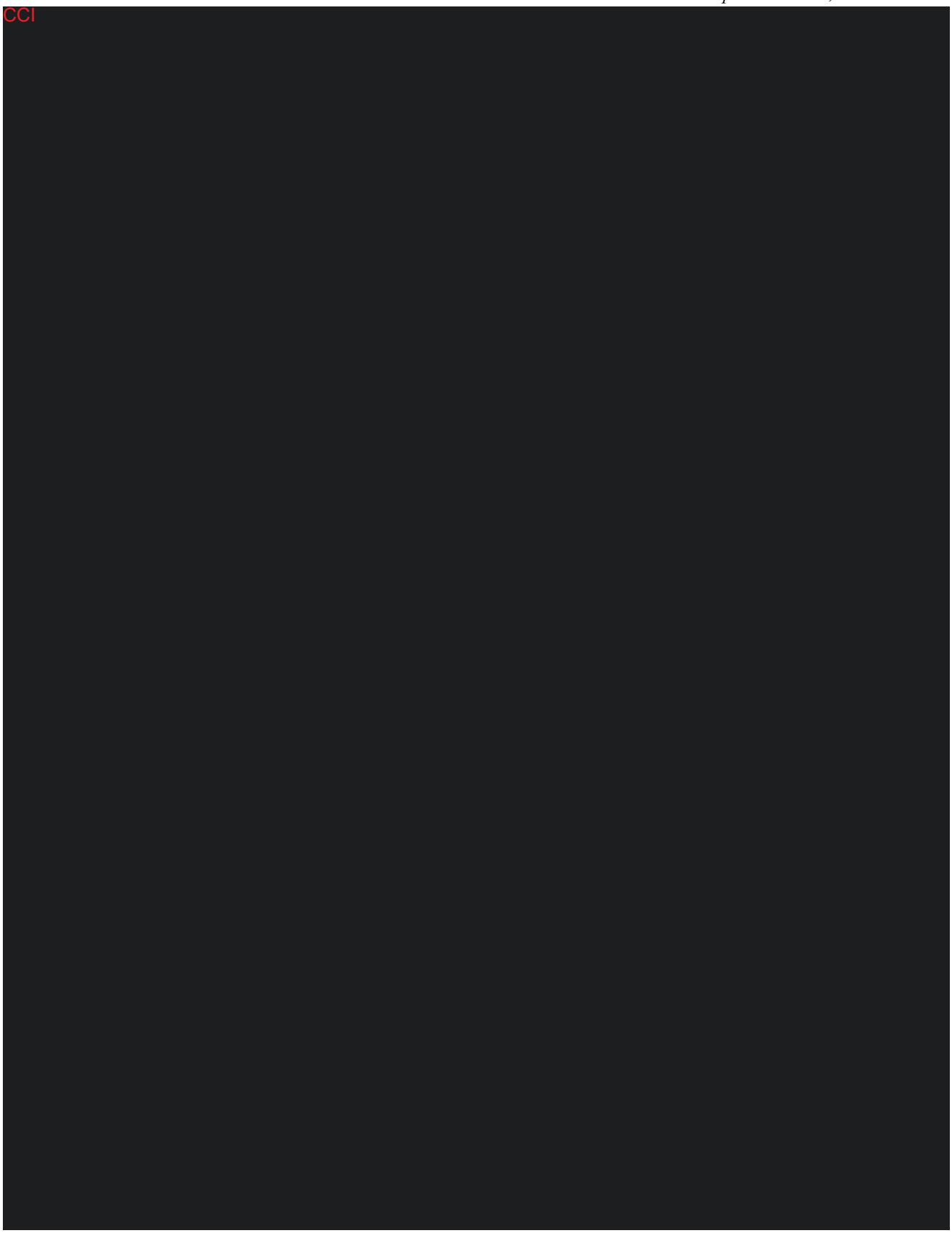

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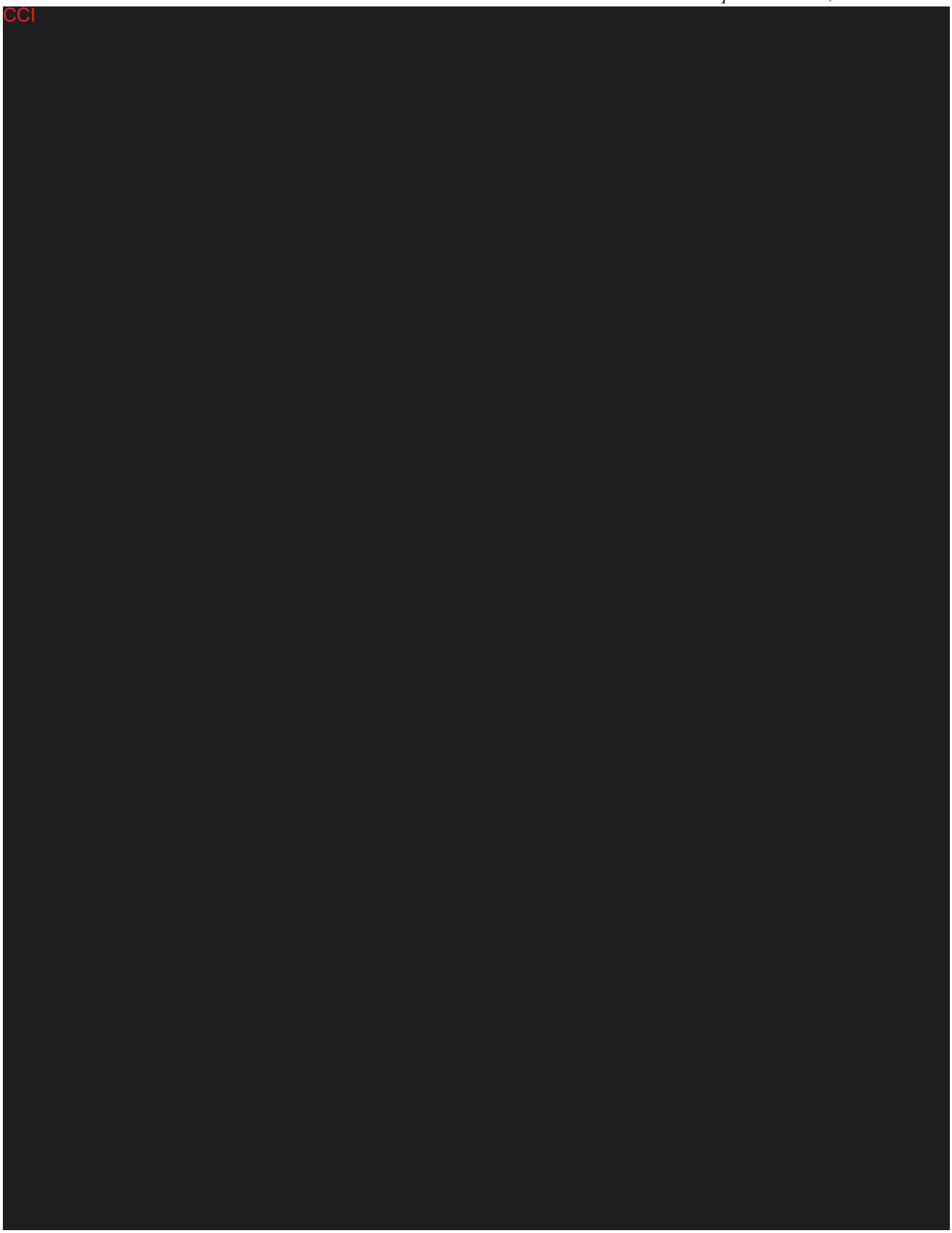

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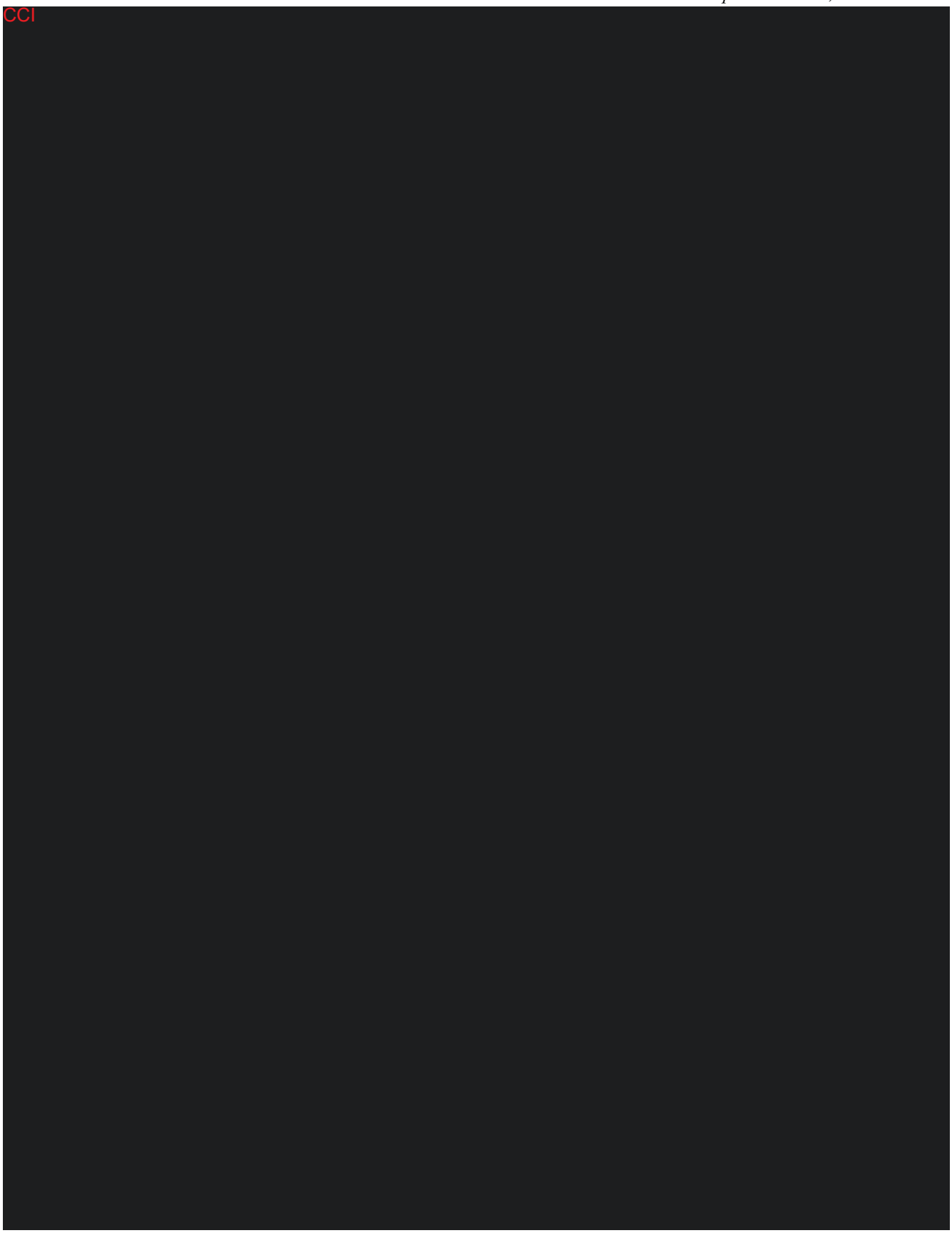

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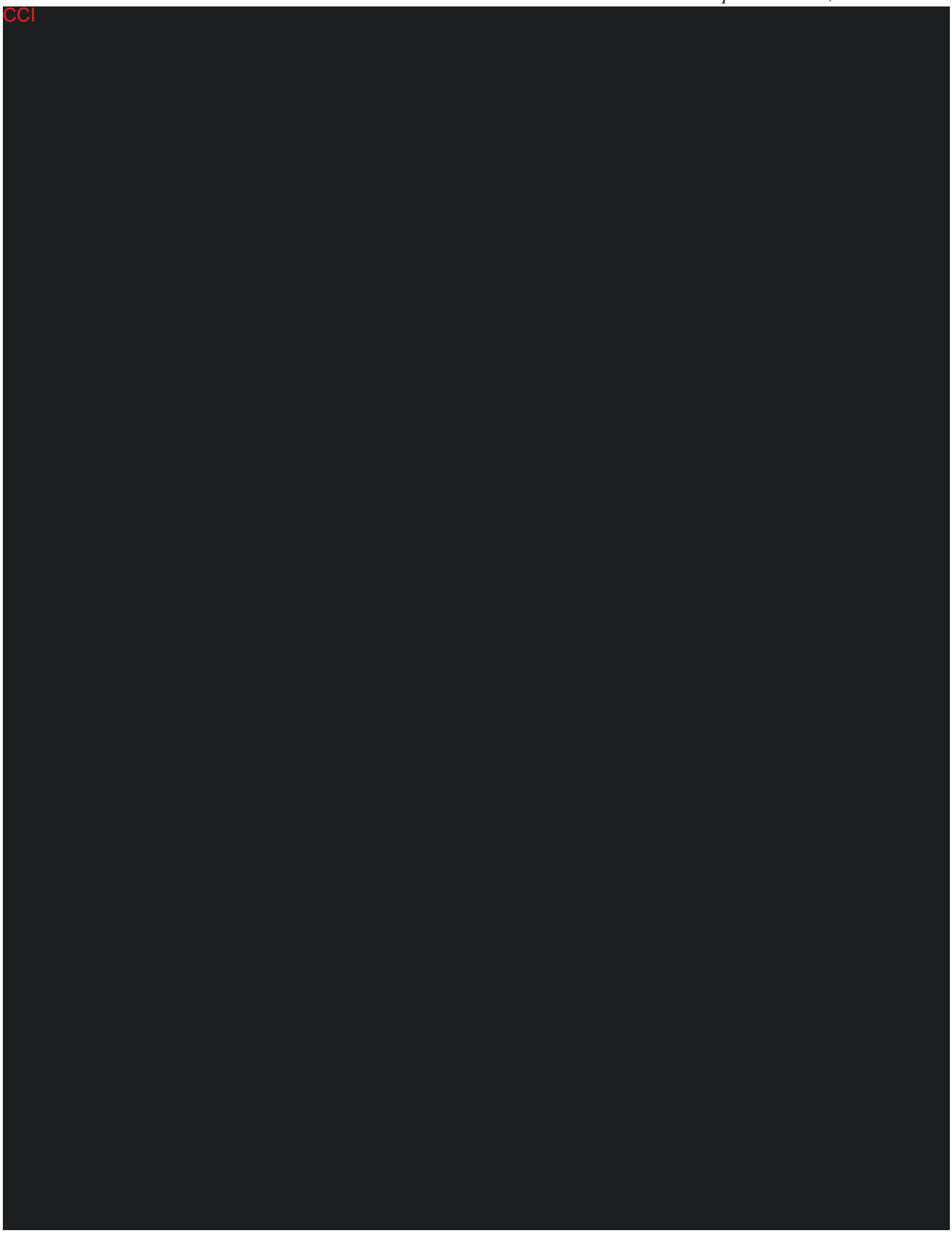

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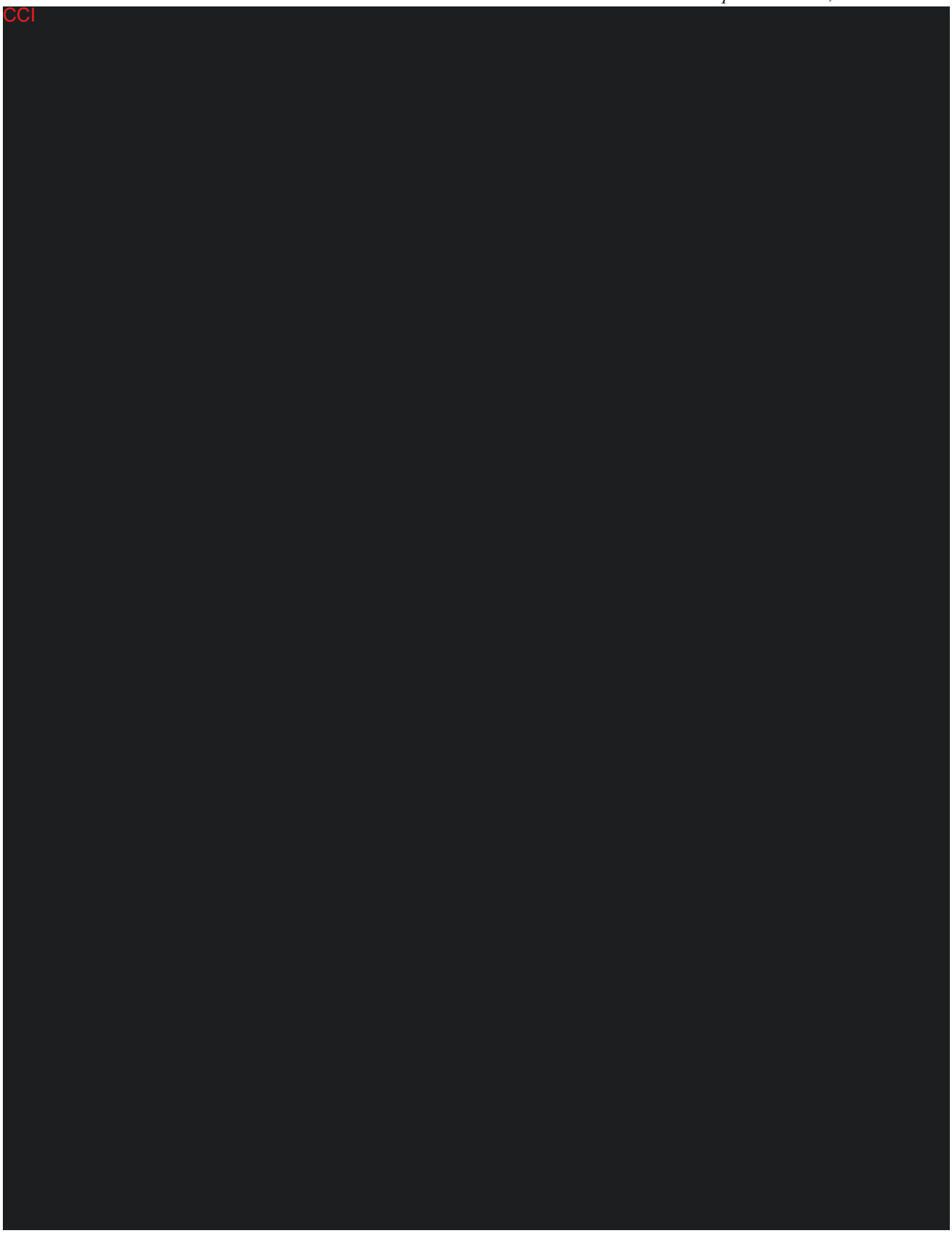

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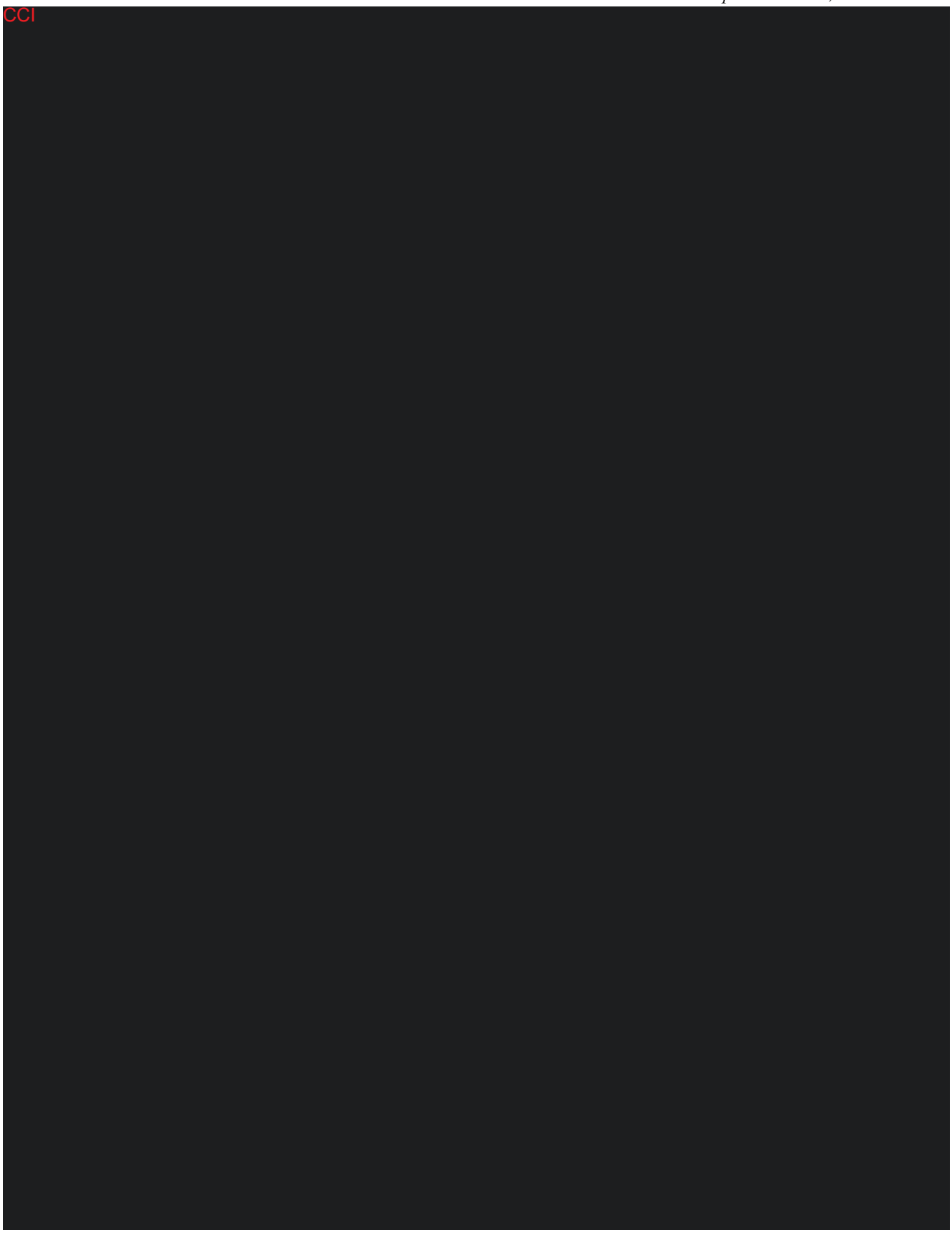

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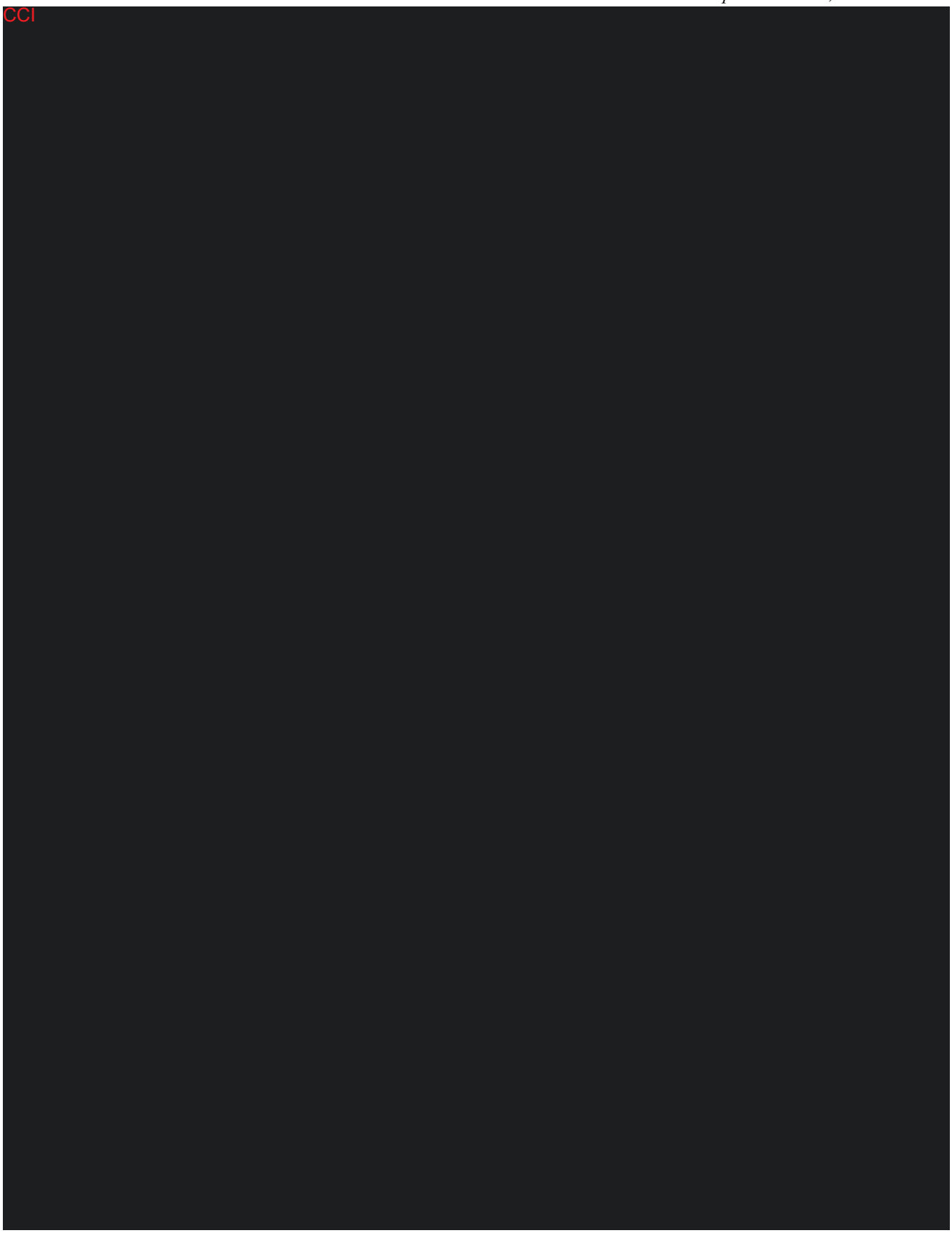

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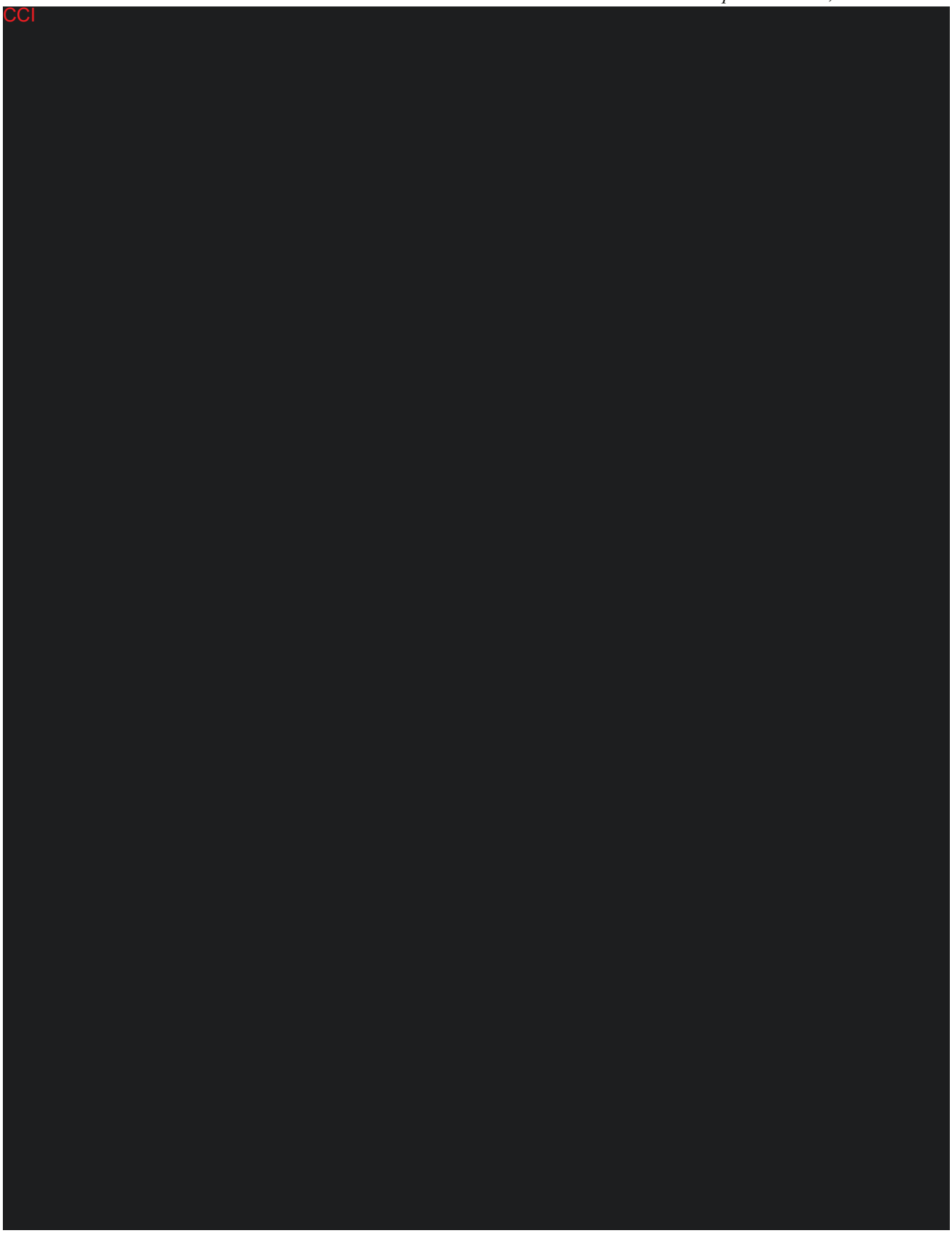

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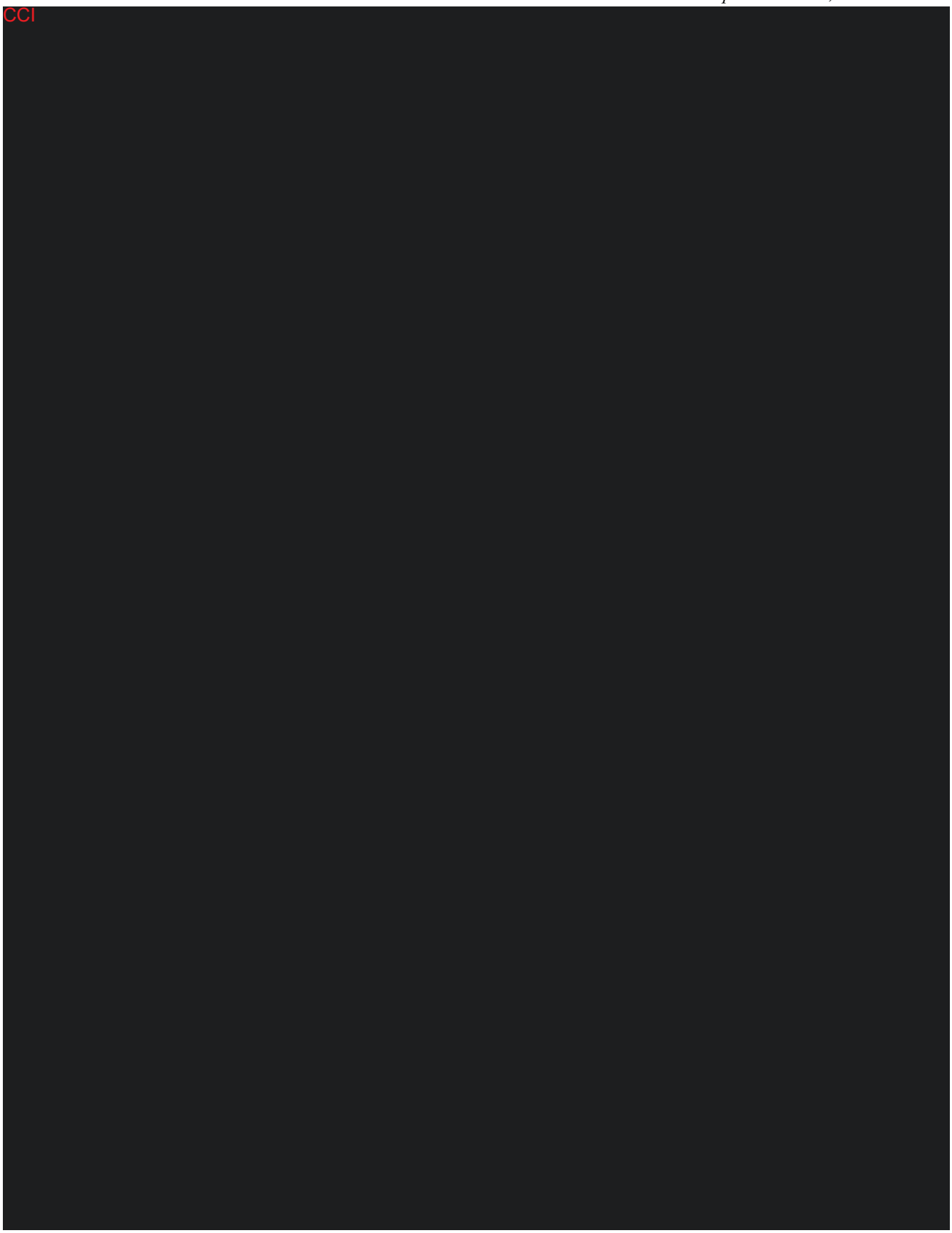

8. REVISION HISTORY

Not applicable; this is the first draft of this document.

9. APPENDICES

9.1. Appendix 1: International Working Group Guidelines for AML

Response Criteria for AML (modified from Cheson et al. 2003)

Reference: Cheson BD, Bennett JM, Kopecky KJ, Buchner T, Willman CL, Este EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol.* 2003 Dec;21(24):4642-4649.

Acute Myeloid Leukemia (AML) is a clonal expansion of myeloid blasts in bone marrow, blood, or other tissue (ICD-O code 961/3. The most significant change from the FAB classification is that the requisite blast percentage for a diagnosis of AML be ≥ 20% myeloblasts in the blood or marrow.

There are two exceptions to the above rule.

- Acute erythroleukemia (erythroid/myeloid subtype) is defined by the presence in the bone marrow of greater than or equal to 50% erythroid precursors in the entire nucleated cell population and greater than or equal to 20% myeloblasts in the non-erythroid cell population.
- Pure erythroid leukemia is defined as a neoplastic proliferation of immature cells committed exclusively to the erythroid lineage (> 80% of the marrow nucleated cells) with no evidence of a significant myeloblastic component.

Diagnostic and Staging Criteria

Definitions:

1. Bone marrow cellularity: The volume of hematopoietic nucleated cells, expressed as a percentage of marrow volume less volume of fibrosis.
2. Blasts: For AML, the following cell types are considered equivalent to blasts and are included in the calculation of blast percentages. (Note that erythroblasts are not counted as blasts in calculating blast percentages).
    a. Myeloblasts include both agranular and granular variants.
    b. Neoplastic promyelocytes, for Acute Promyelocytic Leukemia. Neoplastic promyelocytes are defined as promyelocytes with heavy granulation and irregular nuclei and/or primitive promyelocytes with very large numerous Auer rods.
    c. Monoblasts and promonocytes for Acute Monoblastic and Monocytic Leukemia
    d. Megakaryoblasts for Acute Megakaryoblastic Leukemia.
3. Bone Marrow Blast Percentage is calculated as the percent of blasts among all nucleated marrow cells.

Table 9.1 Response Criteria in AML

Response Criterion	Neutrophils (µL)	Platelets (µL)	Bone Marrow Blasts (%)	Other
Early treatment assessment	NA	NA	< 5	
Morphologic leukemia—free state	NA	NA	< 5	Flow cytometry EMD
Morphologic CR	> 1,000	≥ 100,000	< 5	Transfusion EMD
Cytogenetic CR	> 1,000	> 100,000	< 5	Cytogenetics – normal EMD
Molecular CR	> 1,000	> 100,000	< 5	Molecular-negative EMD
Partial remission (PR)	> 1,000	> 100,000	> 50% decrease to 5-25% OR Blasts < 5% if Auer rod positive	

Abbreviations: AML, acute myelogenous leukemia; EMD, extramedullary disease; CR, complete remission.

Descriptive Definitions of Remission

A. **Morphologic complete remission (CR):** ANC > 1,000/ µL, platelet count ≥ 100,000/µL, < 5% bone marrow blasts, no Auer rods, no evidence of extramedullary disease. (No requirements for marrow cellularity, hemoglobin concentration).

B. **Morphologic complete remission with incomplete blood count recovery (CRi):** Same as CR but ANC may be < 1,000/ µL or platelet count < 100,000/ µL.

C. **Partial remission (PR):** ANC > 1,000/ µL, platelet count > 100,000/ µL, and at least a 50% decrease in the percentage of marrow aspirate blasts to 5-25%, or marrow blasts < 5% with persistent Auer rods.

D. **Morphologic leukemia-free state (MLFS):** Also referred to as "bone marrow CR", this designation requires less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells. There should be no blasts with Auer rods or persistence of extramedullary disease. The presence of an unique phenotype (by flow cytometry) identical to what was found in the pretreatment specimen (e.g., CD34, CD7 coexpression) should be viewed as persistence of leukemia.

E. **Stable Disease (SD):** Not fulfilling criteria for CR, CRi, PR, MLFS, or disease progression

F. **Disease Progression (PD):** Presence of > 50% increase in bone marrow blasts to a level of at least 50% and/or a doubling of the percentage of peripheral blood blasts to a level of at least 50%.

G. **Inevaluable (IN):** This box should be checked off if no hematologic evaluation done or if a bone marrow aspirate and/or biopsy was done and there were no spicules/fragments in the aspirate (and biopsy was not representative, if done).

9.2. Appendix 2: Interim Analysis Details

As described in Sections 3.1 and 3.12, there are two scheduled interim analyses for this study. The following operational details apply to both analyses.

1) Leading up to the analysis, data cleaning efforts in preparation of the analyses will focus on all survival follow-up information. In particular, the following endpoints are required for the described analyses:
   - Treatment assignment
   - Date of randomization
   - The three stratified factors (duration of first CR on previous treatment [> 6 months vs ≤ 6 months if any] , number of prior therapies [1 versus > 1], and peripheral leukemic blast counts [≥ 10,000/μL versus < 10,000/μL])
   - Survival status
   - Date of death or date of last follow-up for censored patients
2) The analysis will be performed as described in Sections 3.1 and 3.12.
3) After the analysis has been performed, a summary reporting the results will be prepared by a biostatistician.