STATISTICAL ANALYSIS PLAN

A Phase II, Open-label Study of Efficacy and Safety of the Selective Inhibitor of Nuclear Export/SINE Compound KPT-330 (Selinexor) in Patients with Advanced Gynaecologic Malignancies

Protocol KCP-330-005

Protocol Number:	KCP-330-005
Protocol Version and Date:	Amendment 2.2: Version 3.2, 04 August 2016 Amendment 2.1: Version 3.1, 08 January 2016 Amendment 2: Version 3.0, 12 November 2014 Amendment 1: Version 2.0, 09 September 2014 Original: Version 1.0, 11 November 2013
Name of Test Drug:	Selinexor (KPT-330)
Phase:	Phase 2
Methodology:	Multi-center, Open-label, Two-stage, Phase II study
Sponsor:	Karyopharm Therapeutics, Inc. 85 Wells Avenue Newton, MA 02459 USA Tel: 617-658-0600 Fax: 617-658-0601
Sponsor Representatives:	PPD , PhD PPD , PPD
Analysis Plan Date:	24 July 2017
Analysis Plan Version:	Version 3.0

APPROVAL SIGNATURE PAGE

Protocol Title:	A Phase II, Open-label Study of Efficacy and Safety of the Selective Inhibitor of Nuclear Export/SINE Compound KPT-330 (Selinexor) in Patients with Advanced Gynaecologic Malignancies
Short Title:	SIGN (KCP-330-005)
Sponsor:	Karyopharm Therapeutics, Inc. 85 Wells Avenue Newton, MA 02459 USA
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Date: _____

Reviewer/Approver: PPD

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PPD, Clinical Statistics
PPD

Signature: _____

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 biostatistical author.

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.

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Sponsor Signatory:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
β-HCG	Beta human chorionic gonadotropin
AE	Adverse event
ALT (SGPT)	alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate aminotransferase
ATC	Anatomic therapeutic classification
BSA	Body surface area
BUN	Blood urea nitrogen
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
DCR	Disease control rate
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EOS	End of study
EOT	End of treatment
GCIG	Gynecological Cancer Intergroup
GFR	Glomerular filtration rate
GI	Gastrointestinal
HPV	Human papillomavirus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
INR	International normalization ratio
IRB	Institutional review board
IWRS	interactive web-response system
Ki67	Antigen KI-67
KM	Kaplan-Meier
LDH	Lactate dehydrogenase

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
m^2	Square meter (body surface area)
mg	Milligram
mITT	Modified Intent-to-treat
mL	Milliliter
MRI	Magnetic resonance imaging
ORR	Overall response rate
OS	Overall survival
PD	Progression of disease
PDn	Pharmacodynamics
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PP	Per-protocol
PR	Partial response
PT	Prothrombin time
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
Rel Day	Relative study day
RNA	Ribonucleic Acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SI	International System of Units
SINE	Selective inhibitor of nuclear export
SMC	Safety Monitoring Committee
SOC	System Organ Class
Std Dev	Standard deviation
SUV	Standardized uptake value
TEAE	Treatment-emergent adverse event
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labeling
ULN	Upper limit normal
WBC	White blood cell
WHO	World Health Organization
XPO1	Exportin 1

1. INFORMATION FROM THE STUDY PROTOCOL

1.1. Introduction and Objectives

1.1.1. Introduction

Gynaecological malignancies include all cancer types of the woman's reproductive organs. The main types are cervical, ovarian, uterine, vaginal, and vulvar cancer. Ovarian cancer continues to be a leading cause of cancer-related deaths in women and is the leading cause of deaths attributed to gynaecological malignancies. Ovarian cancer was the eighth most common cancer in women in 2008 worldwide with roughly 235,000 new diagnoses. Approximately 140,000 women died from ovarian cancer making it the seventh leading cause of cancer death in the world (Jemal & Bray, 2011). Cervical cancer is the second most common cancer affecting women worldwide, and it remains a major health problem in developing countries because of high oncogenic human papilloma virus (HPV) infection rates, the absence of screening programs and the lack of access to affordable vaccination programs (Monk & Herzog 2007). In 2008, endometrial cancer (uterine cancer) was the 6th leading malignancy in women worldwide, approximately 288,000 new cases were diagnosed (Jemal & Bray, 2011). In 2013, endometrial cancer was the most common gynaecological malignancy in the United States and other developed countries (Siegel et al., 2013).

Ovarian, endometrial, and cervical cancers are sensitive to anti-neoplastic chemotherapy. Despite this fact, the majority of women with advanced ovarian, cervical and endometrial cancer will ultimately relapse. Altogether, in all three types of gynaecologic malignancies, the treatment of patients with advanced or relapsed disease remains difficult. Thus, new therapy options for women with these diseases are urgently needed.

Study KCP-330-005 is designed to assess the antitumor activity and safety profile of selinexor when administered orally to patients with advanced or metastatic gynecologic malignancies (including ovarian carcinoma, endometrial carcinoma, and cervical carcinoma). Selinexor is an orally available, potent Selective Inhibitor of Nuclear Export/SINE compound that specifically blocks Exportin 1 (XPO1), the major nuclear export protein in the cell, which is over expressed in many types of cancer. Further information about the preclinical and clinical characteristics of selinexor may be found in the current Selinexor Investigator's Brochure (IB).

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 address the study objectives. 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.

The primary and secondary objectives of the study will be addressed separately for 3 parallel cohorts of patients with ovarian carcinoma, endometrial carcinoma, and cervical carcinoma.

1.1.2.1. Primary Objective

- To determine the efficacy of selinexor in patients with advanced or metastatic gynaecological cancers by assessing disease control rate (DCR).

1.1.2.2. Secondary Objectives

- To determine the efficacy of selinexor in patients with advanced or metastatic gynaecological cancers by
  - Overall response rate (ORR)
  - Progression-free survival (PFS)
  - Overall survival (OS), including OS rates at 12 and 24 months
- To evaluate safety and tolerability of selinexor in patients with advanced or metastatic gynaecological cancers
- To evaluate Quality of Life (QoL) for patients with advanced or metastatic gynaecological cancers who are treated with selinexor

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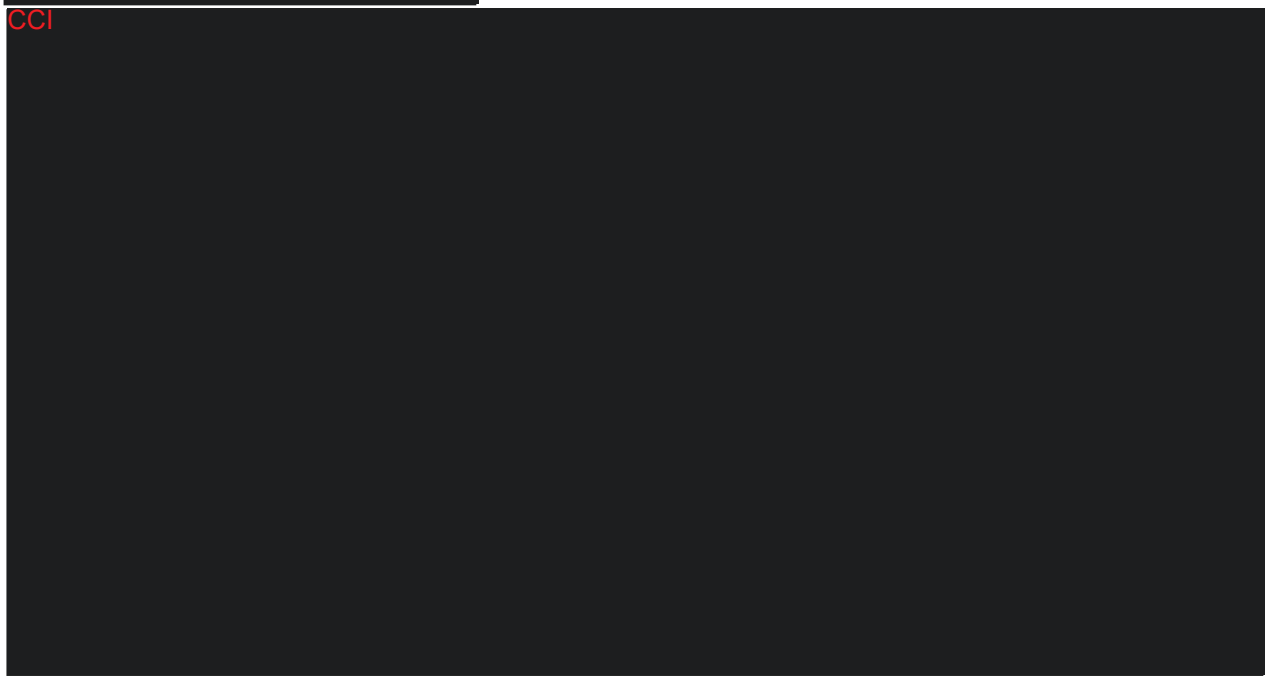

1.2. Study Design

1.2.1. Synopsis of Study Design

This trial has been designed as a multi-center, open-label, Simon two-stage, phase II study in 3 separate and parallel gynaecological cancer cohorts (i.e. Part 1), with an additional set of patients in the ovarian cohort randomized into two different treatment regimens (i.e. Part 2).

This trial has been separated into 2 parts: Part 1 and Part 2. Part 1 follows a non-randomized, single-arm, Simon two-stage optimal design in 3 separate gynaecological cancer cohorts. Part 2 follows a randomized design with 2 treatment regimens in an additional set of patients in the ovarian carcinoma cohort.

Patients are consented, screened, and enrolled in the study after histologically or cytologically confirmed and objectively documented progression of disease (PD) on prior chemotherapy documented by computer tomography (CT)/ magnetic resonance imaging (MRI). Selinexor treatment should be started within two weeks after enrollment.

Part 1: Three parallel cohorts of patients will be enrolled:

- Cohort A: Ovarian carcinoma - Patients with ovarian, fallopian tube, or peritoneal carcinoma who are platinum refractory or platinum resistant and have received at least one line of chemotherapy for relapsed disease will be enrolled. (Part 1 and Part 2)
- Cohort B: Endometrial carcinoma - Patients with endometrial carcinoma who have received at least one line of chemotherapy for relapsed or advanced (stage IVb, IIIc) disease will be enrolled. (Part 1)
- Cohort C: Cervical carcinoma - Patients with cervical carcinoma who have received at least one line of chemotherapy for relapsed or advanced (stage IV) disease will be enrolled. (Part 1)

Part 2: Based on the observed tolerability and efficacy profile in the ongoing ovarian cohort (Cohort A), two additional treatment schedules will be explored to optimize the dosing schedule in a patient population with ovarian carcinoma.

In all parts of the study, clinical and radiological examinations for disease status as well as QoL assessments will be performed at baseline, after 6 and 12 weeks of treatment, and approximately every 8 weeks thereafter.

Treatment will continue until PD or unacceptable toxicity, death, withdrawal of consent by the patient, or discontinuation of the patient due to non-compliance with protocol requirements.

Safety assessments will be performed at the baseline visit and during each cycle through the End-of-Treatment (EOT) visit.

If a patient discontinues treatment due to any reason other than PD, death, or withdrawal of informed consent, the disease evaluations shall continue until PD. This includes patients who wish to discontinue treatment, but agree to have further data captured for the purpose of the study.

After treatment discontinuation, a call will be made to the patient (or the patient's family) approximately every 3 months to inquire about the patient's survival status.

1.2.1.1. Test Product, Dose, and Mode of Administration:

The dose of selinexor to be administered will be determined, by patient, on a mg/m² basis, based on the patient's actual calculated body surface area (BSA) at baseline. Patients with a BSA > 2.5 m² will receive a dose based upon a 2.5 m² BSA.

Each cycle is 28 days (4 weeks) long. In twice-weekly dose schedules (i.e. Part 1 and Part 2, Schedule 1), 8 doses of selinexor will be administered per cycle. In the once-weekly dose schedule (i.e. Part 2 Schedule 2), 4 doses of selinexor will be administered per cycle. Twice-

weekly doses of selinexor must be administered at least 36 hours apart; once-weekly doses of selinexor must be administered at least 5 days apart.

Dose escalations and reductions/interruptions are permitted according to safety guidelines in this protocol or in consultation with a sponsor representative (see Protocol Section 6.3).

Part 1:

Patients will receive oral selinexor 50 mg/m² twice weekly (e.g. Monday and Wednesday, Tuesday and Thursday, Wednesday and Friday or Thursday and Saturday) in each week of a 4-week cycle.

If the patient has not experienced a major toxicity after 12 weeks of treatment, a selinexor dose escalation to 60 mg/m² twice weekly will be allowed.

Dose reductions (minimum dose: 35 mg/m² once weekly) and interruptions are permitted.

Part 2:

There are two dosing schedules for Part 2.

1) Schedule 1 – Patients will receive oral selinexor 35 mg/m² twice weekly (e.g., Monday and Wednesday, Tuesday and Thursday, Wednesday and Friday or Thursday and Saturday) in each week of a 4-week cycle.

   If there has been no major toxicity after 6 weeks, a dose escalation to 50 mg/m² twice weekly in each week of a 4-week cycle will be allowed.

2) Schedule 2 – Patients will receive oral selinexor 50 mg/m² once weekly in each week of a 4-week cycle (e.g., Monday of each week).

   If the patient has not experienced a major toxicity after 6 weeks of treatment, a dose escalation to 60 mg/m² once weekly will be allowed.

Dose reductions (minimum doses - Schedules 1 and 2: 35 mg/m² once a week) and interruptions are permitted.

1.2.2. Randomization Methodology

In Part 1, patients will not be randomized; there is only one treatment regimen.

In Part 2, patients will be randomized in a 1:1 ratio to receive Schedule 1 or Schedule 2 using centralized randomization via an interactive web-response system (IWRS). Randomization will be performed within the ovarian cohort for patients who are enrolled into Part 2 only and will not be specific to the study site. Further details on the randomization procedures can be found in a separate Randomization Plan (see Section 9.1).

1.2.3. Stopping Rules

1.2.3.1. Removal of Patients from Treatment

Patients will be removed from further treatment for the following reasons:

- Disease progression (PD)
- Adverse event (unacceptable toxicity)
- Non-compliance
- Need of treatment with medications not allowed by the study protocol

- Patient no longer consents to participate in the study
- Intercurrent illness that interferes with study assessments
- Incidence or severity of AEs in this study indicates a potential health hazard to the patient
- Investigator discretion
- Pregnancy
- Termination of the study by the Sponsor

When a patient discontinues study treatment, the EoT visit should be performed, if possible. The eCRF section entitled "End of Treatment" must be completed in all cases. If the reason for removal of a patient from the study is an AE or abnormal laboratory test result, the principal specific event or test will be recorded on the eCRF.

If a patient is discontinued from study treatment, the patient should still be followed for PD and survival. If a patient withdraws consent for further participation in the study, follow-up assessments will be discontinued.

1.2.3.2. Study Discontinuation

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. Medical reasons may include, but are not limited to, such features as deemed by the Safety Monitoring Committee (SMC) to constitute an unacceptable risk to the patients in the study, such as lack of efficacy or Serious Adverse Events (SAEs), such as Grade 4 anorexia and fatigue unresponsive to medical treatment.

The sponsor (Karyopharm), in conjunction with appropriate regulatory authorities, will determine if the trial should be modified or terminated. If this occurs, the sponsor will notify Institutional review board (IRB) and Investigators.

1.2.4. Study Procedures

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

Table 1-1 Schedule of Assessments

Assessment	Baseline (Within 14 days prior to Cycle 1 Day 1	Day 1 of each Cycle (up to -3 days)	Day 15 of each Cycle (± 3 days)	After 6 weeks of treatment (±7 days)	After 12 weeks of treatment and every 8 weeks (± 7 days) thereafter until PD	EOT (30 days ± 7 days after last dose of selinexor)	Survival status (every 3 months)
Informed consent [1]	X						
Inclusion and exclusion criteria	X						
Demographics	X						
Medical history [2]	X						
Pregnancy test (if applicable) [3]	X						
Physical examination and ECOG[4]	X	X				X	
Neurological examination[5]	X						
Body height and weight [6]	X	X	X			X	
BSA	X	X					
Vital signs [7]	X	X				X	
Ophthalmic exam[8]	X						
12-lead ECG[9]	X					X	
Pulse oximetry [10]	X					X	
Hematology [11]	X	X	X			X	
GFR Calculation [12] (or measurement)	X						
Clinical Chemistry [13]	X	X	X			X	
Urinalysis [14]	X					X	
Coagulation test [15]	X						
CA-125 (for Cohort A only)	X	X					
Gynecological examination	X			X (optional)	X	X	
CT/ MRI chest and abdomen[16]	X			X	X		
PET-CT[16]	X			X	X		

Assessment	Baseline (Within 14 days prior to Cycle 1 Day 1	Day 1 of each Cycle (up to -3 days)	Day 15 of each Cycle (± 3 days)	After 6 weeks of treatment (±7 days)	After 12 weeks of treatment and every 8 weeks (± 7 days) thereafter until PD	EOT (30 days ± 7 days after last dose of selinexor)	Survival status (every 3 months)
EORTC QLQ-C30[17]	X			X	X	X	
Adverse Events (AE)	X (SAEs beginning at informed consent form signing; AEs beginning at first dose)						
Concomitant medication	X	X	X	X	X	X	
Selinexor dosing [18]		X	X				
Required supportive care[19]	X	X	X				
[redacted] CCI CCI CCI							
Telephone contact[23]							X

1. Informed consent required 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. Pregnancy test applicable for women of childbearing potential. Serum beta human chorionic gonadotropin (β-HCG) test within 7 days before the first dose of study drug. To be repeated by urine test, if date of first result exceeds the 7-day window. Urine pregnancy testing is to be performed as clinically indicated during the study. Any positive urine pregnancy test must be confirmed with a serum β-HCG test.
4. Full physical examination and ECOG at baseline and End of Treatment (EOT) visit. All other physical examinations during the study should be symptom directed.
5. A standard neurological examination to assess motor, sensory, and balance functions to be performed.
6. Body height will be measured at screening only.
7. Vital signs will include blood pressure, pulse, and temperature.
8. Full ophthalmic exam: by an optometrist or ophthalmologist is required at screening and if clinically indicated during the study (e.g. monitoring of pre-existing cataracts, visual disturbances). *Please note:* 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 American Optometric Association (AOA) scale. For new patients or patients for whom no cataracts have been detectable to date, if cataracts are detected they will be graded according to the AOA scale.

9. 12-Lead ECG performed at screening, End of Treatment final visit, and if clinically indicated during the study.
10. Pulse oximetry is performed for patients at rest while breathing room air.
11. Hematology: includes hemoglobin, white blood cell (WBC) count, neutrophils, and platelets. Blood draws can be done 3 days prior to visit.
12. Calculated glomerular filtration rate (GFR) according to the formula of *Cockroft and Gault*.
13. Clinical chemistry: includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, calcium, phosphate, magnesium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), total protein, and albumin. Blood draws can be completed 3 days prior to the visit; testing may be repeated on the day of the visit if clinically indicated.
14. Urinalysis will include urine bilirubin, glucose, hemoglobin, ketones, pH, and protein. Performed at screening, at the End of Treatment visit, and if clinically indicated. Urinalysis can be done up to 3 days prior to visit.
15. Coagulation test includes prothrombin time (PT), international normalization ratio (INR), and activated partial thromboplastin time (aPTT). This will be performed at baseline and if clinically indicated. Blood draw can be done up to 3 days prior to visit.
16. CT/MRI of abdomen must include pelvis. PET-CT is allowed, but ultrasound of the abdomen and x-ray of thorax is not allowed. CT/MRI or PET/CT scans to be performed within four weeks prior to registration. CT scan is required again if patient has relapse and if clinically justified during trial period. On-study tumor assessment should be performed after 6 weeks (± 7 days) and 12 weeks (± 7 days) of treatment. Thereafter, tumor assessments will be performed every 8 weeks (± 7 days) thereafter, independent of cycle delays, until disease progression or death.
17. Patients to complete the EORTC QLQ-C30 at baseline, with tumor assessment during treatment (i.e. at Week 6, Week 12 and every 8 weeks thereafter), and at the End of Treatment visit.
18. Selinexor dosing for Part 1, and Part 2, Schedule 1: Twice weekly (e.g., Monday and Wednesday, Tuesday and Thursday, Wednesday and Friday or Thursday and Saturday) in each week of a 4-week cycle; Part 2, Schedule 2: Once weekly dosing in each week of a 4-week cycle (e.g., Monday of each week). For dosing details, including delayed doses and changes to the visit schedule, see Protocol Section 6.2.2 and Section 6.3).
19. All patients will receive required supportive care to prevent nausea, as described in Protocol Section 6.5.1.

[redacted] CCI

[redacted] CCI

23. After treatment discontinuation, a call will be made to the patient (or the patient's family) approximately every 3 months to inquire about the patient's survival status.

1.2.5. Efficacy, CCI [redacted] and Safety Parameters

1.2.5.1. Efficacy Parameters

The primary efficacy endpoint is DCR, defined as complete response (CR) or partial response (PR) or stable disease (SD) for at least 12 weeks, assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Supportive data will be provided by Duration of SD, calculated from the date of start of study therapy until the date of PD, or last disease assessment should PD not have occurred.

The secondary efficacy endpoints for all cohorts include:

1. Response to therapy per RECIST v1.1, as determined by ORR, defined as either CR or PR per RECIST v1.1, including duration of response (DOR)
2. PFS, calculated from the date of start of study therapy to the date of PD per RECIST v1.1 or date of death if PD does not occur
3. OS, calculated from the date of start of study therapy to the date of death due to any cause, including OS rates at 12 and 24 months
4. QoL, evaluated by the EORTC QLQ-C30

Additional secondary endpoints for the ovarian cancer cohort only include the following:

1. Response to therapy, as determined by DCR, Duration of SD, ORR, and DOR per Gynecological Cancer Intergroup (GCIG) response criteria (RECIST v1.1 and CA-125) (Rustin et al, 2011)
2. PFS, as described above with progression defined per GCIG response criteria (RECIST v1.1 and CA-125)

Data from Part 1 and Part 2 of the study will be analyzed separately for all primary and secondary efficacy endpoints.

CCI [redacted]

1.2.5.3. Safety Parameters

Safety evaluations performed during the study include physical, neurological, and ophthalmic examinations; measurement of vital signs; 12-lead electrocardiogram (ECG); clinical laboratory evaluations including hematology, clinical chemistry, and urinalysis; and monitoring of AEs and concomitant medications.

1.2.5.4. Safety Monitoring Committee

A Safety Monitoring Committee (SMC) will provide additional oversight on the safety of the investigational product, selinexor (KPT-330), as used in this study. The SMC is responsible for reviewing accumulated safety data from the study.

The SMC will have access to all data necessary to formulate their opinion on the safety of the study. This includes efficacy data at the scheduled meetings as this is relevant to assessing the acceptability of the AE profile observed.

2. PATIENT POPULATIONS

2.1. Population Definitions

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

- Modified Intent-to-Treat (mITT) Population: All patients who receive at least one dose of study medication, have measurable disease per RECIST at baseline, and have at least one post-baseline efficacy follow-up information. If the patient has measurable disease per RECIST at baseline, but discontinued treatment prior to the first assessment due to death, toxicity, or PD, they will still be included even if there is no post-baseline efficacy follow-up information. This population will be used for primary analyses of efficacy.
- Per-Protocol (PP) Population: All patients in the mITT population who are compliant with study assessments and who have no protocol violations that would compromise the assessment of efficacy. This population will be used for supportive inferences concerning efficacy. If there are major differences between the results in this population and those obtained in the mITT population, this will be taken into consideration in the decision to continue to later phase studies, or in the design of further studies.
- GCIG Evaluable Population: All patients in the ovarian cancer cohort (Cohort A) who receive at least one dose of study medication, have measurable disease per RECIST at baseline or a baseline CA-125 assessment, and have at least one post-baseline efficacy follow-up information (i.e. either a post-baseline scan or CA-125 assessment). If a patient discontinued treatment prior to the first assessment due to death, toxicity, or PD, they will still be included even if there is no post-baseline efficacy follow-up information. This population will be used for additional efficacy analyses specific to patients with ovarian cancer.
- mITT Extended Population: All patients who receive at least one dose of study medication and have at least one post-baseline efficacy follow-up information. If the patient discontinued treatment prior to the first assessment due to death, toxicity, or PD, they will still be included even if there is no post-baseline efficacy follow-up information. This population will be used for supportive efficacy analyses of select time-to-event endpoints (PFS and OS).
- Safety Population: All patients who have received any amount of study medication. This population will be used as the primary population for analysis of all safety endpoints.

Analysis of efficacy parameters in Part 2 will be based on the randomized treatment assignment for Part 2. Analysis of safety parameters will be based on treatment received, even if different from that randomized in Part 2.

2.2. Protocol Violations

Upon assessment of protocol violations, the Sponsor may determine to remove a patient's data from the PP population in an effort to maintain full compliance with study procedures. This will be performed independent of the knowledge of response to therapy. Classification of protocol violation to major or minor will be performed by the study sponsor. 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 violation and clearly identify

whether or not this violation warrants 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

CCI [redacted]

3. GENERAL STATISTICAL METHODS

3.1. CCI

CCI

[redacted]

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 medication 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 medication 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.

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

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. 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% confidence interval (CI), as well as number and percentage of censored observations and events.

Data will be presented by study part, cohort, and schedule (Part 2 only) as follows:

- Part 1: Cohort A
- Part 1: Cohort B
- Part 1: Cohort C
- Part 2: Cohort A: Schedule 1
- Part 2: Cohort A: Schedule 2

Formal statistical hypothesis testing will be performed on the primary endpoint with all tests conducted at the one-sided 0.10 level of significance for Part 1 and at the two-sided 0.20 level of significance for Part 2. Summary statistics will be presented, as well as CIs on selected parameters, as described in the sections below.

3.3. Computing Environment

All inferential and descriptive statistical analyses will be performed using SAS statistical software Version 9.4, unless otherwise noted. Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 16.0 (or later). Adverse events will be graded using Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (or later). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version Q12013 (or later).

3.4. Baseline Definitions

The baseline for PFS (Parts 1 and 2), OS (Part 1), and duration of stable disease (Parts 1 and 2) is the date of the start of study therapy. The baseline for duration of response is the date of first documented occurrence of response (CR or PR). For all remaining analyses, baseline will be defined as the most recent measurement prior to the first administration of study drug.

3.5. Methods of Pooling Data

Data will be pooled for analysis across all study sites. Separate analysis by-site is not intended, however, data listings will be presented on a by-patient basis, ordered by site and patient identifier.

For each cohort using the Simon 2-Stage design, the DCR results will be presented using data from the first stage of the study and pooled data from both Simon stages together.

3.6. Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned.

3.7. Multiple Comparisons/Multiplicity

Multiplicity is not of concern for this early phase study with a single primary efficacy endpoint. The study is designed to look for preliminary evidence of efficacy through inclusion of all the secondary endpoints, but confirmation of these endpoints in a late phase study will be required.

Separate analysis will be performed across each cohort, with separate conclusions regarding efficacy within each cohort; therefore, no adjustment to alpha-level for cohort analysis is required.

3.8. Subpopulations

Part 1 of the study will enroll three cohorts of ovarian (Cohort A), endometrial (Cohort B), and cervical (Cohort C) cancers which will be evaluated independently. Part 2 of the study will enroll additional ovarian patients to evaluate efficacy and safety of once-weekly versus twice-weekly dosing.

Subtypes of each tumor (e.g., adenocarcinoma versus squamous carcinoma) will be evaluated both together and separately as exploratory analyses.

The subpopulation of ovarian cancer (Cohort A) patients who have a baseline CA-125 assessment will be evaluated per the GCIG response criteria in secondary analyses. Within the secondary analyses, a further subpopulation of patients with an initial CA-125 level of at least twice the upper limit of the reference range will be assessed.

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 electronic case report form (eCRF) will be included in data listings that will accompany the CSR.

No imputation of missing efficacy data is planned, with the exception of partial time-to-event dates. Patients with an event who have only month and year available for the specific time to event analysis will have the event time imputed to the first day of that month. For time to event analyses, patients who have no efficacy evaluations for disease recurrence will be considered censored at time 0. For OS, patients will be censored on the date they were last known to be alive regardless of disease status. For PFS and Duration of SD or DOR, patients without documented PD will be censored on the date of last radiologic disease assessment.

When tabulating time since initial diagnosis, partial dates will be handled as follows. If the day of the month is missing, the day is set to the last day of the month. If the day and month are both missing, the day and month will be assumed to be December 31st.

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 and will be imputed according to

the rules outlined below. 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.

AE Onset date:

If onset date is completely missing, onset date will not be imputed.
If (year is present and month and day are missing) or (year and day are present and month is missing):

- If year = year of first dose, then set month and day to month and day of first dose.
- If year < year of first dose, then set month and day to December 31st.
- If year > year of first dose, then set month and day to January 1st.

If month and year are present and day is missing:

- If year = year of first dose and
  - If month = month of first dose then set day to day of first dose date.
  - If month < month of first dose then set day to last day of month.
  - If month > month of first dose then set day to 1st day of month.
- If year < year of first dose then set day to last day of month.
- If year > year of first dose then set day to 1st day of month.

AE Stop date:

If the outcome of the AE was ongoing or unknown then the rules outlined below will not be applied.
If stop date is completely missing, stop date will not be imputed.
If (year is present and month and day are missing) or (year and day are present and month is missing):

- If year = year of study withdrawal, then set month and day to month and day of study withdrawal.
- If year < year of study withdrawal, then set month and day to December 31st.
- If year > year of study withdrawal, then set month and day to December 31st.

If month and year are present and day is missing:

- If year = year of study withdrawal and
  - If month = month of study withdrawal then set day to day of study withdrawal date.
  - If month < month of study withdrawal then set day to last day of month.
  - If month > month of study withdrawal then set day to last day of month.
- If year < year of study withdrawal then set day to last day of month.
- If year > year of study withdrawal then set day to last day of month

For prior or concomitant medications, missing or partial dates will be imputed as follows:

Start date:

- If start date is completely missing, start date will not be imputed.

- If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to January 1.
- If year and month are present and day is missing, set day to the 1st day of month.

Stop date:

- If end date is completely missing, end date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to December 31st.
- If year and month are present and day is missing, set day to the last day of month

For the QoL analysis, missing data will be handled as described in the EORTC QLQ-C30 Scoring Manual. If less than half of the scores are missing for any domain, the remaining items will be used applying the standard equations for calculating the scale scores. If at least half of the scores are missing, the scale will be missing. For single item measures, the score will be missing. This method is further described in Section 4.3.

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

In accordance with the Simon's two-stage optimal design of Part 1, there will be a preliminary assessment of efficacy for each cohort after the first 8 patients enrolled in that cohort have 6-month data available to assess DCR. Note that this initial analysis for a cohort may take place sooner than when the 8th patient has available data, should there be 3 or more disease control achievers after fewer than 8 patients are enrolled. Should the trial be terminated at the first stage, all efficacy and safety analyses as noted above will be performed. Patient enrollment into the trial will continue while the first stage analysis is being conducted.

3.13. Final Analyses

The final analysis of the primary endpoint DCR for each cohort will take place after the target number of patients evaluable for DCR has been reached. Additional data summarization may take place after all available survival data are collected, or after Sponsor decision, as appropriate.

4. STUDY ANALYSES

4.1. Patient Disposition

Patient disposition will be tabulated and presented separately by cohort and overall for Part 1 and by schedule and overall for Part 2. It will include the number enrolled, the number in each patient population for analysis, the number who discontinued treatment and the primary reason for discontinuation, the number who completed or withrew from the study and primary reason for study withdrawal.

The EOT Visit will occur ≤ 14 days after the patient receives their last dose of study treatment. A Safety Follow-up Call/Visit will be performed 30 days (+7 days) after last dose of study treatment. Follow-up ends when the patient has either completed that 30-day follow-up, withdrawn consent, been withdrawn by the Investigator, died, or been lost to follow-up. The end of study (EOS) will occur upon completion of the 30-day follow-up period for the last patient treated, or when Karyopharm has decided to end the study. Reason for treatment and study discontinuation will be recorded on the eCRF.

A by-patient data listing of study completion information including the reason for study withdrawal, if available, will be presented. By-patient listings of inclusion/exclusion criteria not met and follow-up visit survival status will also be presented.

Relevant Output

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4.2. Demographics, Baseline Characteristics, and Medical History

Demographics, baseline characteristics, and medical history will be summarized and presented by cohort and overall for Part 1 and by schedule and overall for Part 2. Age at date of informed consent, height, weight, and BSA will be summarized using descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum). The number and percentage of patients in each gender, ethnicity and race category will be presented. BSA will be presented using the Dubois and Dubois formula, where BSA = $0.007184 \times \text{Height (cm)}^{0.725} \times \text{Weight (kg)}^{0.425}$ (Dubois and Dubois, 1916).

Baseline characteristics include: Eastern Cooperative Oncology Group (ECOG) performance status; duration from initial diagnosis; response to previous therapy (Y/N).

Medical history will be summarized by System Organ Class (SOC) and Preferred Term. Medical history including baseline symptoms as well as a detailed history of the patient's disease, prior cancer therapies (including start and stop dates), PD during or after prior therapy, as well as discontinuations due to intolerability.

Disease history will include stage at initial diagnosis, primary tumor location, carcinoma subtype, whether at least one recurrence/relapse has been recorded, stage at most recent recurrence/relapse, and whether there are any current metastatic sites of cancer. Time since initial diagnosis, time since initial diagnosis to first recurrence/relapse, and time since most recent recurrent/relapse, will be summarized in months using descriptive statistics.

Prior treatments will include number and percentage of patients with prior radiation therapy (including setting and best overall response of most recent prior therapy), prior antineoplastic therapy (including best overall response and whether disease progressed during or after therapy of most recent prior therapy), and prior surgery type. Number of prior surgeries will be summarized.

Demographic, baseline, and medical history data, including previous antineoplastic therapies, previous radiation therapies, previous surgeries, tumor diagnosis, and disease-related toxicities from prior therapies and pregnancy test results for each patient will be provided in data listings.

Relevant Output

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4.3. Efficacy Evaluation

Efficacy analyses will be conducted using both the mITT and PP populations. Select secondary endpoints will be presented on the mITT extended population and the GCIG evaluable population as described below.

4.3.1. Primary Efficacy Analysis

The analysis of DCR will be performed for each study cohort by calculating the point estimate of the percentage of patients in that cohort who have CR, PR, or SD for at least 12 weeks, assessed according to RECIST v1.1, taking into account the visit window of ±7 days at the 12 week assessment (i.e., at least stable disease for ≥ 77 days).

Duration of SD will be calculated as follows:

- For patients with documented PD, duration will be calculated from the date of start of study therapy until the date of PD.
- For patients without documented PD, duration will be calculated from the date of start of study therapy until the date of last disease assessment.
- For patients without at least one post baseline disease assessment, duration will be censored at time 0.

To be consistent with Simon's two-stage optimal design, a lower one-sided 90% CI will be presented for the DCR in each study cohort. Additionally, for descriptive purposes a two-sided 95% CI will be calculated for each cohort, using exact methods. The DCR for each cohort will be presented for the first stage of the study and for both stages combined, consistent with Simon's two-stage optimal design.

The analysis of differences in DCR for the randomized part of the study (Part 2) will be performed using Fisher's Exact test, accompanied by two-sided 80% and 95% CIs. Data will be presented by schedule and overall in two separate analyses. The first analysis will include all patients randomized to Schedule 1; the second will only include patients who were randomized to Schedule 2.

The analysis of duration of disease control will be based on the KM method for estimation of summary statistics, and will include the 25th, 50th (median), and 75th percentiles and associated 95% CIs.

4.3.2. Secondary Efficacy Analyses

All secondary efficacy analyses will be performed for the pooled data from both Simon stages, so no presentation of results for the first stage of the study is planned.

1. Response to therapy per RECIST v1.1: response for patients in each cohort will be determined by ORR, defined as either CR or PR using RECIST v1.1, calculated as a proportion and including a two-sided 95% CI for that cohort. In addition, to assist in evaluating the evidence of efficacy, a lower one-sided 90% CI for ORR will be calculated for each cohort in Part 1, and a two-sided 80% CI for ORR will be calculated for each schedule in Part 2. DOR will be also calculated from the date of first documented occurrence of response (CR or PR) until the date of documented progression, or last disease assessment, should progression not have occurred. The analysis of DOR will be based on the KM method for estimation of summary statistics, and include the 25th, 50th (median), and 75th percentiles and associated 95% CIs.
2. Response to therapy per GCIG response criteria (RECIST v1.1 and CA-125): response for patients in the ovarian cohort (Part 1 and Part 2) will also be assessed for DCR, Duration of SD, ORR, and DOR, as described above, using the GCIG response criteria. Number and frequency of patients in the ovarian cancer cohort who can be assessed using the GCIG response criteria will be presented. This analysis will be performed on the GCIG Efficacy Population only. In addition, a subset analysis for each endpoint will be conducted on the subgroup of patients with an initial CA-125 level of at least twice the upper limit of the reference range.

For the time-to-event endpoints (duration of SD and DOR), date of first response will be the first of response or progression per CA-125 or RECIST v1.1, whichever occurs first. Patients without documented progression will be censored at the day of their last evaluable disease assessment, either per RECIST or CA-125.

3. PFS: PFS for patients in each cohort will be calculated from the date of start of study therapy to the date of progression based on RECIST 1.1, or date of death due to any cause should progression not have occurred. Patients who do not have documented PD or drop out prior to study end will be censored at the day they were last known to be progression-free (i.e. day of their last evaluable disease assessment). The analysis of PFS for patients in each cohort will be based on the KM method for estimation of summary statistics, and include the 25th, 50th (median), and 75th percentiles and associated 95% CIs.

   In addition to being performed on the mITT and PP populations, there will be three additional PFS analyses:

   a. As described above, but performed on the mITT extended population (i.e. including patients with non-measurable disease per RECIST at baseline).

   b. PFS will also be presented with progression defined per GCIG response criteria (RECIST 1.1 and CA-125). PFS for patients in each cohort will be calculated from the date of start of study therapy to the date of progression based on RECIST 1.1 or CA-125, whichever occurs first, or date of death due to any cause should either type of PD not have occurred. Patients who do not have documented PD will be censored at the day they were last known to be progression-free (i.e. day of their last evaluable disease assessment, either per RECIST or CA-125). This analysis will be performed on the GCIG efficacy population only.

   c. An additional sensitivity analysis may be performed that includes clinical progression (not documented per RECIST) as an event for PFS. For this analysis, PFS for patients in each cohort will be calculated from the date of start of study therapy to the date of progression based on RECIST 1.1 or date of clinical progression identified by the Investigator, whichever occurs first, or date of death due to any cause should either type of PD not have occurred. Patients who do not have documented PD or drop out prior to study end will be censored at the day they were last known to be progression-free (i.e. day of their last evaluable disease assessment per RECIST). This analysis will be performed on the mITT population.

4. OS: OS for patients in each cohort will be calculated from the date of start of study therapy to the date of death due to any cause. Patients who are alive at the time of the analysis or are lost to follow-up will be censored at the day they were last known to be alive. The analysis of OS for patients in each cohort will be based on the KM method for estimation of summary statistics, and include the 25th, 50th (median), and 75th percentiles and associated 95% CIs. OS rate at 12 and 24 months (OS12 and OS24) will also be presented for each cohort, determined from the KM estimate at 12 and 24 months. In addition to being performed on the mITT and PP populations, OS will also be performed on the mITT extended population.

5. QoL: QoL will be evaluated for patients in each cohort, and for all study patients combined by EORTC QLQ-C30 after 6 and 12 weeks of treatment and approximately every 8 weeks thereafter. The EORTC QLQ-C30 questionnaire has 30 general questions, and an additional cohort-specific set of 24 (for cervical and endometrial cancer) (CX24, EN24) or 28 (for ovarian cancer) questions (OV28). Each question is scored using a scale of 1 to 4, representing answers of Not at All, A Little, Quite a Bit, Very much; with the exception of the items contributing to the global health status, which are scored on a scale of 1 to 7, representing a range of Very Poor to Excellent.

   The analysis will be performed on the sub-score of the initial (general) 30 questions of the EORTC QLQ-C30, and separately for the cohort-specific sub-score totals, as described in the EORTC QLQ-C30 Scoring Manual and in Section 4.3.5. All of the scales and single-item measures range in score from 0 to 100, where a high score represents a higher response level. A high score for a functional scale represents a high level of functioning, a high score for the global health status represents a high QoL, and a high score for a symptom scale represents a high level of symptoms or problems. Transformed scores and change from baseline for each scale will be summarized by timepoint, by cohort or schedule, and overall. By-patient listings will be presented for response assessments, including RECIST and GCIG results by visit (the best overall response will be flagged), investigator assessment of target and non-target lesions, and EORTC QLQ-C30 responses.

4.3.3. CCI

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Relevant Output

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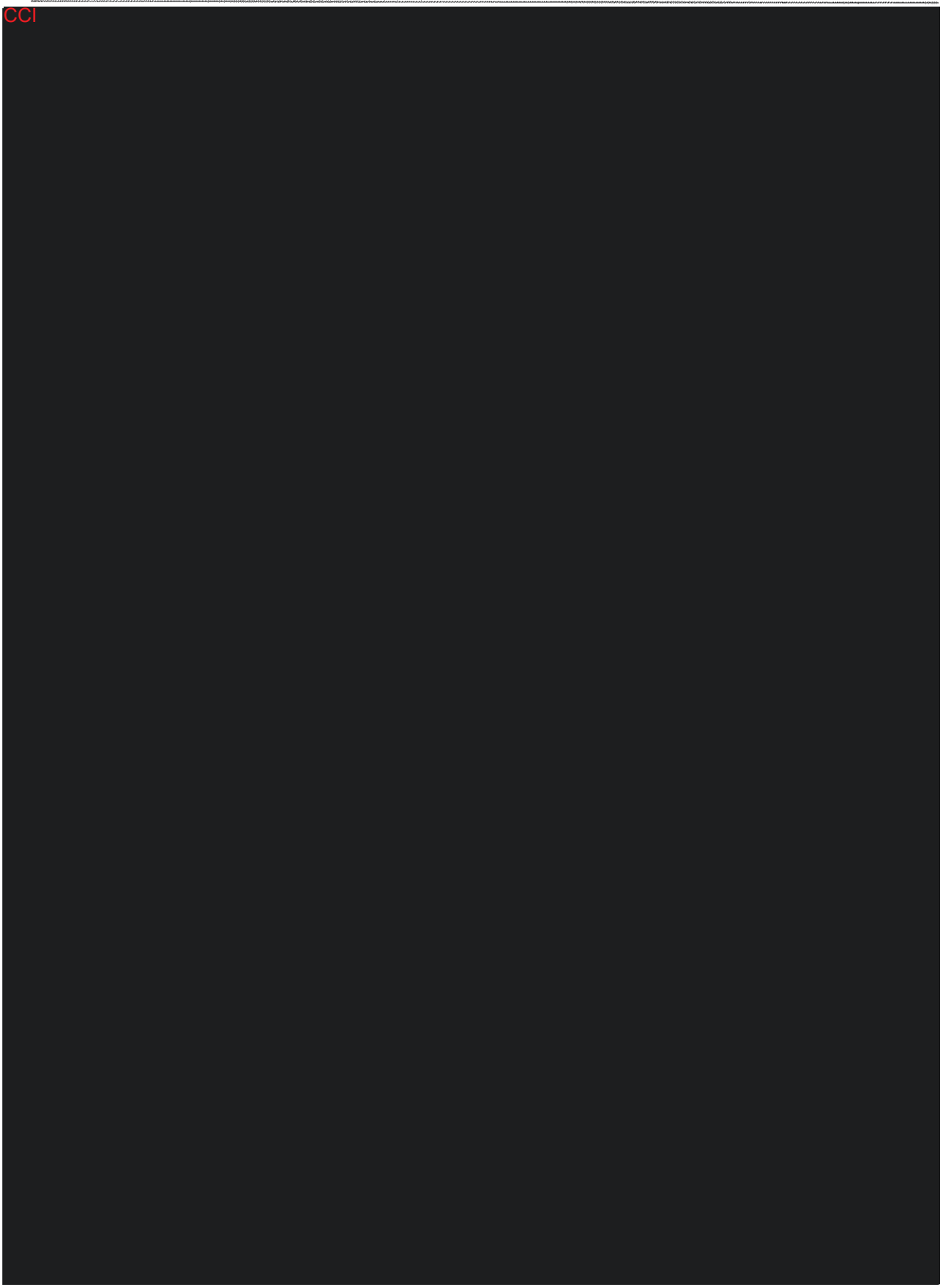

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4.3.4. GCIG Disease Assessment

Disease response per GCIG response criteria will be derived as defined in

Table 4-1 and in Appendices 12 through 14 of the study protocol.

If there was no measurable disease per RECIST at baseline, GCIG response is derived as presented in Table 4-2. If there was measurable disease per RECIST at baseline, GCIG response is derived as presented in Table 4-3. Date of response or progression is the date of the earlier of the 2 assessments (CA-125 or RECIST).

Table 4-1 CA-125 Disease Response

Response Category	Criteria	Additional information
Complete Response	50% reduction in CA-125 levels from a pretreatment sample. The value must also return to within normal range and be maintained for 28 days (i.e. <10% change between response and confirmation sample)	To have a response, the pre-treatment sample must be at least twice the upper limit normal range (ULN). The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response.
Partial Response	50% reduction in CA-125 levels from a pretreatment sample that is maintained for 28 days, but result is not yet within normal range.	For a partial response, the CA-125 is not yet within normal range, the pre-treatment sample must be at least twice the ULN.
Normalized	CA-125 returned to within normal range, but was not twice the ULN at baseline	
Disease Progression	Any of the following scenarios are categorized as PD. For patients with CA-125 elevated at baseline: - If CA-125 normalized (within normal range) at any point, then increases to twice ULN on 2 occasions at least 1 week apart, date of PD is when CA-125 was first measured at twice ULN. - If CA-125 never normalizes (within normal range), then increases to twice the nadir value on 2 occasions at least 1 week apart, date of PD is when CA-125 was first measured at twice the nadir value. For patients with normal CA-125 at baseline: - If CA-125 increases to twice ULN on 2 occasions at least 1 week apart, date of PD is when CA-125 was first measured at twice ULN.	
Non-PR/ Non-PD	None of the above are true	

Table 4-2 Overall GCIG Criteria for Patients without Measurable Disease per RECIST at Baseline

CA-125	Non-target Lesions	New Lesions	Overall GCIG Response
Response and Normalized (CR)	CR	No	CR
Response (PR)	Non-PD	No	PR
Normalized but no response	Non-CR/Non-PD	No	SD
Non-PR/non-PD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 4-3 Overall GCIG Criteria for Patients with Measurable Disease per RECIST at Baseline

Target Lesions	Non-target Lesions	New Lesions	CA-125 Response	Overall GCIG Response
CR	CR	No	Normal [1]	CR
CR	Non-CR/Non-PD	No	Not PD [2]	PR
CR	CR	No	PR	PR
CR	Not evaluable	No	PR but not normal	PR
PR	Non-PD or Not all evaluated	No	Not PD	PR
Not all evaluated	Non-PD	No	PR	PR
PD or New Lesion >28 days from CA-125 Response [3]			PR	PR
SD	Non-PD	No	PR	PR
SD	Non-PD or Not all evaluated	No	Not PR/ Not PD	SD
PD or New Lesion ≤28 days from CA-125 Response [3]			PR	PD
PD	Any	Yes or No	Any	PD
Any	PD	Yes or No	Any	PD
Any	Any	Yes	Any	PD
Any	Any	Yes or No	PD	PD

Note: See Table 4-1 for CA-125 response definitions.
[1] "Normal" includes both Normalized and CR.
[2] "Not PD" includes Normalized, CR, or PR.
[3] Patients who have CA-125 response that occurs more than 28 days from PD according to RECIST 1.1 are considered a PR, according to best response, but PD if the RECIST 1.1 PD is within 28 days of CA-125 response.

4.3.5. EORTC QLQ Scoring

The EORTC QLQ assessments will be scored according to the EORTC QLQ-C30 Scoring Manual, as described below.

Raw Score:

For all scales, the Raw Score (RS) is the mean of the component items, where I = Item:

- Raw Score: RS = $(I_1 + I_2 + \ldots + I_n)/n$

The items for each scale are identified in Table 4-4, Table 4-5, Table 4-6, and Table 4-7.

Transformed Score:

For each domain, the linear transformation is as follows:

- Functional scales: Score = {1- ((RS −1)/range)}*100
- Symptom scales / items and Global health status / QoL: Score ={(RS −1)/range}*100

Range is the difference between the maximum possible value of RS and the minimum possible value. Most items are scored 1 to 4, giving range = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with range = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have range = 1.

Example: Emotional Functioning: RS = (Q21+Q22+Q23+Q24)/4

EF Score = {1- (RS-1)/3}*100

Missing Scores:

If less than half of the scores are missing for any domain, the remaining items will be used applying the standard equations given above for calculating the scale scores. If at least half of the scores are missing, the scale will be missing. For single item measures, the score will be missing.

Example: Q23 is missing

Emotional Functioning: RS = (Q21+Q22+Q24)/3

EF Score = {1- (RS-1)/3}*100

Table 4-4 EORTC QLQ-C30 Scoring – General Questions

Domain	Scale		Number of Items	Item Range*	Version 3.0 Item Numbers
Global health status	Global health status /QoL	QL2	2	6	29, 30
Functioning Scales	Physical functioning	PF2	5	3	1 to 5
	Role functioning	RF2	2	3	6, 7
	Emotional functioning	EF	4	3	21 to 24
	Cognitive functioning	CF	2	3	20, 25
	Social functioning	SF	2	3	26, 27
Symptom scales/items	Fatigue	FA	3	3	10, 12, 18
	Nausea and vomiting	NV	2	3	14, 15
	Pain	PA	2	3	9, 19
	Dyspnoea	DY	1	3	8
	Insomnia	SL	1	3	11
	Appetite loss	AP	1	3	13
	Constipation	CO	1	3	16
	Diarrhoea	DI	1	3	17
	Financial difficulties	FI	1	3	28

* Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.

Table 4-5 EORTC QLQ-OV28 Scoring - Ovarian Cancer Supplement

Domain	Scale	Number of Items	Item Range*	Version 3.0 Item Numbers
Symptom scales/items	Abdominal/GI	6	3	1 to 6 (31 to 36 in eCRF)
	Peripheral neuropathy	2	3	11, 12 (41, 42)
	Hormonal	2	3	18, 19 (48, 49)
	Body image	2	3	20, 21 (50, 51)
	Attitude to disease/treatment	3	3	22 to 24 (52 to 54)
	Chemotherapy side effects	5	3	13 to 17 (43 to 47)
	Other single items	4	3	7 to 10 (37 to 40)
	Sexuality**			25 to 28 (55 to 58)

* Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.

** The scaling performance of items 25-28 has yet to be established.

Table 4-6 EORTC QLQ-CX24 Scoring - Cervical Cancer Supplement

Domain	Scale		Number of Items	Item Range*	Version 3.0 Item Numbers
Functional Scales	Body image	CXBI	3	3	15-17 (45-47 in eCRF)
	Sexual activity	CXSXA	1	3	19 (49)
	Sexual enjoyment	CXSXE	1	3	24 (54)
	Sexual/vaginal functioning	CXSV	4		20-23 (50-53)
Symptom scales	Symptom experience	CXSE	11	3	1-7, 9, 11-13 (31-37, 39, 41-43)
	Lymphoedema	CXLY	1	3	8 (38)
	Peripheral neuropathy	CXPN	1	3	10 (40
	Menopausal symptoms	CXMS	1	3	14 (44)
	Sexual worry	CXSW	1	3	18 (48)

* Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.

Table 4-7 EORTC QLQ-EN24 Scoring - Endometrial Cancer Supplement

Domain	Scale		Number of Items	Item Range*	Version 3.0 Item Numbers
Functional Scales	Sexual interest	ENSXI	1	3	49
	Sexual activity	ENSXA	1	3	50
	Sexual enjoyment	ENSXE	1	3	54
Symptom scales	Lymphoedema	ENLY	2	3	31-32
	Urological symptoms	ENUR	4	3	34-37
	Gastrointestinal symptoms	ENGI	5	3	38-42
	Poor body image	ENBI	2	3	47-48
	Sexual/vaginal problems	ENSXV	3	3	51-53
	Pain in back and pelvis	ENBP	1	3	33
	Tingling/numbness	ENTN	1	3	43
	Muscular pain	ENMP	1	3	44
	Hair loss	ENHL	1	3	45
	Taste change	ENTC	1	3	46

* Item range is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving range = 3.

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Relevant Output

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4.5. Safety Analyses

Safety analyses will be conducted using the safety population.

4.5.1. Study Drug Exposure

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

Duration of study drug exposure will be calculated as the number of day patients were administered study drug, as determined below, and will be summarized by cohort 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.

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

Percent compliance will be summarized for each patient from date of first dose through the treatment period per the following definition:

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

Patient compliance with study drug will be summarized by cohort 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.

Total drug taken will be presented in mg, and 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. For patients receiving a mg/m^2 dose, amount of drug prescribed will be calculated using baseline BSA calculated using the Dubois and Dubois formula listed in Section 4.2 (Dubois and Dubois, 1916).

Dose intensity (defined as total drug taken divided by duration of exposure, presented in mg/day and mg/week), number of missed doses, number of dose interruptions, duration of dose interruption, number of dose reductions, and number of dose escalations will also be summarized. 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.

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

Relevant Output

CCI

[redacted]

4.5.2. Adverse Events

AEs will be coded using the MedDRA dictionary and displayed for all study patients combined, in tables and listings using 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 administration of study medication through 30 days following last dose or any event considered drug-related by the investigator through the end of the study. AEs with partial dates will be assessed using the available date information and will first be imputed according to the rules outlined in Section **Error! Reference source not found.** to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent.

Adverse events will be summarized by patient incidence rates, therefore, in any tabulation, a patient contributes only once to the count for a given AE preferred term.

An overall summary of AEs will be provided and will include the number and percentage of patients with any treatment-emergent AE (TEAE), further separated by maximum severity, with at least one treatment-related TEAE, with any TEAE with a CTCAE severity Grade ≥3, with any treatment-emergent SAE, with any treatment-related (determined by the Investigator as possibly related or related) treatment-emergent SAE, with any TEAE leading to discontinuation of study drug, 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, non-serious TEAEs, TEAEs by CTCAE severity grade, and TEAEs with a CTCAE severity grade ≥3. Common TEAEs occurring in ≥10% of the overall safety population will be presented by preferred term, in descending frequency, by cohort and overall.

No formal hypothesis-testing analysis of AE incidence rates will be performed.

All AEs (treatment emergent and post-treatment) occurring on-study will be listed in patient data listings.

By-patient listings will also be provided for the following: AEs leading to death, SAEs, and AEs leading to discontinuation of study medication.

Relevant Output

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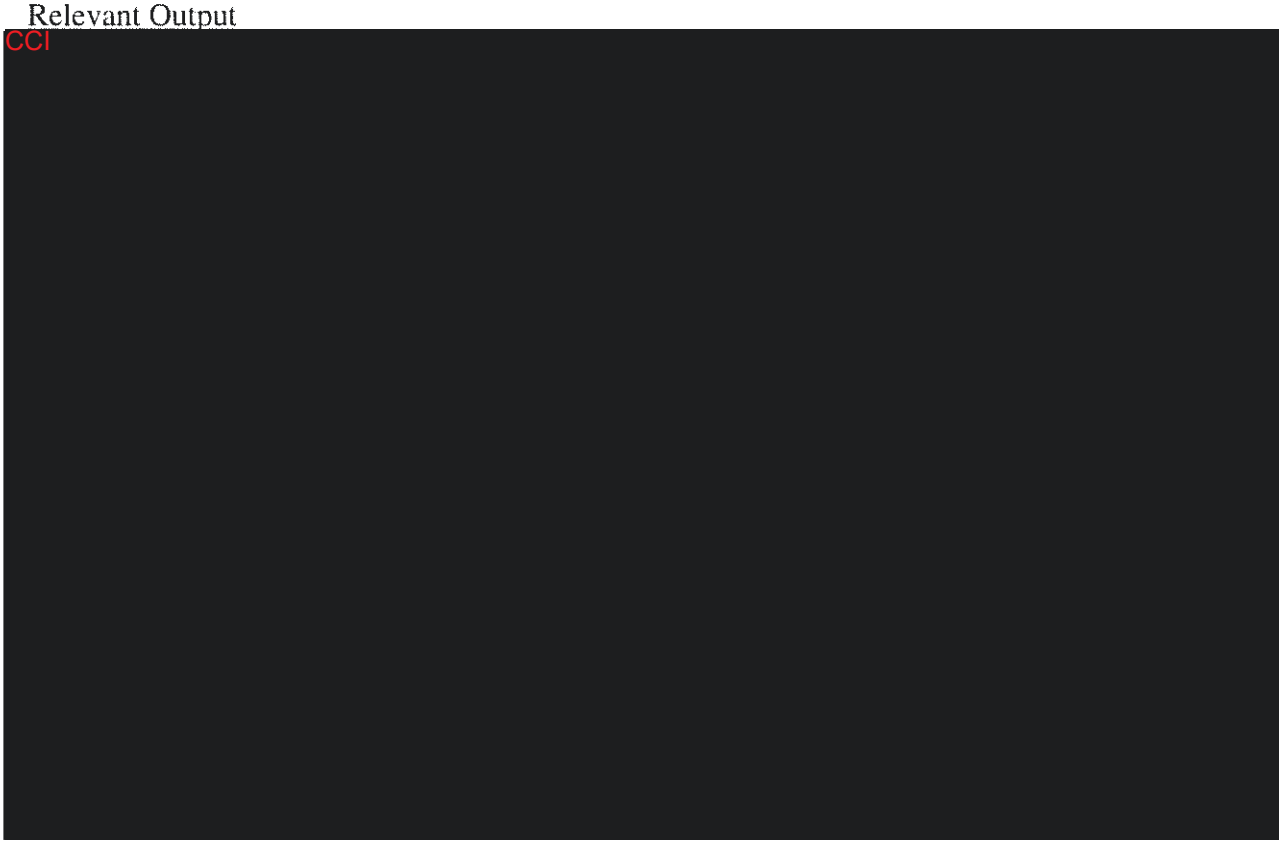

4.5.3. Laboratory Data

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

The actual value and change from baseline (Day 1, or in general, the last evaluation prior to initiation of study treatment) to each on-study evaluation will be summarized for each clinical laboratory parameter, including hematology, clinical chemistry, coagulation, and urinalysis, for all study patients combined. 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 laboratory 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 values relative to CTCAE classification ranges will be produced. Unscheduled visits will not be included in the laboratory summaries, other than the shift table for worst on-study values.

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 and summary table.

Relevant Output

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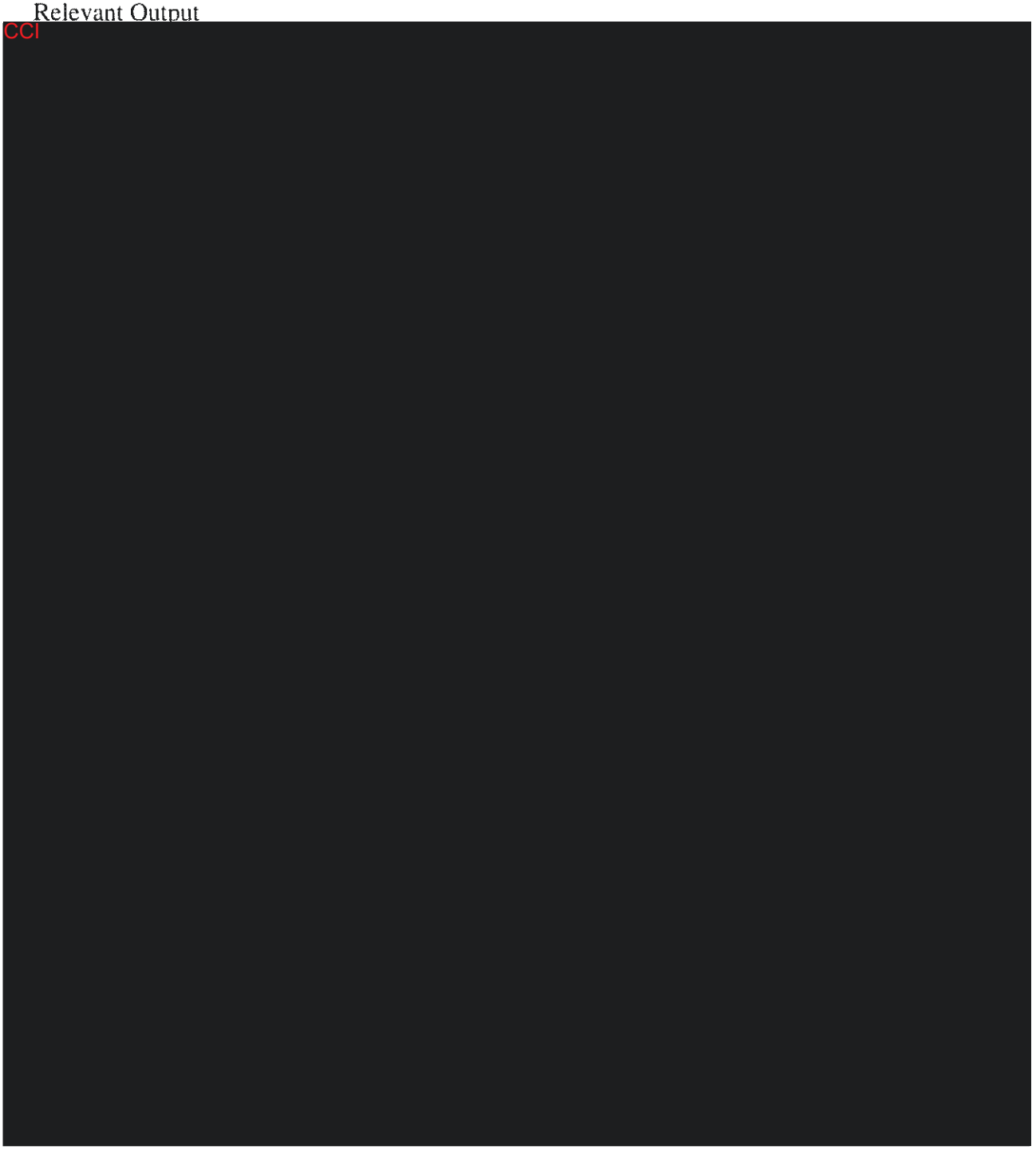

4.5.4. Vital Signs and Physical Examination

The actual value and change from baseline (Day 1, or in general, the last evaluation prior to initiation of study treatment) to each on-study evaluation will be summarized for vital signs for all study patients combined.

Vital sign measurements will be presented for each patient in a data listing.

Physical examination results at screening will be summarized.

All physical examination findings will be presented in data listings.

Relevant Output

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4.5.5. Electrocardiogram

ECG results will be summarized descriptively, including heart rate and PR, QRS, QT, and QTc (calculated by the Fridericia correction formula) intervals. QTc intervals calculated by the Bazett formula will be transformed to Fridericia. 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.

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

Relevant Output

CCI [redacted]

4.5.6. Neurological Examinations

Neurological examination findings will be presented via shift tables, summarizing the changes from baseline to worst value for each parameter.

All neurological examination findings will be presented in a data listing.

Relevant Output

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4.5.7. Ophthalmic Examinations

Ophthalmic examination results for visual acuity, tonometry, slit lamp exam, and dilated funduscopy at each time point will be summarized.

All ophthalmic examination findings will be presented in data listings.

Relevant Output

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4.5.8. Concomitant Medications

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. Patients may continue their baseline medication(s), but all concomitant medication(s) must be reported in the eCRF. Any diagnostic, therapeutic or surgical procedure performed during the study period should be recorded, including the dates, description of the procedure(s) and any clinical findings.

Patients will receive concomitant medications to manage cancer symptoms, AEs, and intercurrent illnesses that are medically necessary as standard care. Medications to treat concomitant diseases like diabetes, hypertension, etc. are allowed.

Concomitant medications will be coded using the WHO Drug Dictionary. Results will be tabulated by anatomic therapeutic classification (ATC) and preferred term.

Concomitant medications will be tabulated by cohort and overall, where any medications that did not end prior to first dose of study medication and any medications started after the first dose of study medication will be included. If an end date is missing or the medication is ongoing, the medication will be included in the tabulation.

The use of concomitant medications and concomitant procedures will be included in a by-patient data listing. Separate by-patient listings will present prophylactic therapies and antineoplastic therapies received following study drug.

Relevant Output

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5. CHANGES TO PLANNED ANALYSES

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In Protocol Section 8.4.1, it is noted that no imputation of missing efficacy data is planned. In Section 3.10 of this document, it is noted that partial time-to-event dates with only month and year available will be imputed by setting the day to the first day of the month.

Protocol Section 8.3 describes 3 populations (mITT, PP, and Safety population) to be used for study analyses. In Section 2.1 of this document, two additional populations are included, the GCIG Evaluable population and the mITT Extended population. In addition, the mITT population definition is updated to include the criterion that patients have measurable disease per RECIST v1.1 at baseline.

6. REFERENCES

DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Medicine. 1916; 17:863-71.

Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001

Greimel E, Nordin A, Lanceley A, et al. Psychometric validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire- Endometrial Cancer Module (EORTC QLQ-EN24) Eur. J Cancer (2010), doi:10.1016/j.ejca.2010.08.014

Greimel ER, Kuljanic Vlasic K, Waldenstrom AC, et al. The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Cervical Cancer Module: EORTC QLQ-CX24. Cancer 14:1812-1822, 2006.

Jemal A, Bray F, Center MM et al. Global Cancer Statistics. CA Cancer J Clin 2011;6:69-90.

Monk BJ, Herzog TJ. The evolution of cost-effective screening and prevention of cervical carcinoma: implications of the 2006 consensus guidelines and human papillomavirus vaccination. American Journal of Obstetrics and Gynecology 2007;197:337–9.

Mosteller RD. Simplified Calculation of Body Surface Area. N Engl J Med. 1987 Oct 22;317(17):1098.

Rustin GJS, Vergote I, Eisenhauer E, et al. Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIC). Int J Gynecol Cancer 2011;21: 419-423.

Siegel R, Naishadham D, Jemal A. Cancer statistics 2013. CA Cancer J Clin 2013;63(1):11-30.

Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10:1-10.

7. CLINICAL STUDY REPORT APPENDICES

7.1. List of Statistical Tables

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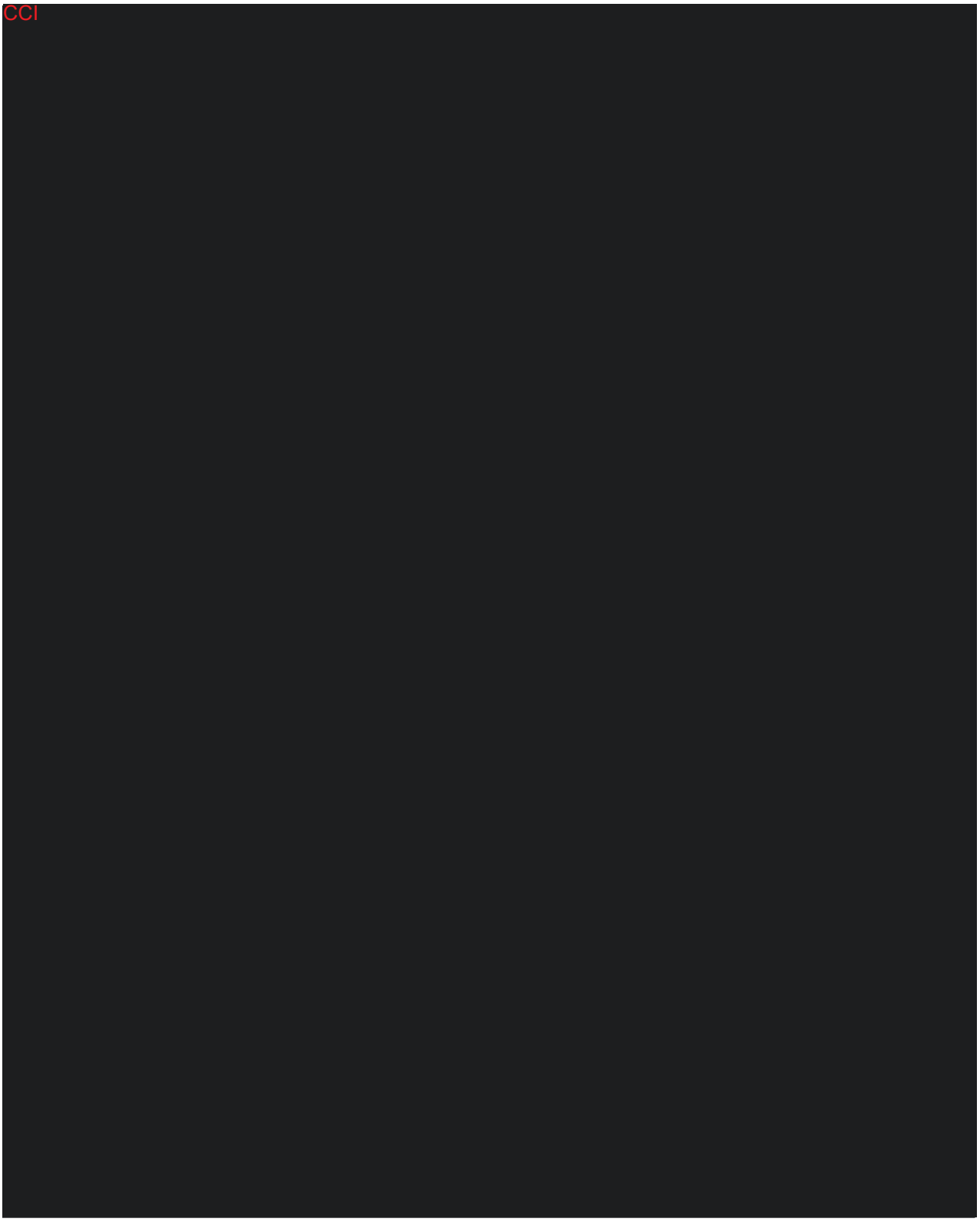

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7.2. List of Statistical Figures

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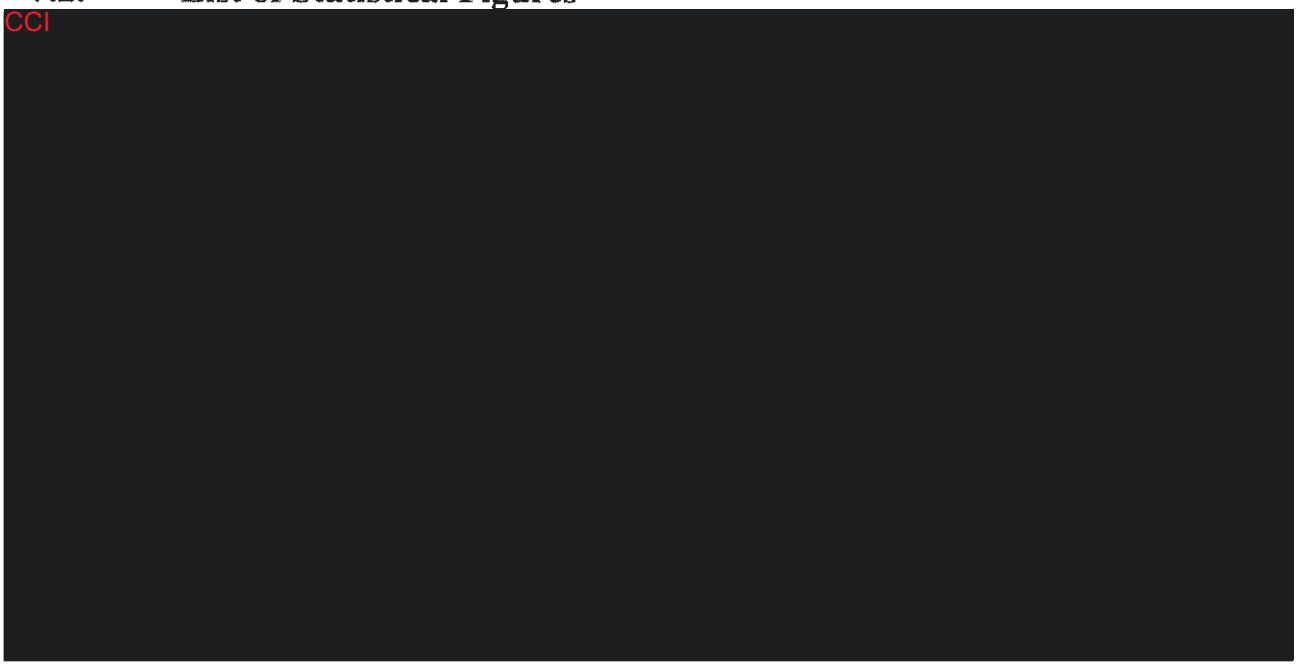

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7.3. List of Statistical Data Listings

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7.4. Table and Figure Shells

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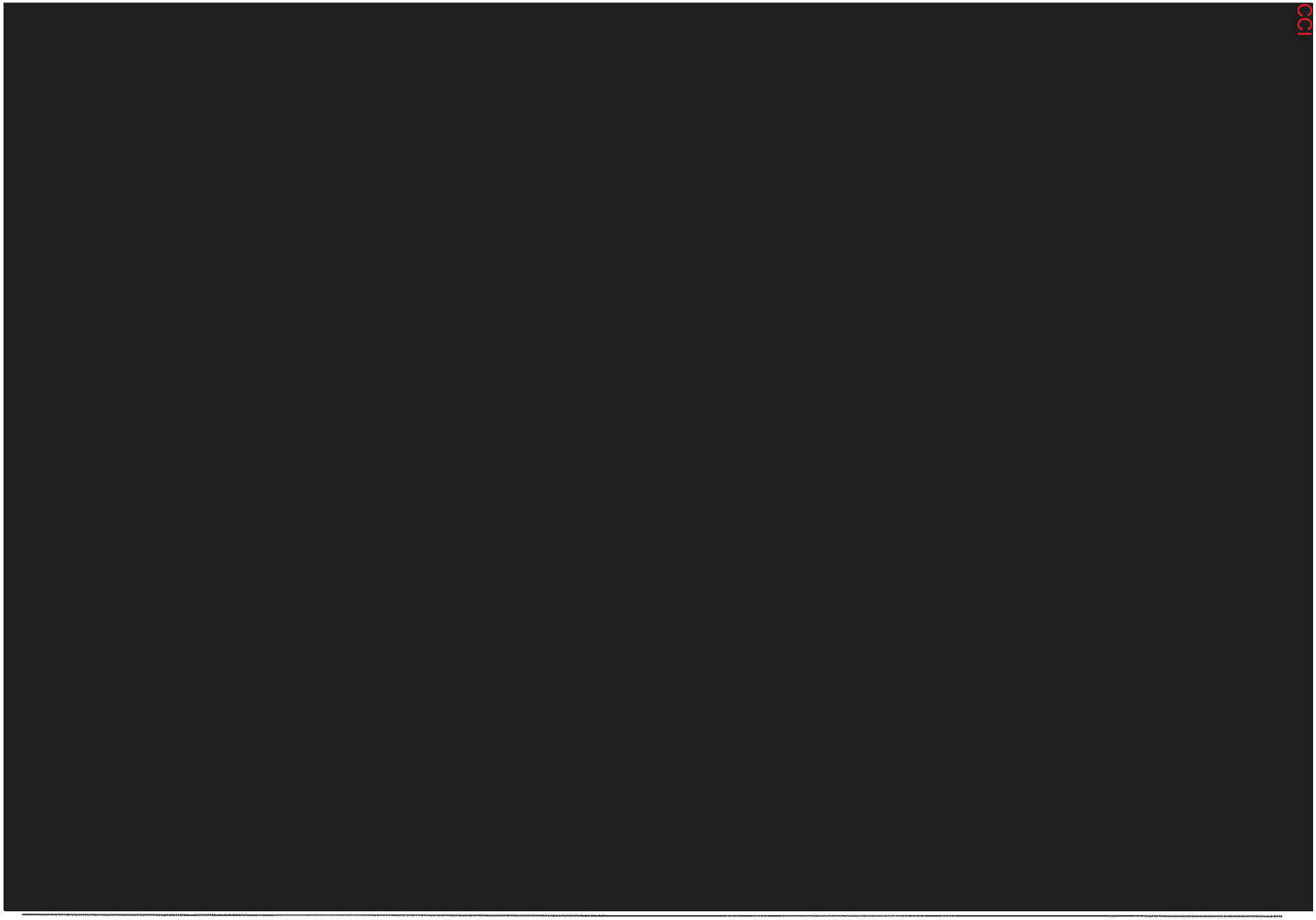
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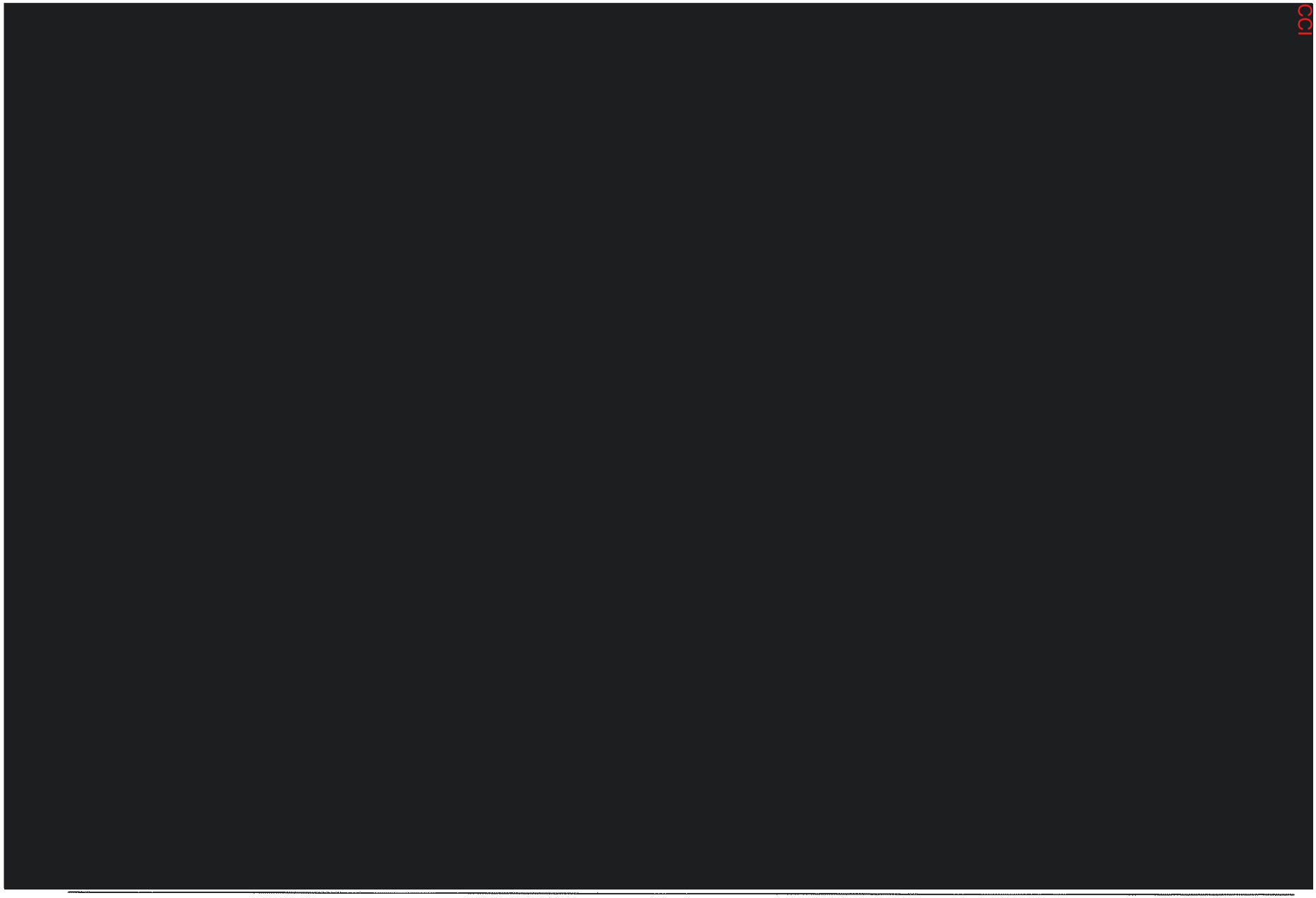

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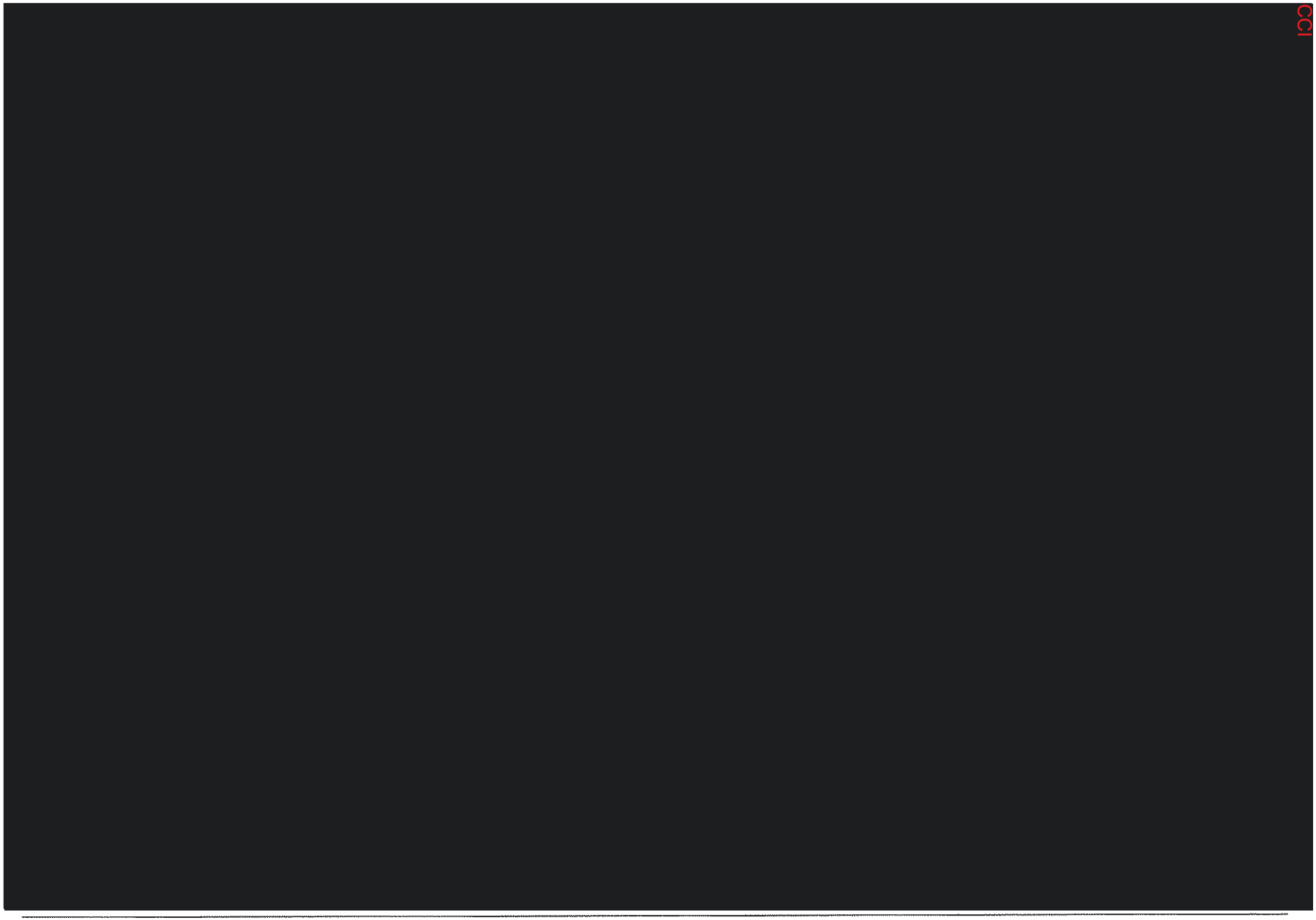
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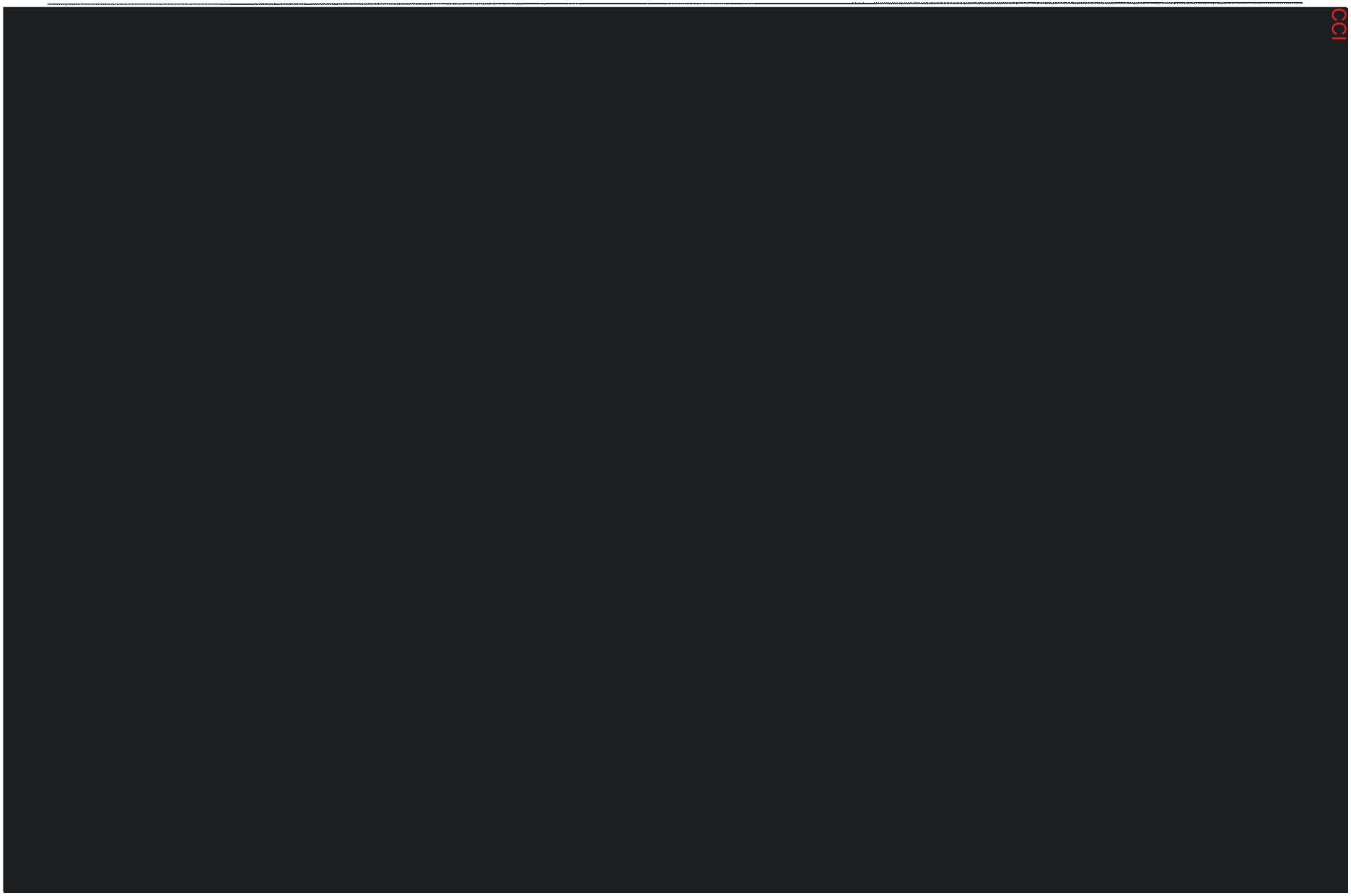
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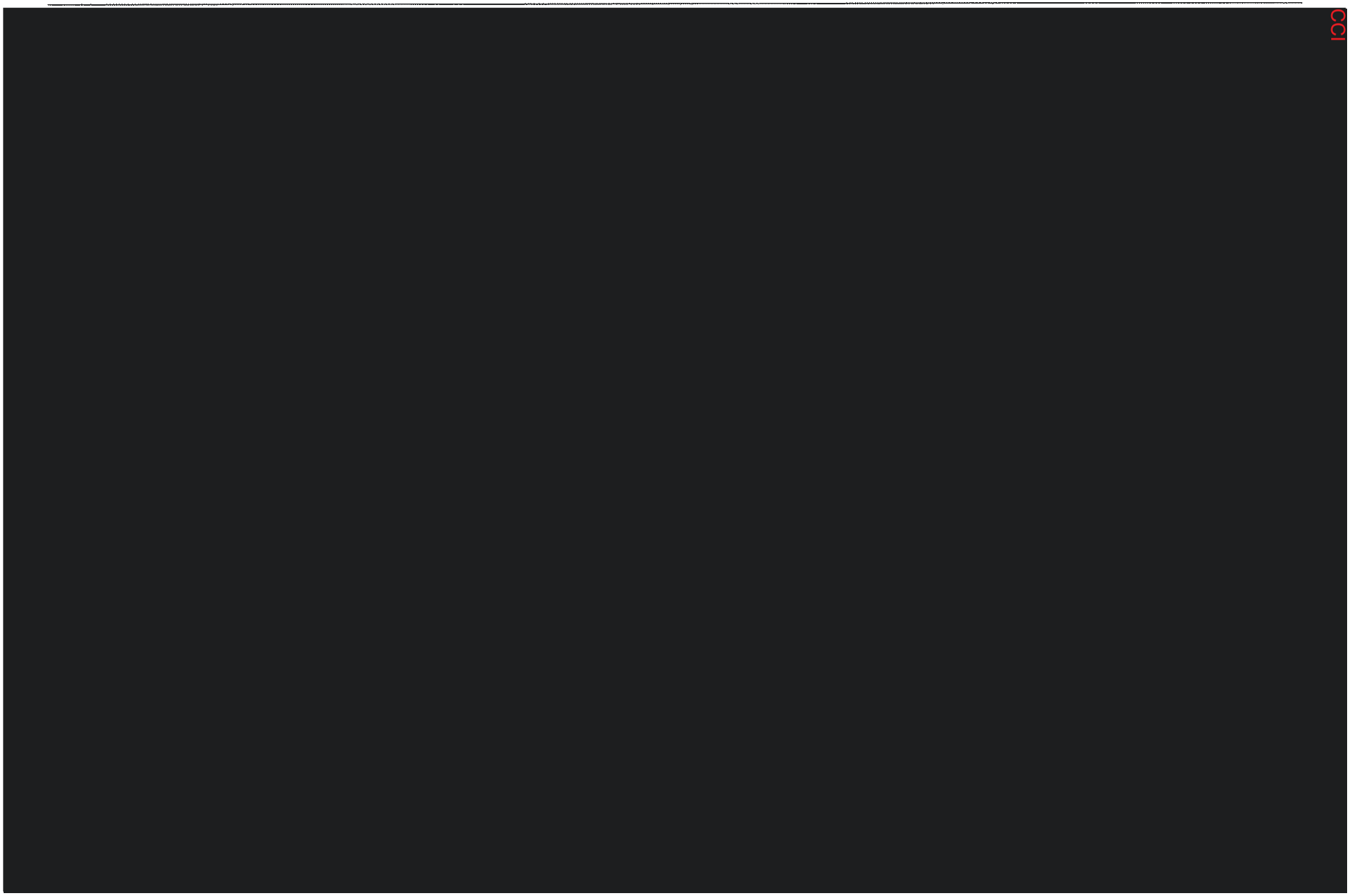
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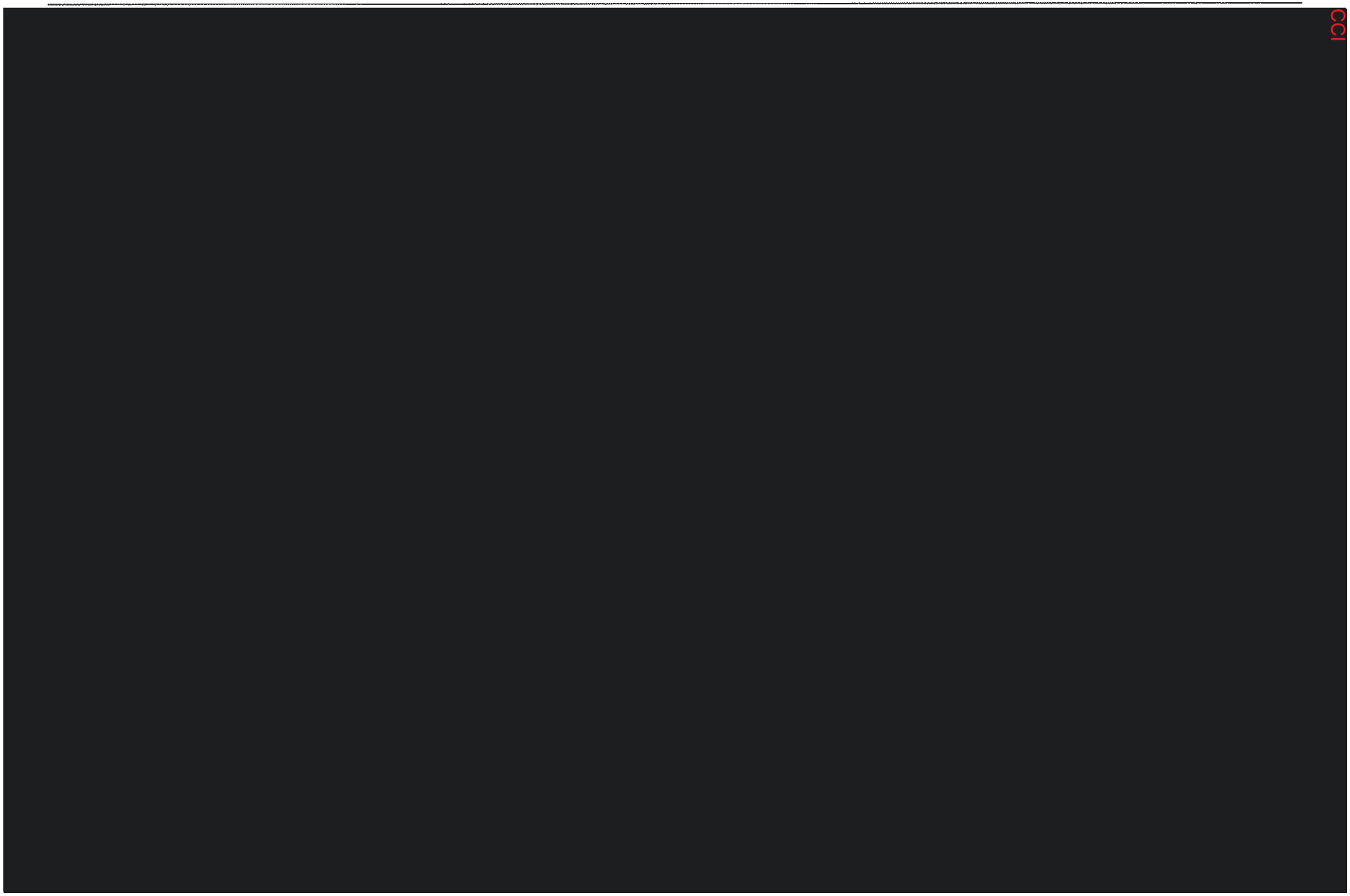
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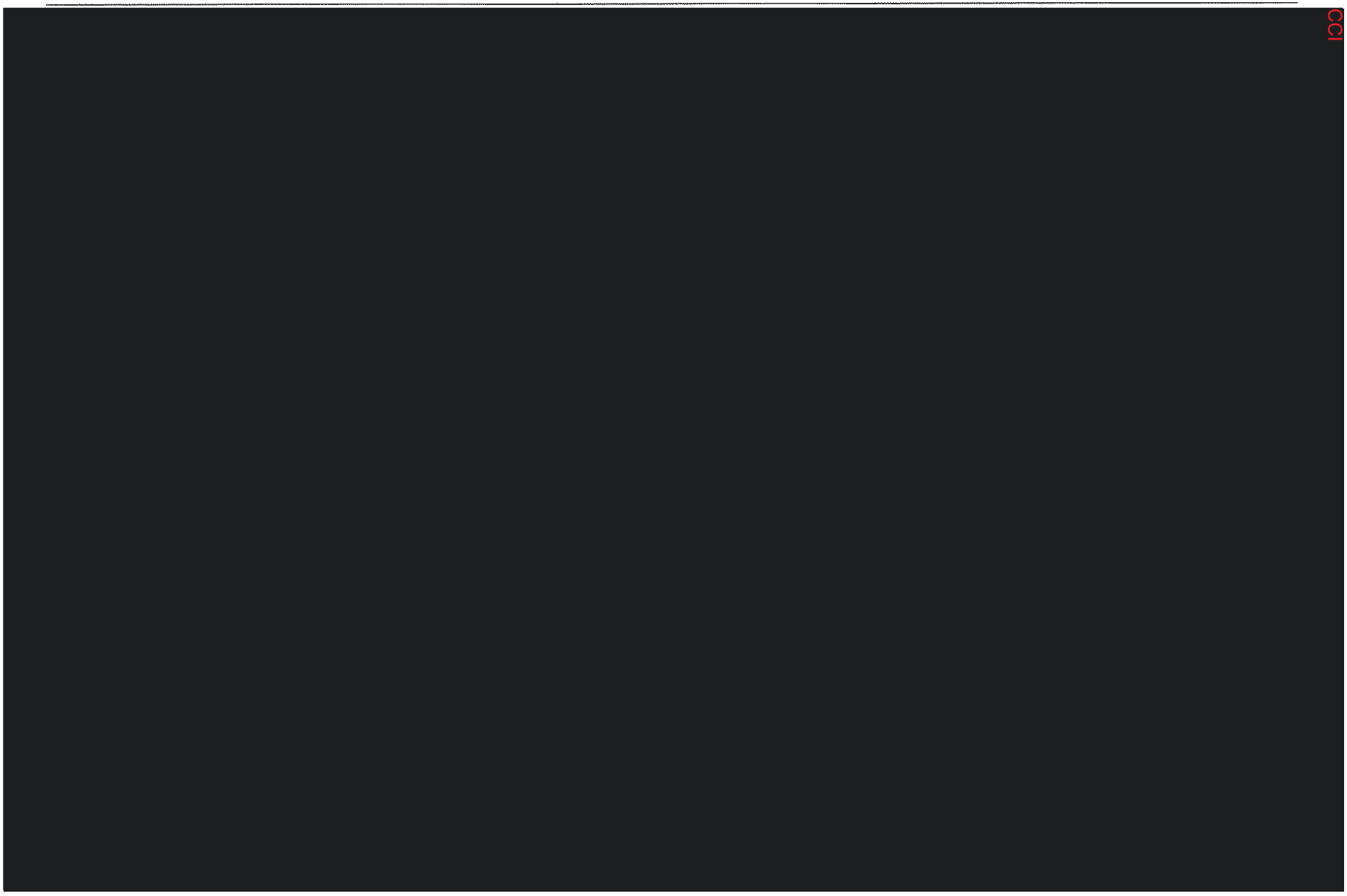
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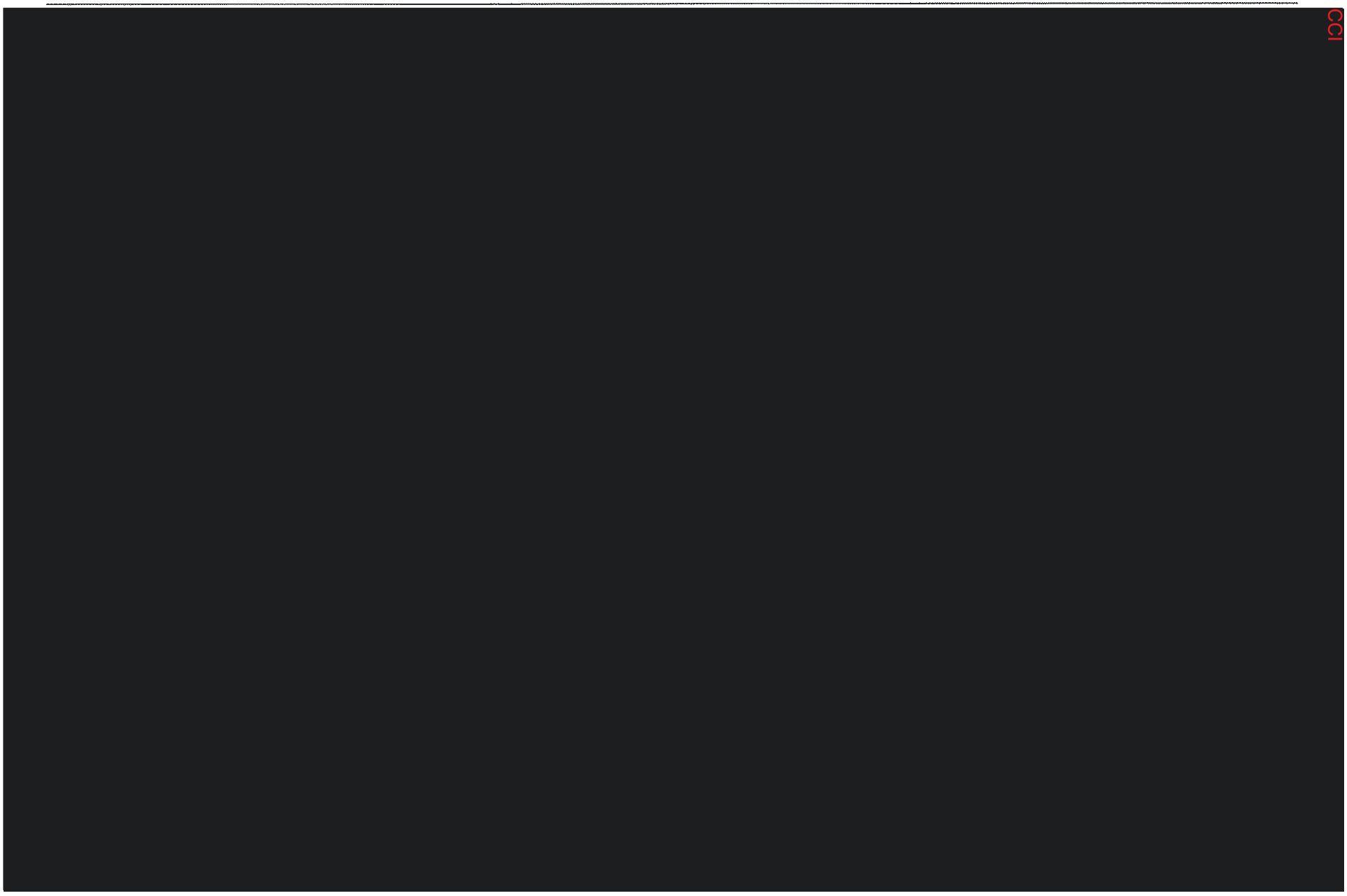
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8. REVISION HISTORY

8.1. Statistical Analysis Plan Version 2.0: 20 April 2015

Rationale of Revisions

Changes were made to the SAP according to Protocol Version 4.0 dated 23 March 2015, including an update to the study title and sponsor representatives. Changes throughout the document include minor editorial changes and the addition of Part 3, the breast cancer cohorts.

Description of Revisions Affecting Section 1

- Section 1.1: Introduction – Additional text was added describing background on the addition of the breast cancer cohorts.
- Section 1.1.2: Study Objectives – The secondary objectives were updated to add more detail. CCI [redacted]
- Section 1.2: Study Design - The description of the dosing schedule and schedule of assessments were updated per the protocol amendment noted above.

Description of Revisions Affecting Section 2

- Section 2.1 Population Definitions – The definition of the mITT population was updated to include patients that discontinued treatment prior to the first assessment due to death, toxicity, or disease progression. The criterion of receiving at least 2 cycles of therapy was removed from the PP population.
- Section 2.2 Protocol Violations – The data monitoring group was removed from this section, as this is not separate from Veristat for this study.

Description of Revisions Affecting Section 3

- Section 3.1 Sample Size Justification – Text was added to include sample size justifications for Part 3, as well as the addition of the term "evaluable".
- Section 3.7 Multiple Comparisons – Text was added to verify that confirmation of secondary endpoints in a later phase study will be required.

Description of Revisions Affecting Section 4

- Section 4.3 Efficacy Evaluation - This section was updated to note that the visit window of ±7 days at the 12 and 24 week assessments is taken into account when calculating the point estimate of the percentage of patients in that cohort who have CR, PR, or SD for at least 12 or 24 weeks. Details for scoring the EORTC QLQ were added for the breast cancer supplement.
- Section 4.5.1 Study Drug Exposure – This section was updated to include additional exposure calculations to be presented.

Description of Revisions Affecting Section 6

- Section 6 References – Additional references were added for the breast cancer cohorts.

Description of Revisions Affecting Section 7

- Section 7 Clinical Study Report Appendices – This section title was updated. Table, figure, and listing shells were updated to include presentation of the breast cancer cohorts.

Description of Revisions Affecting Section 8

- This section (Section 8 Revision History) was added to describe revisions from previous versions.

Description of Revisions Affecting Section 9

- The Randomization Plan has been updated to include the breast cancer cohorts. The new version (2.0) is appended to this document.

8.2. Statistical Analysis Plan Version 3.0: 07 April 2016

Rationale of Revisions

Changes were made to the SAP according to Protocol Version3.1 dated 08 January 2016. Note that Protocol Version 4.0 was never submitted to an IRB or regulatory authority, so while the previous SAP and Randomization Plan were finalized off of that version, it is removed from the title page of this document. The randomization methodology has not been changed.

Changes throughout the document include minor editorial changes and the removal of Part 3, the breast cancer cohorts.

Description of Revisions Affecting Section 1

CCI [redacted]

- Section 1.2.1 Synopsis of Study Design was updated to include minor editorial changes and additional information regarding dose reductions and escalations.
- Section 1.2.3 Stopping Rules was updated to add further detail on reasons a patient may come off treatment.
- Section 1.2.4 Study Procedures was updated to include modifications to the schedule of assessments.
- Section 1.2.5.1 Efficacy Parameters was updated to include editorial changes, further clarification on endpoints, and the GCIG response criteria assessments for the ovarian cancer cohort.

Description of Revisions Affecting Section 3

- Section 2.1 Population Definitions was updated to further define each efficacy population, including by adding 2 new populations (GCIG Evaluable and mITT Extended).
- Section 2.2 Protocol Violations was updated to include that violations will be assessed independent of knowledge of response to therapy.

Description of Revisions Affecting Section 3

- Section 3.1 Sample Size Justification was updated to remove the planned breast cancer cohorts description.
- Section 3.2 General Methods was updated to clarify presentation of data.
- Section 3.8 Subpopulations was updated to include the subsets of ovarian patients with a baseline CA-125 assessment and with a baseline CA-125 assessment at least twice the upper limit of normal.
- Section 3.10 Missing, Unused, and Spurious Data was updated to include further detail on partial dates, both for time to event and baseline data. Detail on missing data for QoL analysis was also added.

Description of Revisions Affecting Section 4

- Section 4.2 Demographics, Baseline Characteristics, and Medical History was updated to note that baseline BSA will be summarized using the Dubois and Dubois formula. In addition, the most recent therapy will be summarized for prior therapy summaries. Tables will be presented for both the mITT and Safety populations.
- Section 4.3 Efficacy Evaluation was updated to include the following:
  - An additional analysis of duration of stable disease based on the Kaplan-Meier method for estimation of summary statistics
  - Additional details regarding analysis of duration of response and PFS
  - Response to therapy per GCIG response criteria (RECIST 1.1 and CA-125) as an evaluation, including details on how to derive the response in Section 4.3.1
  - Additional PFS and OS analyses on the mITT extended population (i.e. including patients with non-measurable disease per RECIST at baseline)
  - Potential for an additional exploratory analysis of PFS including clinical progression as an event

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- Section 4.5 Safety Analysis was updated to include further detail on exposure data. Detail was added for the ECG evaluations, to provide the formula used to calculate QTc intervals calculated by the Fridericia formula. Section 4.5.7 Ophthalmological Examinations was added.

Description of Revisions Affecting Section 5

- Additional changes from the protocol are described.

9. APPENDICES

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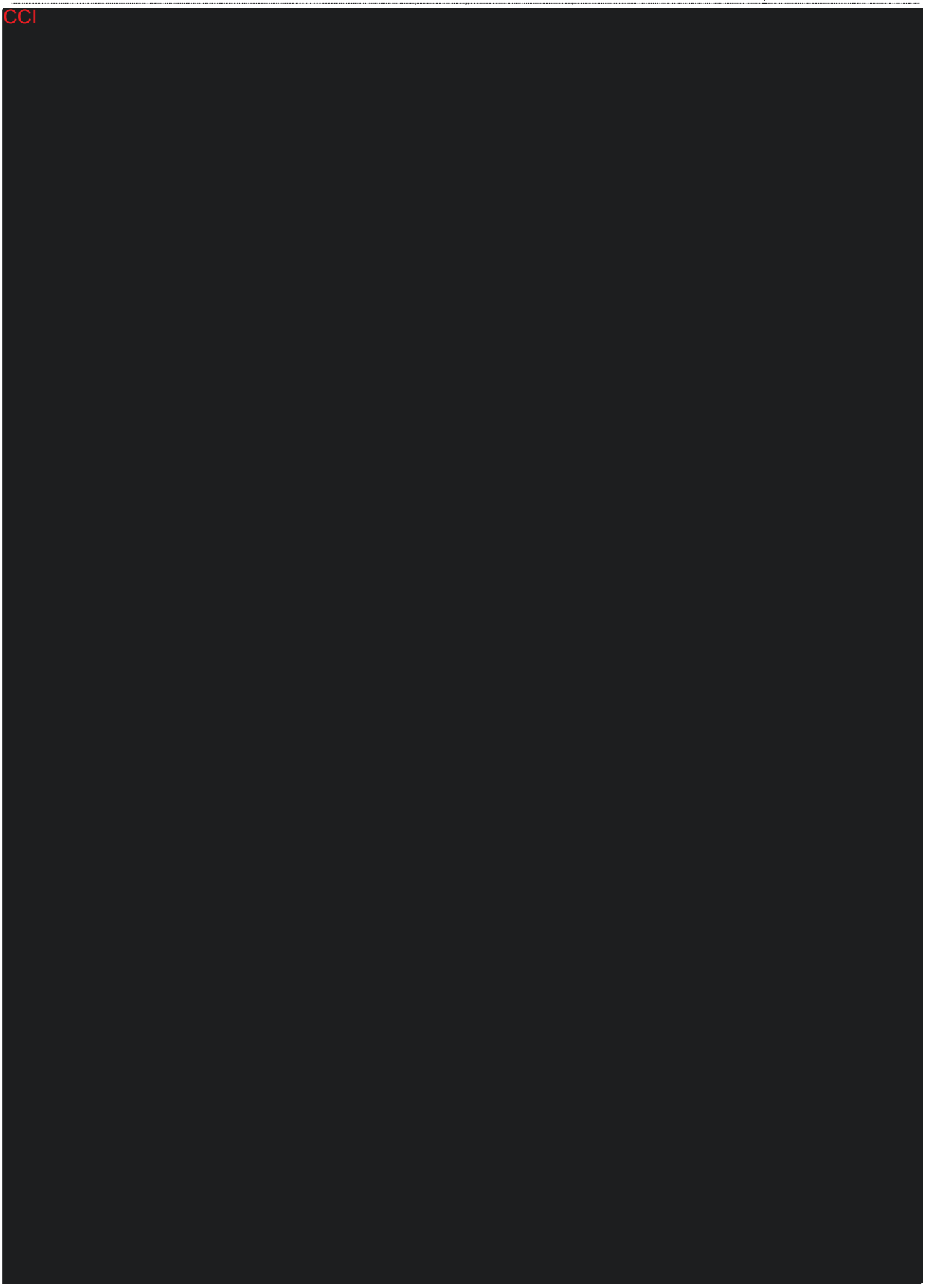

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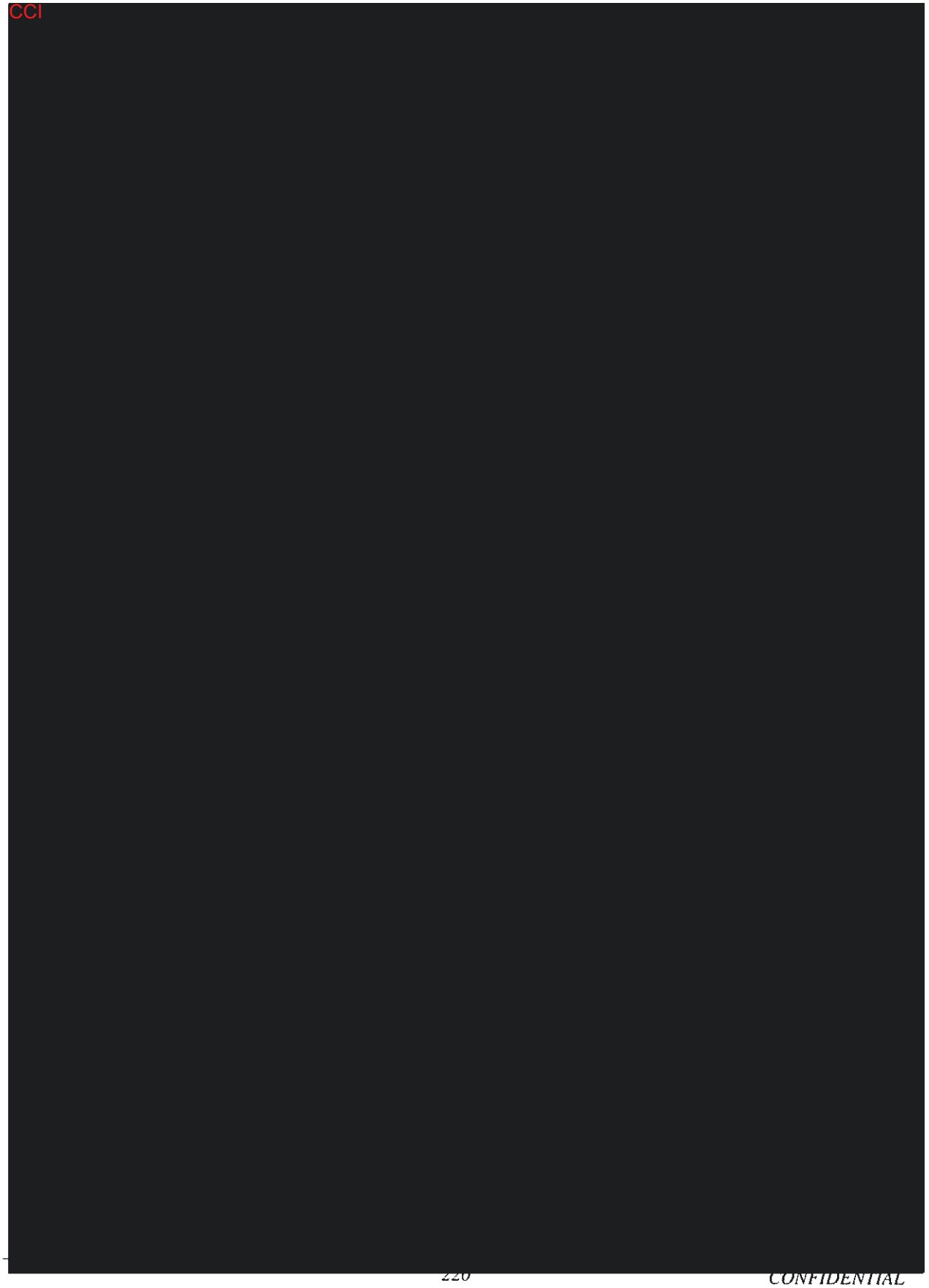
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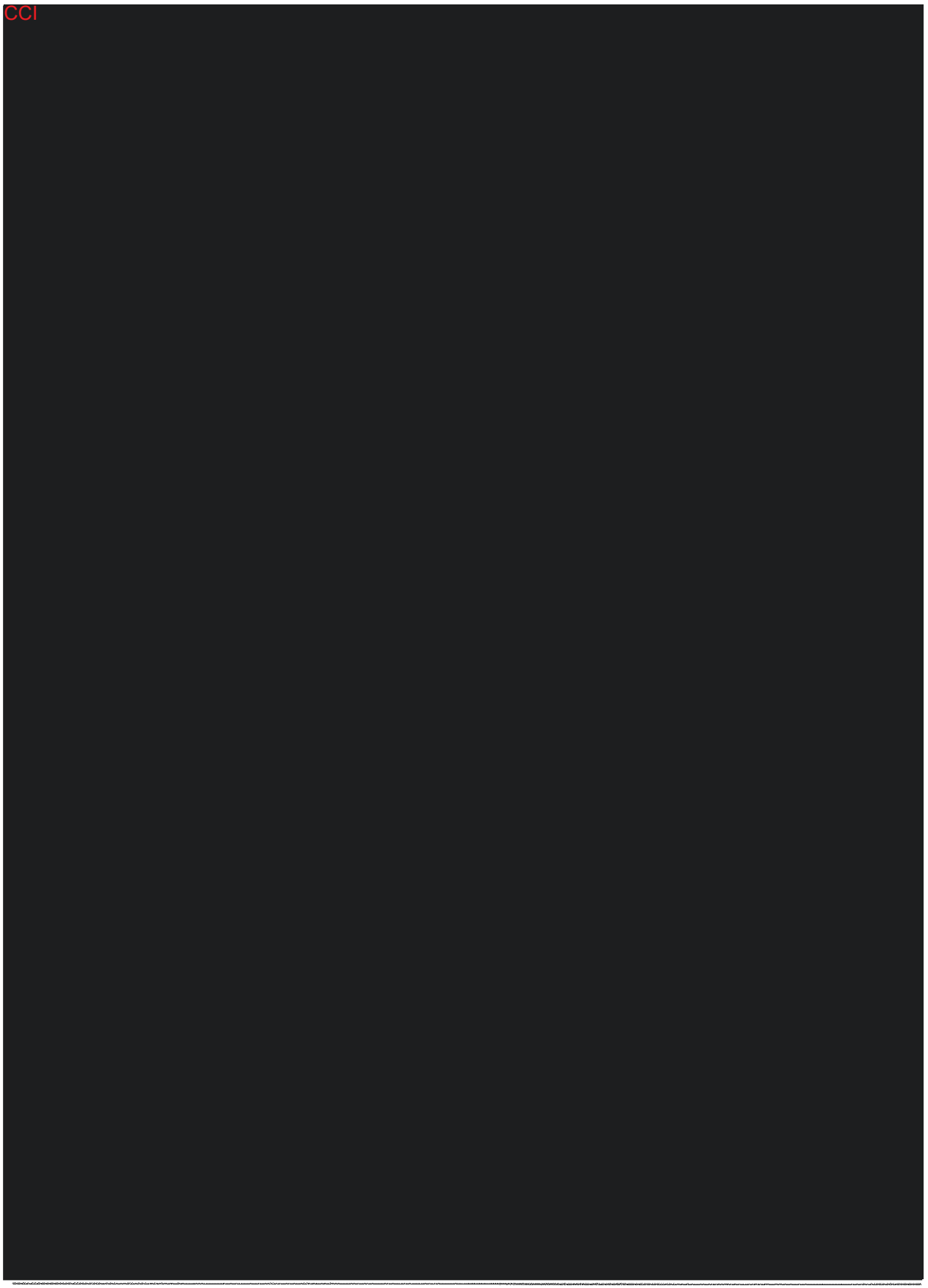

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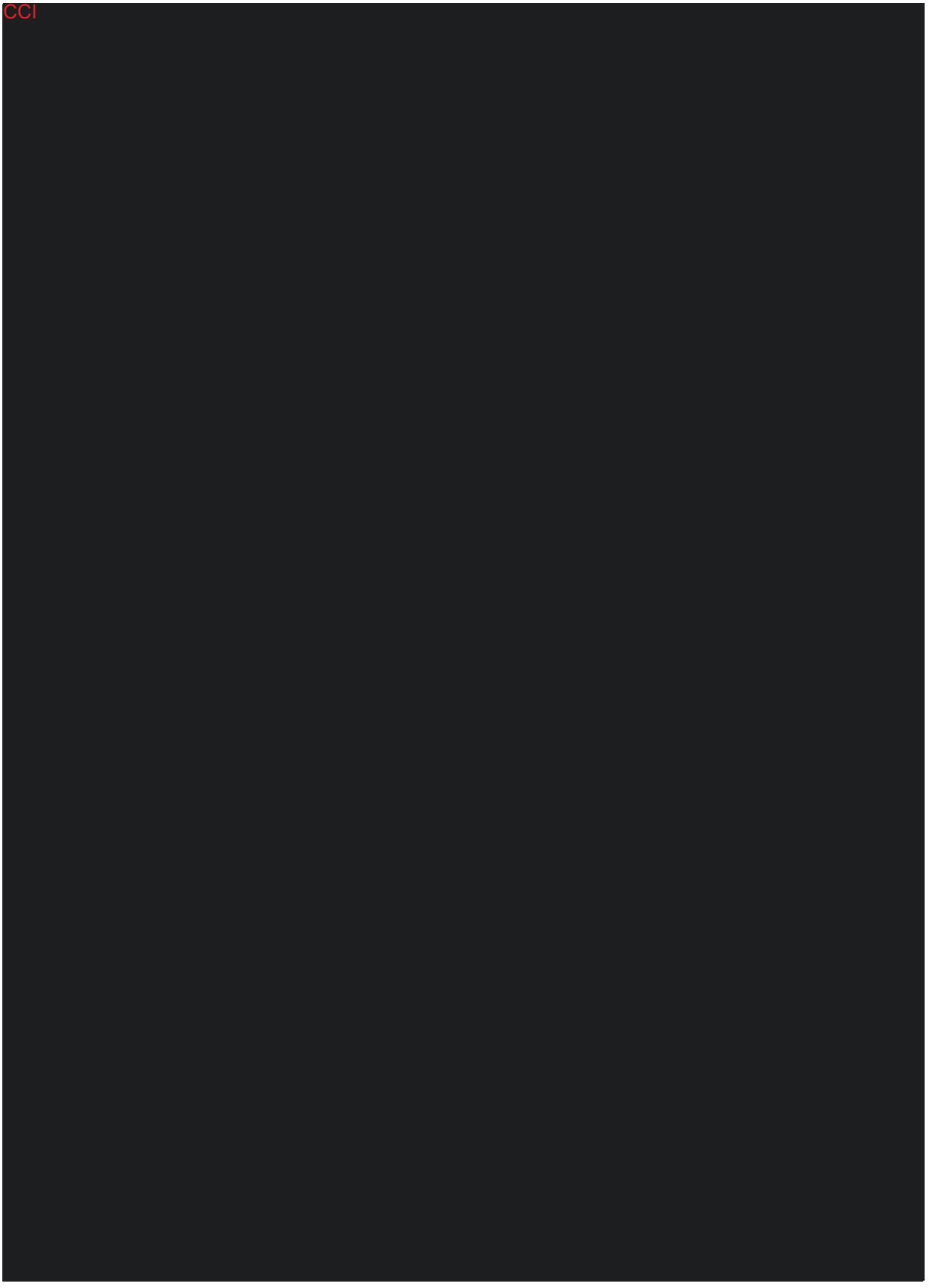
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