Official Protocol Title:	Protocol/Amendment No.: 001-05 A Randomized Phase 3, Double-Blind Study of Chemotherapy With or Without Pembrolizumab Followed by Maintenance With Olaparib or Placebo for the First Line Treatment of BRCA non-mutated Advanced Epithelial Ovarian
NCT number:	NCT03740165
Document Date:	05-Jan-23

Supplemental Statistical Analysis Plan (sSAP)

Table of Contents

1 INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization. The patient reported outcome (PRO) analysis plan will also be included in this sSAP. There will be a separate biomarker analysis plan.

2 SUMMARY OF CHANGES

The following changes made to the sSAP were included in protocol amendment MK-7339-001-03 and 04:

- Increased target enrollment number from 1086 to 1284 participants.
- Added progression-free survival (PFS) hypotheses in participants with PD-L1 CPS ≥10.
- Added overall survival (OS) hypothesis in participants with PD-L1 CPS ≥10.
- Moved overall survival (OS) to be a key secondary endpoint.
- Updated the multiplicity strategy.
- Deleted interim analysis 3 and revised the timing of interim analysis 1 and 2.
- Revised power calculations to reflect the addition of increased sample size.
- Implemented Weighted Parametric Group Sequential Design (WPGSD) approach.
- Revised TWiST endpoint definition and moved it to exploratory endpoints.
- Removed analysis of efficacy in CPS ≥10 from exploratory objectives.

The following changes made to the sSAP were not directly related to changes required due to a protocol amendment (MK-7339-001-04):

- Details of analysis of PRO data included.
- Details of analysis of secondary and exploratory endpoints.
- Added an additional subgroup variable.
- Added appendix to describe the technical details of cLDA model and minimum alpha spending approach.
- Editorial, formatting, and typographical corrections.

3 ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below. The comprehensive plan is provided in Sections 3.2 through 3.12.

Key Elements of the Statistical Analysis Plan	
Study Design Overview	**A Randomized Phase 3, Double-Blind Study of Chemotherapy With or Without Pembrolizumab Followed by Maintenance With Olaparib or Placebo for the First-Line Treatment of BRCA non-mutated Advanced**

Key Elements of the Statistical Analysis Plan	
	Epithelial Ovarian Cancer (EOC) (KEYLYNK-001 / ENGOT-ov43 / GOG-3036)
Treatment Assignment	Approximately 1284 participants will be randomized in a 1:1:1 ratio between 3 treatment arms: • Arm 1: Treatment: carboplatin/paclitaxel for 5 cycles plus pembrolizumab Q3W for up to 35 infusions. Maintenance: olaparib BID • Arm 2: Treatment: carboplatin/paclitaxel Q3W for 5 cycles plus pembrolizumab Q3W for up to 35 infusions Maintenance: olaparib placebo BID • Arm 3 (control Arm): Treatment: carboplatin/paclitaxel plus pembrolizumab placebo Q3W for 5 cycles plus pembrolizumab placebo Q3W for up to 35 infusions. Maintenance: olaparib placebo BID CCI [redacted]
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoints	• Progression-free survival (PFS) based on RECIST 1.1 as assessed by investigator in participants with PD-L1 positive tumors (CPS ≥10) • PFS per RECIST 1.1 assessed by investigator in all participants.
Key Secondary Endpoints	• Overall survival (OS) in participants with PD-L1 positive tumors (CPS ≥10) • OS in all participants
Statistical Methods for Key Efficacy Analyses	The primary and key secondary hypotheses will be evaluated by comparing the treatment arms (Arm 1 vs Arm 3 and Arm 2 vs Arm 3) with respect to PFS and OS using a stratified log-rank test. The hazard ratio [HR] will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no events of interest that warrant elevation to Tier 1 events in this study. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals (CIs) provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method.
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Key Elements of the Statistical Analysis Plan
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3.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data has been declared final and complete.

The Sponsor will generate the randomized allocation schedule for study treatment assignment for this protocol and the randomization will be implemented in IRT.

Blinding issues related to the planned interim analyses are described in Section 3.7.

3.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Protocol Section 3 – Objectives/Hypotheses and Endpoints.

3.4 Analysis Endpoints

Efficacy, safety and PRO endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

3.4.1 Efficacy Endpoints

Primary

PFS: The time from randomization to the first documented PD as assessed by the investigator according to RECIST 1.1, or death due to any cause, whichever occurs first.

Secondary

OS: The time from randomization to death due to any cause.

PFS: The time from randomization to the first documented PD as assessed by BICR according to RECIST 1.1, or death due to any cause, whichever occurs first.

PFS2: The time from randomization to subsequent disease progression (clinical or radiological) after second-line therapy, or death from any cause, whichever first.

TFST: The time from the date of randomization until initiation of first subsequent anticancer therapy or death due to any cause, whichever occurs first.

TSST: The time from the date of randomization until initiation of second subsequent anticancer therapy or death due to any cause, whichever occurs first.

TDT: The time from the date of randomization to discontinuation of study treatment or death due to any cause, whichever occurs first.

pCR: The disappearance of all known disease noted prior to surgery; all biopsies (and peritoneal washings if performed) collected during the interval debulking surgery are microscopically negative for malignancy.

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3.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, laboratory values, and vital signs.

3.4.3 PRO Endpoints

- Change from baseline
- Time to true (confirmed) deterioration (TTD)
- Empirical mean change from baseline in scores over time
- Overall improvement and overall improvement + stability rate for the following scales:
  - EORTC QLQ-C30

    GHS/QoL (items 29 and 30)

    Physical Functioning (items 1 to 5)

    Role Functioning (items 6 and 7)
  - EORTC QLQ-OV28 abdominal/GI (items 31 to 36)

- EQ-5D-5L VAS

3.5 Analysis Populations

3.5.1 Efficacy Analysis Population

The Intention-to-Treat (ITT) population will serve as the population for the primary efficacy analyses. All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized.

The analysis population for pCR consists of all randomized participants with evaluable pCR assessment.

The analysis population for ORR consists of all randomly assigned participants with measurable disease, ORR after re-baseline consists of participants with measurable disease after interval debulking surgery re-baseline.

3.5.2 Safety Analysis Population

The All Participants as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized/allocated participants who received at least 1 dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire Treatment Period; such participants will be included in the treatment group corresponding to the study treatment actually received.

At least 1 laboratory, vital sign, or ECG measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

3.5.3 PRO Analysis Population

The PRO analyses are based on the PRO full analysis set (FAS) population, defined as all randomized participants who have at least 1 PRO assessment available for the specific endpoint and have received at least 1 dose of study medication. Participants will be analyzed in the treatment group to which they are randomized.

3.6 Statistical Methods

3.6.1 Statistical Methods for Efficacy Analyses

Statistical testing and inference for safety analyses are described in Section 3.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 3.8. Nominal p-values will be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

3.6.1.1 Progression-free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (Protocol Section 6.3.1.1 Stratification) will be applied to both the stratified log-rank test and the stratified Cox model. Median PFS and its 95% confidence intervals (CIs) will be updated post the second interim analysis; however, no formal statistical test will be performed.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 (based on investigator for primary analysis). Death is always considered as a confirmed PD event. Participants who do not experience a PFS event will be censored at the last disease assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 based on investigator assessment, 1 primary and 2 sensitivity analyses with a different set of censoring rules will be performed. For the primary analysis, if the events (PD or death) are immediately after more than 1 missed disease assessment, the data are censored at the last disease assessment prior to missing visits. Also, data after new anticancer therapy are censored at the last disease assessment prior to the initiation of new anticancer therapy. The first sensitivity analysis follows the complete follow-up intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. The second sensitivity analysis, it considers discontinuation of treatment or initiation of an anticancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for participants without documented PD or death. Participants who are randomized but not treated are considered as discontinuation of treatment at the randomization date. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in [Table 1].

Table 1 Censoring Rules for Primary and Secondary Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anti-cancer treatment
Abbreviation: PD = progressive disease.			

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Similar analyses will be performed for the secondary endpoint of PFS per RECIST 1.1 by BICR assessment. Only the primary censoring rule will be applied for the analysis of PFS by BICR assessment.

3.6.1.2 Overall Survival (OS)

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test (based on the stratification factors defined in Protocol Section 6.3.1.1 Stratification). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (Protocol Section 6.3.1.1 Stratification) will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date of last known contact. The Restricted Mean Survival Time method may be conducted for OS to account for the possible non-proportional hazards effect.

3.6.1.3 PFS2

An analysis of PFS2, defined as the time from randomization to subsequent disease progression after second-line therapy, or death from any cause, whichever first, will be carried out. Participants alive and for whom a disease progression following initiation of new anticancer treatment has not been observed will be censored at the third-line therapy start date if any or the last time the participant was known to be alive and without second disease progression [Table 2] The stratified Cox proportional hazard model will be used to estimate the HR and its 95% CI.

Table 2 PFS2 – Events and Censoring Rules

Situation	Analysis
1) Radiological or clinical progression per investigator after second-line start and before third-line start	Event on date of progression
2) If not 1), and death occurred, and third-line therapy not started	Event on date of death
3) If not 1), and third-line therapy not started, and death not occurred	Censored at last known alive date
4) If not 1), and third-line therapy started	Censored at start date of third-line therapy

A summary of the primary analysis strategy for the key efficacy endpoints is provided in [Table 3].

Table 3 Efficacy Analysis Methods for Key Efficacy Endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses:			
PFS (RECIST 1.1) by investigator	Testing: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT (in participants with CPS ≥10 and in all participants)	Censored according to rules in Table 1.
Secondary Analyses:			
OS	Testing: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT (in participants with CPS ≥10 and in all participants)	Censored at last known alive date
PFS (RECIST 1.1) by BICR	Estimation: Stratified Cox model with Efron's tie handling method	ITT (in participants with CPS ≥10 and in all participants)	Primary censoring rule in Table 1.
PFS2	Estimation: Stratified Cox model with Efron's tie handling method	ITT (in participants with CPS ≥10 and in all participants)	Participants alive and for whom no secondary disease progression has been served will be censored at the third line therapy start date if any or the last time known to be alive and without second disease progression.

Abbreviations: BICR = blinded independent central review; CPS = combined positive score; ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival; PFS2 = progression-free survival after next-line treatment; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

3.6.1.4 Time to first subsequent anticancer treatment (TFST), the time to second subsequent anticancer treatment (TSST), and the time to discontinuation of study treatment (TDT)

The non-parametric Kaplan-Meier method will be used to estimate the TFST, TSST and TDT curve in each treatment arm. The treatment difference in TFST, TSST and TDT will be assessed by the stratified log-rank test in participants with PD-L1 positive tumors (CPS≥10) and in all participants. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR) between the treatment arms. The HR and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (Protocol Section 6.3.1.1) will be applied to both the stratified log-rank test and the stratified Cox model.

3.6.1.5 Pathological Complete Response (pCR)

pCR of pembrolizumab in combination with carboplatin/paclitaxel versus carboplatin/paclitaxel alone when administered as neoadjuvant therapy. The stratified Miettinen and Nurminen's method will be used for the comparison of pCR rates between pooled of Arm 1 and Arm 2 vs Arm 3. The difference in pCR rate and its 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported for participants with PD-L1 positive tumors (CPS≥10) and in all participants. The stratification factors used for randomization (Protocol Section 6.3.1.1) if applicable will be applied to the analysis.

3.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECG measurements.

The analysis of safety results will follow a tiered approach [Table 4]. The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) and events that meet predefined limits of change (PDLCs) in laboratory values, vital signs, and ECG parameters are either pre-specified as "Tier 1" endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the observed proportions of participants with an event.

Tier 1 Events

Safety parameters that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. AEs of special interest that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. Additionally, there are no known AEs associated with participants for which determination of a p value is expected to impact the safety assessment. Therefore, there are no Tier 1 events in this study.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events (via the Miettinen and Nurminen method [1985]).

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 events because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of

participants in 1 of the treatment groups) and SAEs (≥5% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not as a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3-5 AE, a drug-related Grade 3-5 AE, and discontinuation due to an AE will be considered Tier 3 endpoints. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 4 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Serious AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	AEs (incidence ≥10% of participants in one of the treatment groups)	X	X
Tier 3	Any AE		X
	Any Grade 3-5 AE		X
	Any Serious AE		X
	Any Drug-Related AE		X
	Any Serious and Drug-Related AE		X
	Any Grade 3-5 and Drug-Related AE		X
	Discontinuation due to AE		X
	Death		X
	Specific AEs, SOCs (incidence <10% of participants in all of the treatment groups)		X
	Change from Baseline Results (lab toxicity shift, vital signs)		X

3.6.3 CCI [redacted]

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3.6.3.1 CCI [redacted]

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3.6.3.2 CCI [redacted]

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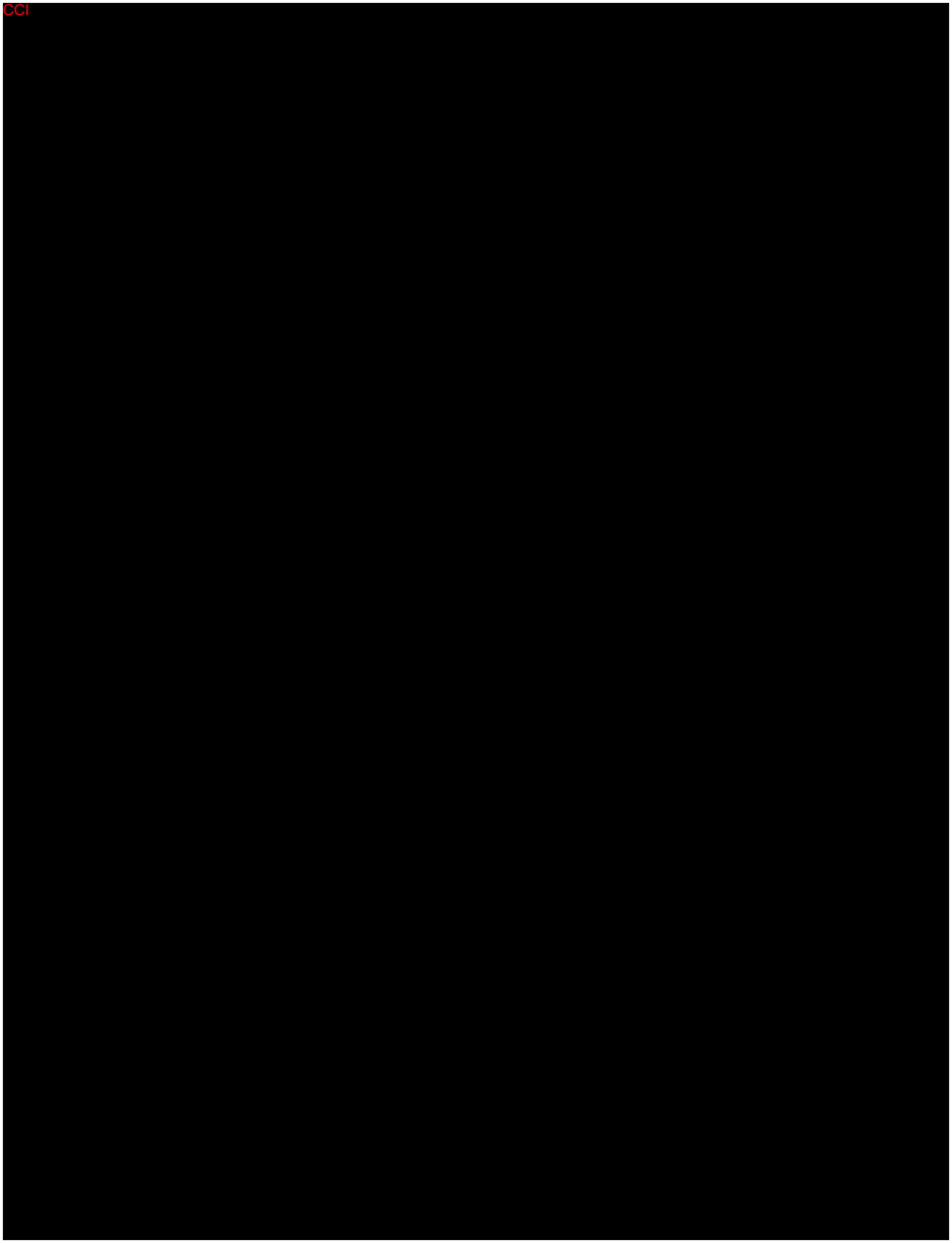

3.6.3.3 CCI [redacted]

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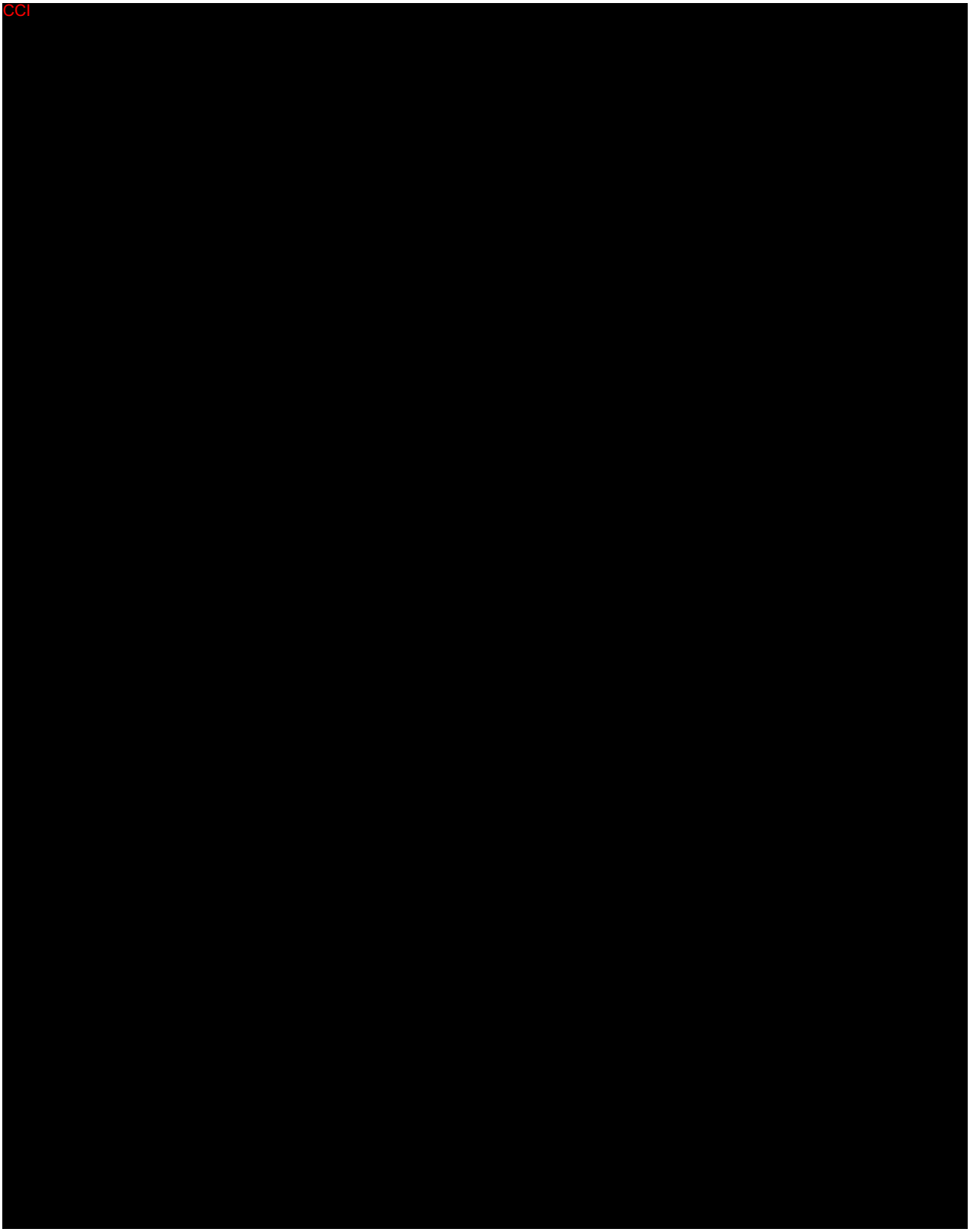

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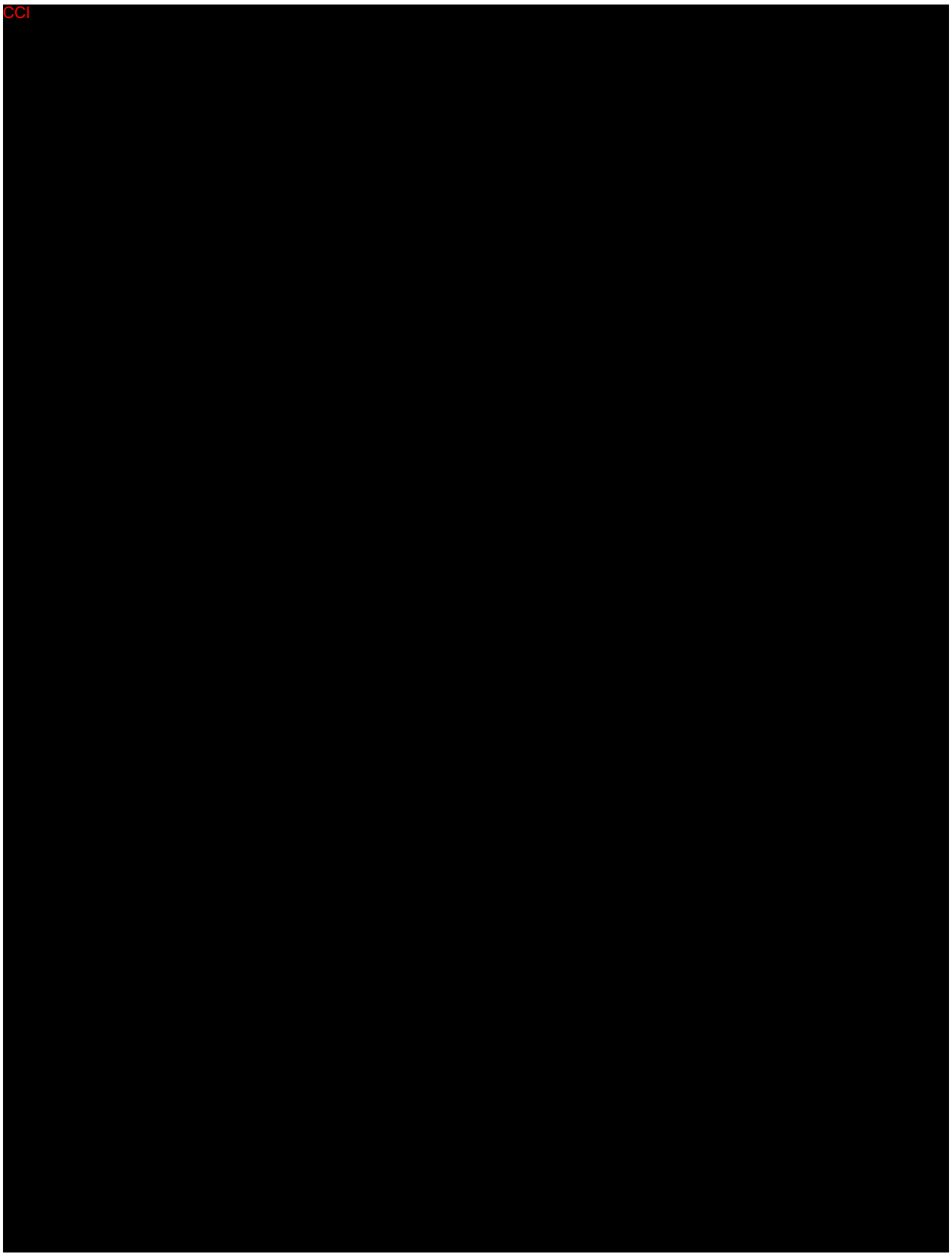

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3.6.4 Summaries of Baseline Characteristics and Demographics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants randomized, and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables. The reasons for exclusion from the ITT population (if any) will be summarized.

3.7 Interim Analyses

An eDMC will serve as the primary reviewer of the results of the interim analyses of the study and will make recommendations for discontinuation of the study or protocol modifications to an Executive Oversight Committee of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee (and potentially other limited Sponsor personnel) may be unblinded to results at the treatment level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the external unblinded statistician. Additional logistical details will be provided in the eDMC Charter.

Treatment-level results from the interim analysis will be provided to the eDMC by the external unblinded statistician. Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

3.7.1 Safety Interim Analyses

The eDMC will conduct regular safety monitoring. The timing of the safety monitoring will be specified in the eDMC charter.

3.7.2 Efficacy Interim Analyses

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3.8 CCI [redacted]

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3.8.1 CCI [redacted]

3.8.1.1 CCI [redacted]

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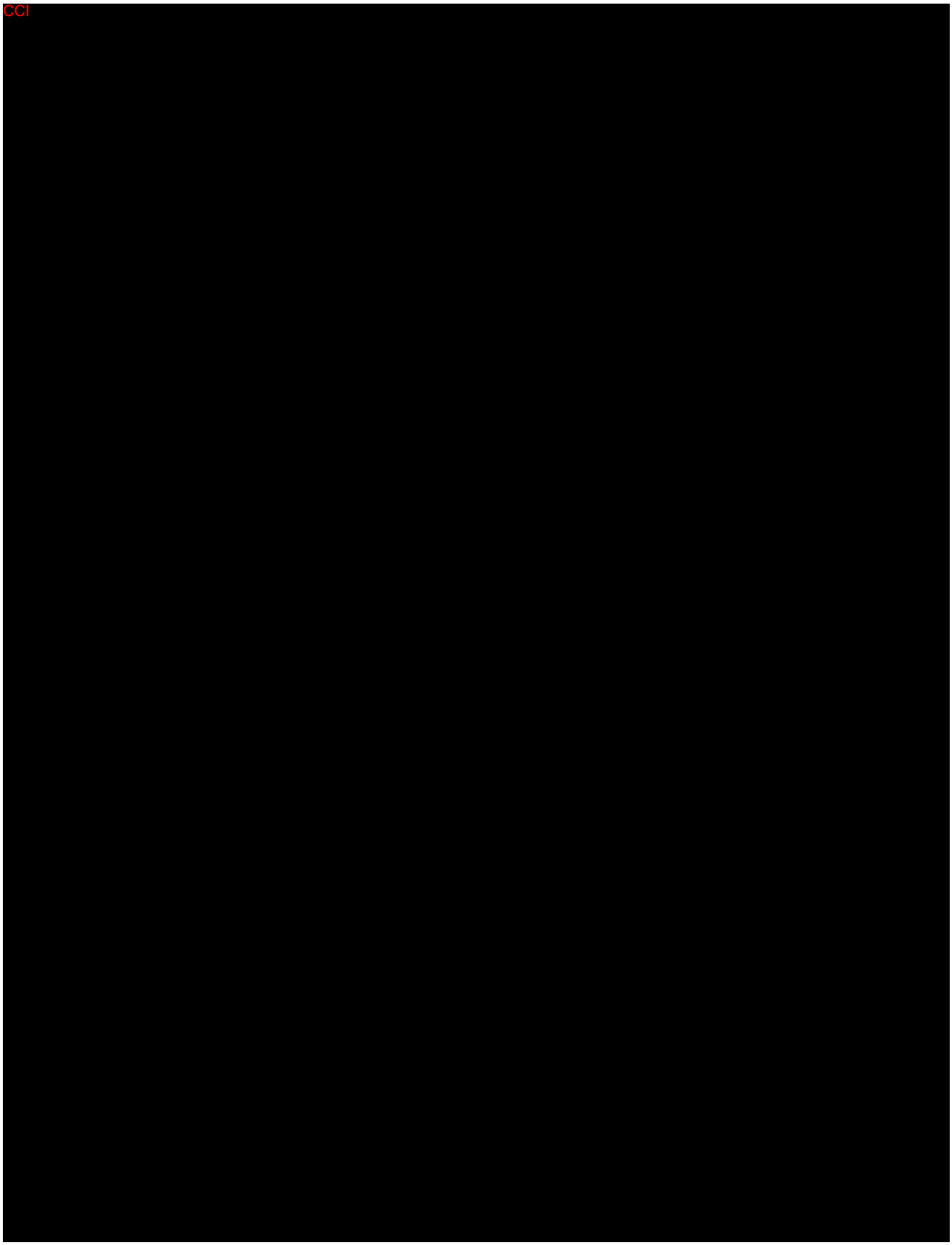

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3.8.1.2 CCI

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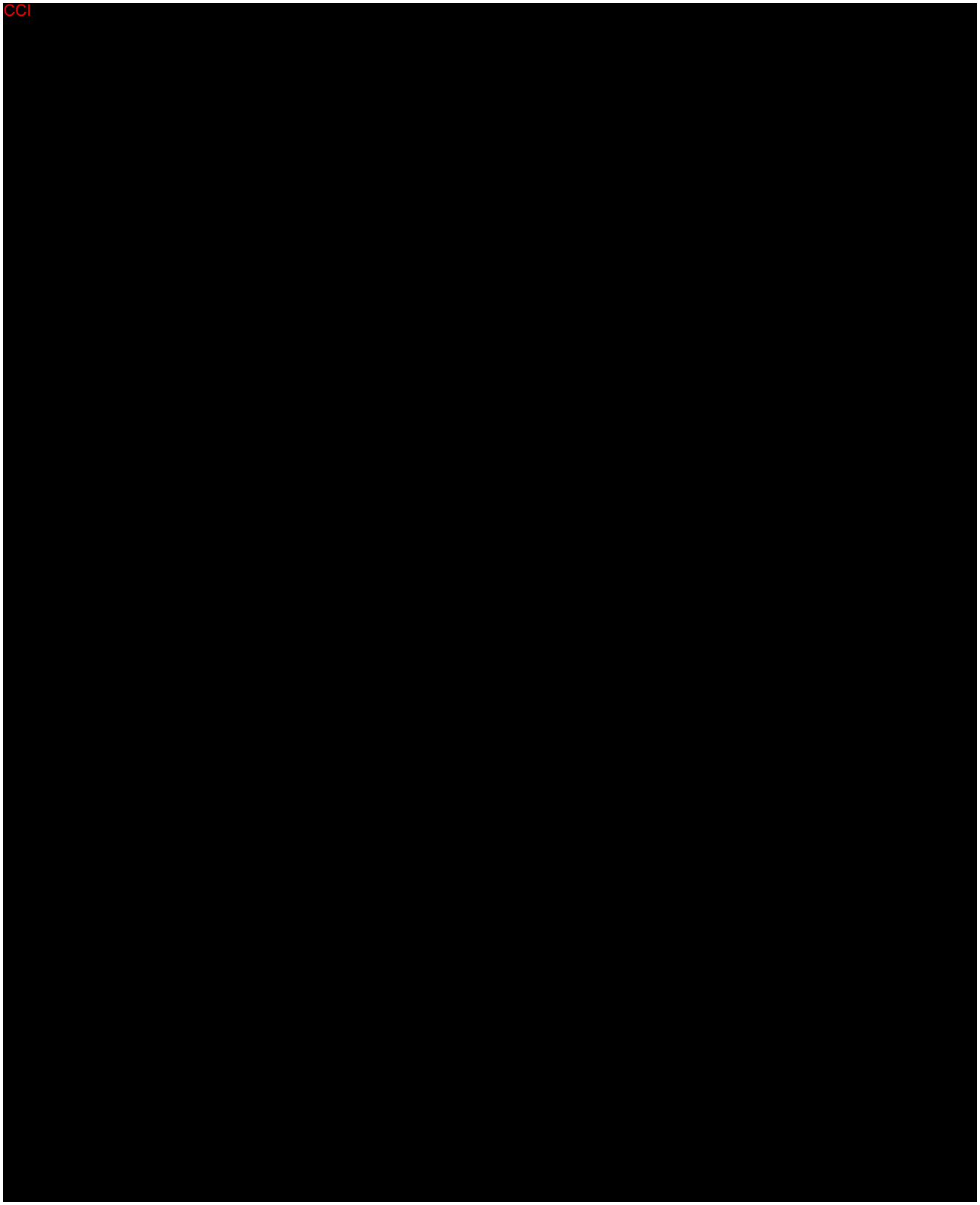

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3.8.2 CCI [redacted]

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3.9 Sample Size and Power Calculations

The study plans to randomize ~1284 participants CCI [redacted]

PFS is the primary endpoint and OS is the key secondary endpoint for the study.

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The sample size and power calculations were performed using R ("gsDesign" package).

3.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect for PFS and OS (with a nominal 95% CI) will be estimated and plotted by treatment group within each category of the following classification variables:

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- Actual surgery received and outcomes (interval debulking, R0 following primary debulking, R1 following primary debulking, no surgery)
- Actual Bevacizumab received (yes, no)
- Race (white, non-white)
- ECOG performance status (0, 1)

A Forest plot will be produced, which provides the point estimates and CIs for the treatment effect across the categories of subgroups listed above. The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above. If the number of participants in a category of a subgroup variable is less than 10% of the ITT population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot. The subgroup analyses for PFS and OS will be conducted using an unstratified Cox model.

3.11 Compliance (Medication Adherence)

Drug accountability data for study treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

3.12 Extent of Exposure

Extent of exposure for a participant is defined as number of cycles in which the participant receives the study treatment infusion for pembrolizumab/pembrolizumab placebo, and the number of days in which the participant receives olaparib/olaparib placebo. Summary statistics will be provided on the extent of exposure for pembrolizumab and olaparib, separately, for the APaT population.

4 APPENDIX

4.1 Technical Details for cLDA Model

The cLDA model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of baseline and the values observed at each post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The cLDA model is specified as follows:

$$E(Y_{ijt}) = \gamma_0 + \gamma_{jt} I(t > 0) + \beta X_i,\ j = 1,2,3,\dots,n;\ t = 0,1,2,3,\dots,k$$

where Y_{ijt} is the PRO score for subject i, with treatment assignment j, at visit t, γ_0 is the baseline mean for all treatment groups, γ_{jt} is the mean change from baseline for treatment group j at time t, $X_i$is the stratification factor (binary) vector for this participant, and β is the coefficient vector for stratification factors. An unstructured covariance matrix will be used to model the correlation among repeated measurements. If the unstructured covariance model fails to converge with the default algorithm, then Fisher scoring algorithm or other appropriate methods can be used to provide initial values of the covariance parameters. In the rare event that none of the above methods yield convergence, a structured covariance such as Toeplitz can be used to model the correlation among repeated measurements. In this case, the asymptotically unbiased sandwich variance estimator will be used. The cLDA implicitly treats missing data as missing at random (MAR).

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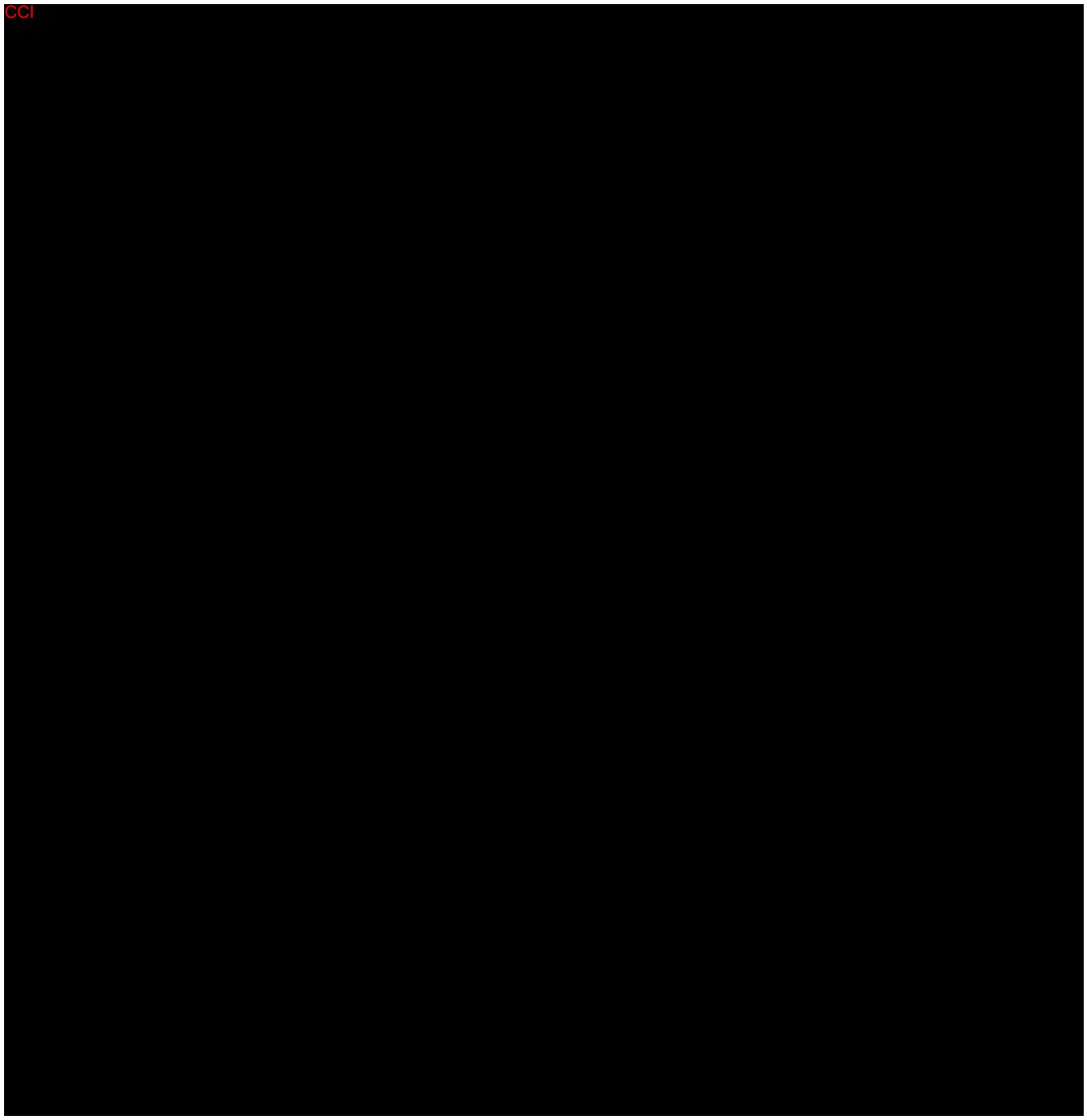

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