PROTOCOL A3921139

A MULTI-CENTER OPEN-LABEL STUDY OF CP-690,550 IN SUBJECTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS

STATISTICAL ANALYSIS PLAN (SAP)

Version	Date	PPD
1.0	1 February 2012	PPD UK) PPD
2.0	29 June 2016	PPD
3.0	12 August 2020	PPD

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

This document is Version 3 of the statistical analysis plan (SAP) for Protocol A3921139 based on protocol Amendment 11. Although this study used a Data Monitoring Committee (DMC), no changes were based on any result from DMC review.

Major changes from Version 2 to Version 3 include:

- Section 2 was updated based on the protocol Amendments 9, 10 and 11.
- Section 5.5 was updated to mention protocol deviations related to COVID-19.
- Section 6.2 was updated to include incidence rates for adverse events of special interest.
- Section 7.1 was updated to include approach for handling subjects that moved to Study A3921288 (Riveting) or Japan post-marketing surveillance study, or discontinued due to regulatory approval in Japan, or had dose escalation.
- Section 8.2.4 was updated to include listing of subjects with dose reduction due to pulmonary embolism (PE) risk factors and analyses for incidence rates.

Major changes from Version 1 to Version 2 include:

- Section 2 and Section 4.2.1 were updated based on the protocol Amendment 8.
- Section 5.3 was updated to add subpopulations.
- Section 7 was updated to add the non-responder imputation (NRI) for binary endpoints, and last observation carried forward (LOCF) for continuous endpoints.
- Section 8.2 was updated to include details of data summaries to be done in each subpopulation.
- Appendix 1 was updated for definition and use of visit windows.
- C [redacted]

2. INTRODUCTION

The purpose of this document is to provide further details about the statistical analysis methods specified in the protocol.

Ulcerative colitis (UC) is a chronic, relapsing, inflammatory disease of the colon characterized by alternating episodes of remission and spontaneous relapse. The prevalence has been estimated to range from 37 to 246 cases per 100,000 persons in North America and 21 to 243 cases per 100,000 persons in Europe. It is most commonly diagnosed in late adolescence and early adulthood, with the peak incidence occurring between 20-39 years of age.

Current therapy for the treatment of UC includes 5-aminosalicylic acid (5-ASA), systemic and/or topical steroids, immunosuppressants such as azathioprine/6-mercaptopurine and cyclosporine, and tumor-necrosis factor alpha (TNFα) blockers. However, despite these treatment options, a significant proportion of UC patients still require colectomy for refractory or severe fulminant disease, or in some cases for cancer prevention. Although patients with UC are often considered to be cured by restorative proctocolectomy, the quality of life may be poor and the surgery can be associated with short-term and long-term complications, including a decreased female fecundity and the development of pouchitis. At present, no current pharmacological therapy is able to provide a cure for UC. The primary treatment goal is to induce remission and then to maintain this state. Therefore, identification of new effective therapies is an important area of research.

This study is designed to evaluate the long term safety and tolerability of tofacitinib in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

2.1. Study Design

This is a Phase 3, multi-center, open-label study in subjects who have completed or demonstrated treatment failure in the maintenance study A3921096, or who were non-responders after completing 8 weeks of treatment in the induction Study A3921094 or A3921095. Approximately 900 subjects are expected to become eligible for the study. This study will continue up to approximately July 2020. Individual subject duration of participation will vary depending on when the subject was enrolled into the study and the study end date. Therefore, the duration of participation for an individual subject may range from approximately 4 years to more than 7 years. If the study continues beyond Month 72 for an individual subject, the investigator should continue to follow the same visit schedule and study procedures outlined during the study visits of year 4.

Subjects who completed Study A3921096 or had early withdrawal due to treatment failure as defined in the A3921096 protocol are eligible to enroll in this study, A3921139. In addition, subjects who complete 8 weeks of treatment in Study A3921094 or A3921095 and are classified as non-responders are eligible to enroll in this study. The eligibility of a subject for this study will be assessed based on study data collected at Week 8/9 of Study A3921094 or A3921095 (for non-responders) or the Week 52/53 visit (for completers) or early termination visit (early withdrawals due to treatment failure) of Study A3921096. The study data collected at the Week 8/9 visit for Study A3921094 or A3921095 (for non-responders) or the Week 52/53 visit or early termination visit of Study A3921096 will be recorded as the baseline data for Study A3921139.

Eligible subjects will be assigned to either tofacitinib 5 mg BID or 10 mg BID depending on whether the subject is in remission at baseline of Study A3921139. Remission is defined by a total Mayo score ≤2 with no individual subscore >1, and rectal bleeding subscore of 0. Eligible subjects who are in remission at Week 52 of Study A3921096 will be assigned to receive tofacitinib 5 mg BID. For treatment assignment, the central read assessment of the Mayo endoscopic subscores will be used to determine if a subject is in remission. Subjects who complete Study A3921096 but do not meet the remission definition or who are early

withdrawals due to treatment failure in Study A3921096 are eligible to receive tofacitinib10 mg BID. Treatment failure is defined by an increase in Mayo score of at least 3 points from the baseline value of the maintenance study (A3921096), accompanied by an increase in rectal bleeding subscore by at least 1 point, and an increase of endoscopic subscore of at least 1 point (yielding an absolute endoscopic subscore of ≥2) after a minimum of 8 weeks of treatment in the maintenance study. In the scenario where the endoscopic subscore is a '3', and the maintenance baseline endoscopic subscore is already a '3' (maximum value), then an increase by at least 1 point will not be needed in order to meet treatment failure. However, all other components of the treatment failure criteria will still need to be met. Subjects who complete induction Study A3921094 or A3921095 and are classified as non-responders are also eligible to receive tofacitinib 10 mg BID.

Tofacitinib dose can be adjusted from 5 mg BID to 10 mg BID for efficacy and from 10 mg BID to 5 mg BID after meeting specific laboratory abnormalities or other protocol defined criteria regarding efficacy. Dose adjustments can only occur after a subject has received at least 8 weeks of treatment in Study A3921139.

Subjects from the induction Study A3921094 or A3921095 (ie, non-responders) who fail to demonstrate clinical response at Month 2 of this study will be withdrawn from the study. Clinical response is defined by a decrease from the induction study baseline (A3921094 or A3921095) Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. The endoscopic subscore based on central reading will be used to assess clinical response.

Subjects who enroll into this study, who are on tofacitinib 10 mg BID for at least 2 consecutive years, and who are in stable remission on tofacitinib 10 mg BID for at least 6 months may have the opportunity to enter Study A3921288 (A Phase 3b/4, Multi-Center, Double-Blind, Randomized, Parallel Group Study of Tofacitinib in Subjects with UC in Stable Remission) if they meet the eligibility criteria. These subjects must:

- Have received tofacitinib 10 mg BID for a minimum of 2 consecutive years in Study A3921139 (and not have their tofacitinib dose reduced to 5 mg BID due to safety or efficacy.
- Be in stable remission on tofacitinib 10 mg BID for the 6 month period in Study A3921139 up to and including the baseline visit of Study A3921288, defined as meeting all the following criteria:
    - A partial Mayo score <=2, with no individual subscore >1 and a rectal bleeding subscore of 0 at each study visit during the 6 month period in Study A3921139 prior to and at baseline of Study A3921288; AND
    - At least one assessment of remission based on Mayo score.
- Not be receiving any corticosteroids to treat their UC for at least 4 weeks prior to the baseline visit of Study A3921288.

Study A3921288 will evaluate the efficacy and safety of tofacitinib in subjects in stable remission on 10 mg BID who decrease the dose to and remain on 5 mg BID compared to subjects who remain on 10 mg BID.

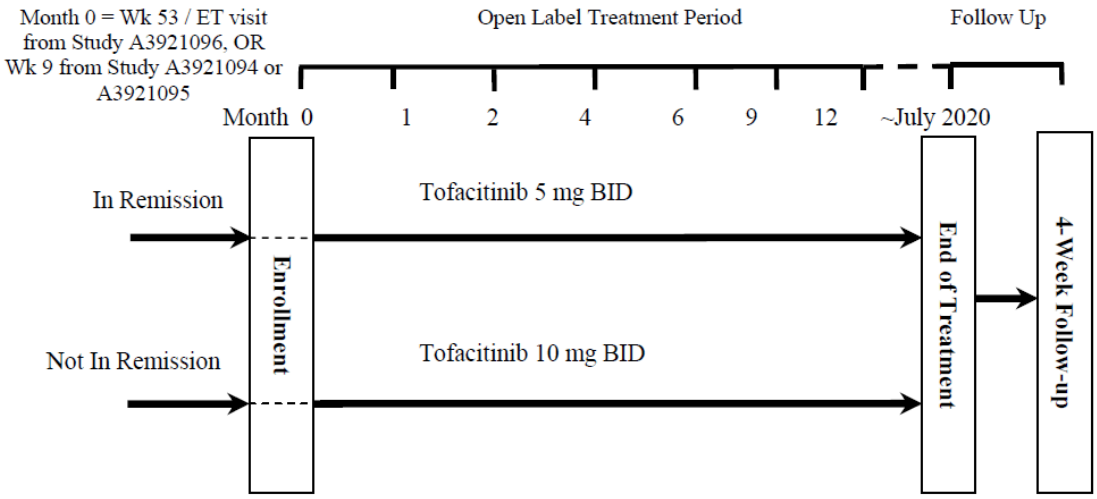
All subjects who withdraw early or who complete this open-label study, with the exception

of those subjects entering Study A3921288, will have a 4-week safety follow-up evaluation after the last dose of study medication.

Subjects will be required to remain on stable doses of their concomitant medications for UC during the study period. Subjects who enter this study on corticosteroids (eg, subjects who withdraw from Study A3921096 due to treatment failure or non-responders at the end of Study A3921094 or A3921095) will need to continue the steroid tapering regimen described in Study A3921096. If a subject requires rescue therapy or undergoes surgery, the subject should be withdrawn from the study and appropriate agents should be given at the discretion of the investigator.

Per protocol Amendment 11, Version 18 June 2019, the study investigator or designee will be required to ask each subject at each study visit if he/she has any newly-developed risk factors for PE, and if one is identified, the subject will need to have their tofacitinib dose adjusted to 5 mg BID if they are taking open label 10 mg BID.

Figure 1. Study Design



- Study visits will occur every 3 months after the first year until approximately July 2020.
- All subjects will have a 4-week follow-up evaluation after their last dose of study medication.

2.2. Study Objectives

Primary objective:

- To assess the safety and tolerability of long-term tofacitinib therapy in subjects with UC.

Secondary objectives:

- To evaluate the efficacy of long-term tofacitinib therapy in subjects with UC.
- To evaluate the effect of long-term tofacitinib therapy on quality-of-life in subjects with UC.

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

This is an open-label study. Assignment to tofacitinib will be open to the investigators, patients and the Pfizer study team. There will be no need for unblinding. Knowledge of open-label treatment assignment will not unblind the treatment assignment in the previous double-blinded studies (A3921094, A3921095, or A3921096).

Interim analyses may be performed for study monitoring for internal decision making, application for approval or due to regulatory requests. An independent Data Safety Monitoring Board (DSMB), a group of experts external to Pfizer, will review accumulating safety data from this study on an ongoing basis. Review of efficacy data may occur as part of any risk-benefit assessment deemed the responsibility of this committee. Based on these reviews, the DSMB will have the capacity to make recommendations to Pfizer that might impact the future conduct of the trial. The DSMB will have access to treatment information during the clinical trial. The management and process of this committee will be in accordance with Pfizer's Standard Operating Procedures and will be documented in the DSMB Charter. The DSMB members will all be individuals who are independent of Pfizer.

The final analysis will be performed after the official release of the database.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No formal hypotheses are to be tested.

4.2. Statistical decision rules

4.2.1. Sample Size Rationale

Approximately 900 subjects are expected to become eligible for the study. Approximately 460 subjects are expected to enroll from the maintenance Study A3921096 assuming a 78% rollover rate from the maintenance study. Approximately 440 subjects are expected to enroll from the induction Study A3921094 or A3921095 assuming that 38% of subjects enrolled in those studies will not achieve clinical response and will not have improving endoscopic subscores after completing induction Study A3921094 or A3921095.

5. ANALYSIS SETS

5.1. Full Analysis Set

The Full Analysis Set (FAS) is defined as all subjects who receive at least 1 dose of study medication in this study.

5.2. Safety Analysis Set

The FAS and the Safety Analysis Set (SAS) are the same.

5.3. Other Analysis Sets

The following subpopulations that are subsets of the FAS population will be used to summarize the efficacy data:

- **Maintenance remission subpopulation:** Subjects that completed the maintenance Study A3921096 in remission. Remission is defined by a total Mayo score ≤ 2 with no individual subscore >1, and rectal bleeding subscore of 0.

- **Maintenance treatment failure subpopulation**: Subjects that were treatment failures or dropped out due to lack of efficacy from the maintenance Study A3921096 and received tofacitinib 10 mg BID or placebo from induction Study A3921094 or A3921095. Treatment failure was defined by an increase in Mayo score of at least 3 points from the baseline value of Study A3921096, accompanied by an increase in rectal bleeding subscore by at least 1 point, and an increase of endoscopic subscore of at least 1 point yielding an absolute endoscopic subscore of ≥2. In the scenario where the endoscopic subscore is a '3', and the maintenance baseline endoscopic subscore is already a '3' (maximum value), then an increase by at least 1 point will not be needed in order to meet treatment failure. Subjects that completed the maintenance Study A3921096 and fulfilled the definition of treatment failure are included in this subpopulation.

- **Other maintenance completers subpopulation**: All other completed subjects from maintenance Study A3921096, that is, those subjects who were neither in remission nor fulfilled the definition of treatment failure.

- **Induction Non-responder subpopulation**: Subjects who were enrolled from induction Study A3921094 or A3921095 directly but did not achieve clinical response and received tofacitinib 10 mg BID or placebo in the induction studies.

Please notice that some subjects may not be included in any of the subpopulations, such as those in maintenance treatment failure but received tofacitinib 15 mg BID in the induction studies, or those who were enrolled from induction studies directly (in error) but were in clinical response. A listing of subjects that do not meet any of the subpopulation categories will be generated. Central read endoscopic subscore was used in defining these subpopulations.

The analysis described in this SAP may be repeated on the specific country and/or region subpopulation sets in order to meet country-specific regulatory requirements. The subpopulation sets will be the subjects in analysis sets defined in this section who have enrolled from sites in the specific country and/or region.

5.4. Treatment Misallocations

If a subject was enrolled into the study but did not receive any study drug then the subject will be excluded from all the analyses.

5.5. Protocol Deviations

A full list of protocol deviations for the study report will be compiled prior to database closure including protocol deviations related to COVID-19. Per-protocol analysis set is not defined. All analyses will be performed for FAS population and its subpopulations.

6. ENDPOINTS AND COVARIATES

Measurement will be collected/derived at visits specified in the protocol. The details of visit windows are defined in Appendix 1. Unless specifically stated otherwise, the baseline value is defined as the last non-missing measurement collected prior to the first administration of study medication in this study, A3921139, at Day 1.

6.1. Efficacy Endpoints

Efficacy endpoints will be based upon the Mayo score and partial Mayo score. The Mayo score is an instrument designed to measure disease activity of ulcerative colitis. Mayo score ranges from 0 to 12 points. It consists of 4 subscores, each graded from 0 to 3 with higher scores indicating more severe disease.

- Stool frequency (0-3);
- Rectal bleeding (0-3);
- Findings of flexible sigmoidoscopy (0-3);
- Physician global assessment (PGA) (0-3).

A partial Mayo score (PMS) is an instrument designed to measure disease activity of UC without endoscopy. Partial Mayo score ranges from 0 to 9 points.

An endoscopy will be performed at Baseline, Month 2, at annual study visits (Months 12, 24 and 36), and at the early withdrawal/early termination visit. The endoscopic subscores at all applicable visits will be read by study site investigator. However, at Month 2 visit, the endoscopic score will be read by both central reader and site investigators prior to Amendment 8. After implementation of Amendment 8, the Month 2 endoscopic subscore will be read by study site investigator only. The endpoints that require the endoscopic subscore component will be derived based on local-read endoscopic subscores, as well as central-read endoscopic subscores, if available.

Further information on the Mayo score is given in Appendix 2.1.

6.1.1. Primary Endpoint

As this is an open-label extension study, there is no primary efficacy endpoint.

6.1.2. Secondary Endpoints

- Remission. Remission in this study is defined as a Mayo score ≤2 with no individual subscore >1, and rectal bleeding subscore of 0.
- Clinical remission. Clinical remission in this study is defined as a Mayo score ≤2 with no individual subscore >1.
- Partial Mayo score (PMS) remission. PMS remission in this study is defined as a partial Mayo score ≤2 with no individual subscore >1.
- Mucosal healing. Mucosal healing is defined as a Mayo endoscopic subscore of 0 or 1.

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6.2. Safety Endpoints

- Incidence and severity of adverse events.
- Incidence of serious infections.
- Incidence and severity of clinical laboratory abnormalities, and change from baseline in clinical laboratory values.
- Incidence of vital sign abnormalities and change from baseline in vital signs.
- Incidence of clinically significant changes in physical examinations from baseline.
- Incidence of electrocardiogram (ECG) abnormalities during treatment.
- Summary of adjudicated safety events (eg, cardiovascular, malignancy, opportunistic infections, hepatic events).

- Proportion of subjects with addition of lipid lowering agents.
- Proportion of subjects whose dose is decreased to 5 mg BID from 10 mg BID.

[redacted]

6.3. Other Endpoints

6.3.1. Patient Reported Outcome (PRO) Endpoints

Section 7.2 of the protocol gives details on the IBDQ, [redacted]

- IBDQ remission, defined as total score in Inflammatory Bowel Disease Questionnaire (IBDQ) ≥170 over time.
- The scores and change from Baseline (of Study A3921139) in total IBDQ score and domains (Bowel Symptoms, Systemic Symptoms, Emotional Function and Social Function) over time.

[redacted]

6.4. Covariates

- None.

7. HANDLING OF MISSING VALUES

7.1. Efficacy Endpoints

For binary efficacy endpoints (Remission, Clinical remission, Mucosal healing, PMS remission, Clinical response) derived from Mayo subscores (site-read endoscopic subscore was used), data will be summarized based on the observed-case data and non-responder imputation and last observation carried forward imputation (NRI-LOCF). The NRI-LOCF approach is described as the following:

- For subjects who discontinued from the study, other than those who moved to Study A3921288 or to the Japan post-marketing surveillance study, or due to regulatory approval in Japan, NRI will be used for missing data up to the visit (using the lower bound of visit window as defined in Appendix 1) they would have reached if they had stayed at the study. The missing data before time of discontinuation will be imputed as non-responders.

- For ongoing subjects (for interim analyses only), they will be included in the summary tables only up to visits with non-missing data in the dataset for the interim report. For subjects with intermittent missing data, they will be treated as non-responders. Otherwise no imputation for missing data will be applied since it's hard to separate the true missing data from being late for the scheduled visit.

- For completed subjects, they will be included in the summary tables only up to the completion visit. Missing data before the completion will be imputed using the NRI approach.

- For subjects who discontinued from the study and moved to Study A3921288 or to the Japan post-marketing surveillance study, or due to regulatory approval in Japan, LOCF will be used up to the visit (using the lower bound of visit window as defined in Appendix 1) they would have reached if they had stayed in the study. The missing data before time of discontinuation will be imputed as non-responders. This approach will likely overestimate the proportions of subjects who achieve the binary endpoints since it is assumed that the response status remains after subjects moved to Study A3921288 or the Japan post-marketing surveillance study.

For continuous endpoints total Mayo score and Partial Mayo score, data will be summarized based on the observed-case data and LOCF. The LOCF approach is described as the following:

- For subjects who discontinued from the study, other than moved to Study A3921288 or to the Japan post-marketing surveillance study, or due to regulatory approval in Japan, LOCF approach will be used for missing data up to the visit (using the lower bound of visit window as defined in Appendix 1) they would have reached if they had stayed in the study. Any missing data before time of discontinuation will be imputed using LOCF.

- For ongoing subjects (for interim analyses only), they will be included in the summary tables only up to visits that are included in the dataset for the interim report. For intermittent missing data, LOCF approach will be applied. Otherwise no imputation for missing data will be applied since it's hard to separate the true missing data from being late for the scheduled visit.

- For completed subjects, they will be included in the summary tables only up to the completion visit. Missing data before the completion will be imputed using LOCF approach.

- For subjects who discontinued from the study and moved to Study A3921288 or to the Japan post-marketing surveillance study, or due to regulatory approval in Japan, LOCF approach will be used after the time of discontinuation up to the visit (using the lower bound of visit window as defined in Appendix 1) they would have reached if they had stayed in the study. Any missing data before time of discontinuation will be imputed using LOCF.

To implement LOCF, individual components were carried forward first, then the endpoints were derived using the imputed components.

The central read endoscopic subscore was only assessed at baseline and Month 2 visit for subjects who enrolled prior to protocol Amendment 8. For subpopulations other than induction non-responder subpopulation, the endpoints using central-read endoscopic subscore as a component will be summarized based on observed data only. No NRI or LOCF imputation will be applied. However, for induction non-responder subpopulation, subjects were expected to complete Month 2 visit prior to implementation of protocol Amendment 8, endpoints using central-read endoscopic subscore as a component will be summarized based on both NRI for binary endpoints (or LOCF for continuous endpoints), and observed data for Month 2.

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7.2. PRO Endpoints

For the PRO endpoints based on IBDQ, [redacted] rules suggested by the developers of the questionnaires will be followed in calculating the endpoints with any missing items. If these rules are not sufficient to impute the missing values, then the missing values will be handled as following:

- For IBDQ binary endpoints IBDQ remission and deterioration (worsening) in IBDQ bowel symptom domain, they will be handled in the same way as binary efficacy endpoints as specified in section 7.1 for missing data and data after the dose escalation.
- For IBDQ, [redacted] continuous endpoints, they will be handled in the same way as continuous efficacy endpoints as specified in section 7.1 for missing data and data after the dose escalation.

[redacted]

7.3. Safety Data Endpoints

Safety data will be summarized based on observed-case data. Missing data will not be imputed.

8. STATISTICAL METHODOLOGY AND STATISTCAL ANALYSES

8.1. Statistical Methods

As no formal statistical tests will be conducted, there will be no need to report p-values. Descriptive summary statistics such as number, percentage for categorical endpoints and mean, standard deviation, median for continuous endpoints will be presented, along with some graphical representations using the FAS as defined in Section 5.1.

8.2. Statistical Analyses

8.2.1. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the FAS and subpopulations as detailed in Section 5.3 for overall and by initial dose assignment.

8.2.2. Primary Analysis

The primary analysis is the analysis of safety. See Section 8.2.3 below.

8.2.3. Secondary [redacted] Efficacy Analyses

All efficacy endpoints are considered as secondary [redacted]. Descriptive summary statistics will be reported at scheduled visits in FAS, and subpopulations: maintenance

remission subpopulation, maintenance treatment failure subpopulation, other maintenance completers subpopulation, and induction non-responder subpopulation. However, the endpoints of proportion of subjects with dose increase from tofacitinib 5 mg BID to 10 mg BID will be summarized for maintenance remission subpopulation only.

For FAS or each subpopulation, the data will be summarized based on the following table:

Efficacy Analysis Population/Subpopulation	Treatment group (the default is the assigned dose for initial assignment in A3921139)	By group
FAS	Overall Tofacitinib 5 mg BID Tofacitinib 10 mg BID	Overall
Maintenance Remission subpopulation	Tofacitinib 5 mg BID	Overall By maintenance treatment (4 groups: 10 mg, 5 mg, placebo, 5mg+10mg)
Maintenance Treatment Failure subpopulation	Tofacitinib 10 mg BID	Overall By dose combination received in induction and maintenance (6 groups) and a 7th group of Tofacitinib 10 mg in induction and Tofacitinib 5 mg + placebo in maintenance
Other Maintenance Completers subpopulation	Tofacitinib 10 mg BID	Overall By maintenance treatment (4 groups: tofacitinib 10 mg, Tofacitinib 5 mg, placebo, Tofacitinib 10 mg and 5 mg combined)
Induction Non-responder subpopulation	Tofacitinib 10 mg BID	Overall By Induction treatment (Tofacitinib 10 mg, Placebo)

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

8.2.4. Safety Analyses

The primary analysis is the analysis of safety.

That is, all safety data will be summarized descriptively by initial treatment group and combined Tofacitinib group of A3921139 in the safety analysis set. The adverse event data will be summarized for entire treatment duration.

A listing of subjects with dose reduction due to PE risk factors will be provided.

Incidence Rates (IR) of Adverse Events of Special Interest will be provided. Confidence intervals (95%) will be computed using exact Poisson method.

In general, IR will be calculated only for discrete (0/1) endpoints determined by adverse event data for events of special interest only. The numerator will be the number of unique subjects with a treatment emergent event as defined above during the interval from the first dose in Study A3921139 to last dose of tofacitinib + 28 days at risk period. The denominator of the incidence rate is person time accruing from the subject's first dose of tofacitinib in Study A3921139 to last dose of tofacitinib + 28 days, or to the date of the first event, whichever occurs earlier. For a subject who died, the time will be the minimum of (the date of the last dose + 28 days, or death date).

However, for mortality, malignancies (excluding NMSC and NMSC) and MACE related endpoints, all events regardless of their onset within 28 days or beyond after the last dose of tofacitinib will be included.

The concept of 28 days is applied to subjects without events that discontinued or completed the study. For ongoing subjects, 28 days will not be added to the exposure.

8.2.5. Analyses of Patient reported Outcome (PRO) Endpoints

Descriptive summary statistics will be reported at scheduled visits in FAS, and four subpopulations; Maintenance Remission, Maintenance Failure, Other Maintenance Completers, and Induction Non-responders using the same methods as for the efficacy endpoints for IBDQ[redacted].

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9. APPENDICES

Appendix 1. Definition of Analysis Visit Windows

Analysis visit windows will be used for efficacy variables, and for any safety displays that display by visit.

Visit Label	Target Day	Analysis Visit window
Baseline	Day 1	Up to Day 1
Month 1	Day 30	Days 2-45
Month 2	Day 60	Days 46-90
Month 4	Day 120	Days 91-150
Month 6	Day 180	Days 151-225
Month 9	Day 270	Days 226-315
Month 12	Day 360	Days 316-405
Month 15	Day 450	Days 406-495
Month 18	Day 540	Days 496-585
Month 21	Day 630	Days 586-675
Month 24	Day 720	Days 676-765
Month 27	Day 810	Days 766-855
Month 30	Day 900	Days 856-945
Month 33	Day 990	Days 946-1035
Month 36	Day 1080	Days1036-1125
Month 39	Day 1170	Days 1126-1215
Month 42	Day 1260	Days 1216-1305
Month 45	Day 1350	Days 1306-1395
Month 48	Day 1440	Days 1396-1485
Month 51	Day 1530	Days 1486-1575
Month 54	Day 1620	Days 1576-1665
Month 57	Day 1710	Days 1666-1755
Month 60	Day 1800	Days 1756-1845
Month 63	Day 1890	Days 1846-1935
Month 66	Day 1980	Days 1936-2025
Month 69	Day 2070	Days 2026-2115
Month 72	Day 2160	Day 2116-2205
Month 75	Day 2250	Days 2206-2295
Month 78	Day 2340	Days 2296-2385
Month 81	Day 2430	Days 2386-2475
Month ≥84	Day 2520	Days ≥2476

If more than one observation from the same subject falls into the same window, the value closest to the target day will be used as the observation for that analysis visit. All observations will, however, be included in the listings.

For efficacy endpoints derived based on total Mayo score we will use the same windows from the above table although total Mayo score was not assessed at each visit.

Some PRO data or laboratory data were not scheduled to be assessed at each visit. In this case, the unscheduled 'windowed' visit will be moved to the next scheduled windowed visit for analysis and reporting.

Appendix 2. Further Definition of Endpoints

Appendix 2.1. Mayo Scoring System for Assessment of Ulcerative Colitis Activity

The Mayo Score ranges from 0 to 12, with higher scores indicating more severe disease. It consists of 4 subscores. Each sub-score ranges from 0 to 3. The 4 components of the Mayo Score are:

Stool Frequency:
0 = Normal no. of stools for this patient.
1 = 1 to 2 stools more than normal.
2 = 3 to 4 stools more than normal.
3 = 5 or more stools more than normal.

Rectal Bleeding:
0 = No blood seen.
1 = Streaks of blood with stool less than half the time.
2 = Obvious blood with stool most of the time.
3 = Blood alone passes.

Findings on Endoscopy:
0 = Normal or inactive disease.
1 = Mild disease (erythema, decreased vascular pattern).
2 = Moderate disease (marked erythema, lack of vascular pattern, any friability, erosions).
3 = Severe disease (spontaneous bleeding, ulceration).

Physician's Global Assessment:
0 = Normal.
1 = Mild disease.
2 = Moderate disease.
3 = Severe disease.

The subject's stool diary information will be captured by an interactive voice response system (IVRS) connected through the phone system. Subjects will report stool frequency and the most severe bleeding of the day for rectal bleeding subscore daily at least 5 consecutive days prior to each study visit during the study. Stool frequency subscore will be calculated based on the average number (rounded to an integer) of stools over the prior 3 days minus the normal number of stools per day reported by the subject. The rectal bleeding subscore is the average number (rounded to an integer) of the 3 days prior to the study visit.

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Appendix 2.2.1. Inflammatory Bowel Disease Questionnaire (IBDQ)

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a psychometrically validated patient reported outcome (PRO) instrument for measuring the disease-specific quality of life in subjects with IBD. The IBDQ consists of 32 items with scores ranging from 1 to 7 with 1 being the worst possible response and 7 being the best possible response.

The following endpoints will be derived based on the collected responses. In each instance, the change from Baseline values will be evaluated:

- IBDQ Total Score.
- IBDQ Domain Scores:
  - Bowel Symptoms;
  - Emotional Function;
  - Systemic Symptoms;
  - Social Function.

The Bowel Symptoms Domain score is calculated as the sum of the scores for questions 1, 5, 9, 13, 17, 20, 22, 24, 26 and 29 (Range 10-70).

The Emotional Function Domain score is calculated as the sum of the score for questions 3, 7, 11, 15, 19, 21, 23, 25, 27, 30, 31 and 32 (Range 12-84).

The Systemic Symptoms Domain score is calculated as the sum of the scores for questions 2, 6, 10, 14 and 18 (Range 5-35).

The Social Function Domain score is calculated as the sum of the scores for questions 4, 8, 12, 16 and 28 (Range 5-35).

The total IBDQ score is calculated as the sum of scores for questions 1 to 32 (Range 32-224) with a higher score indicating a better quality of life. Scores of patients with clinical remission usually range from 170 to 190.

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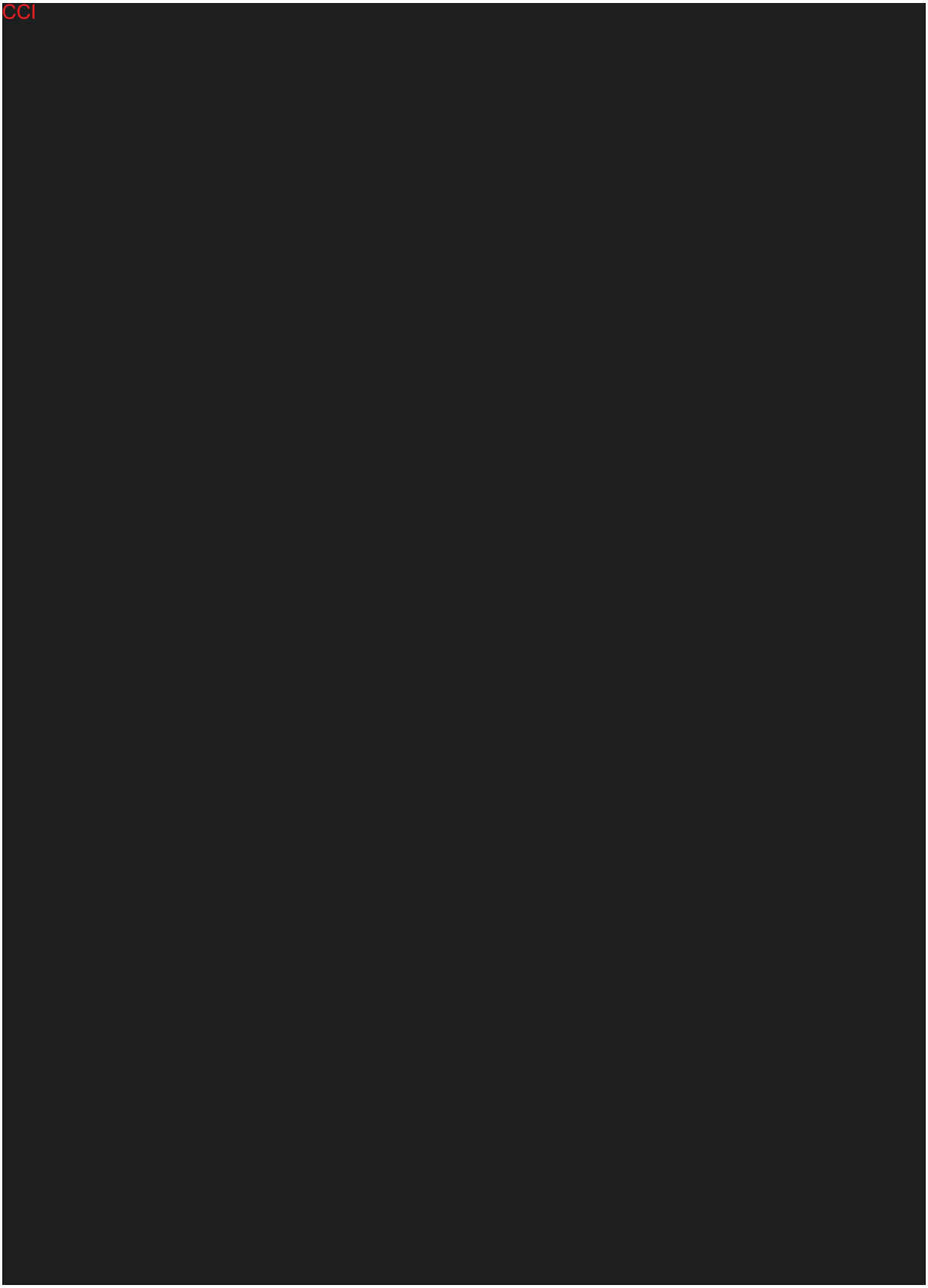

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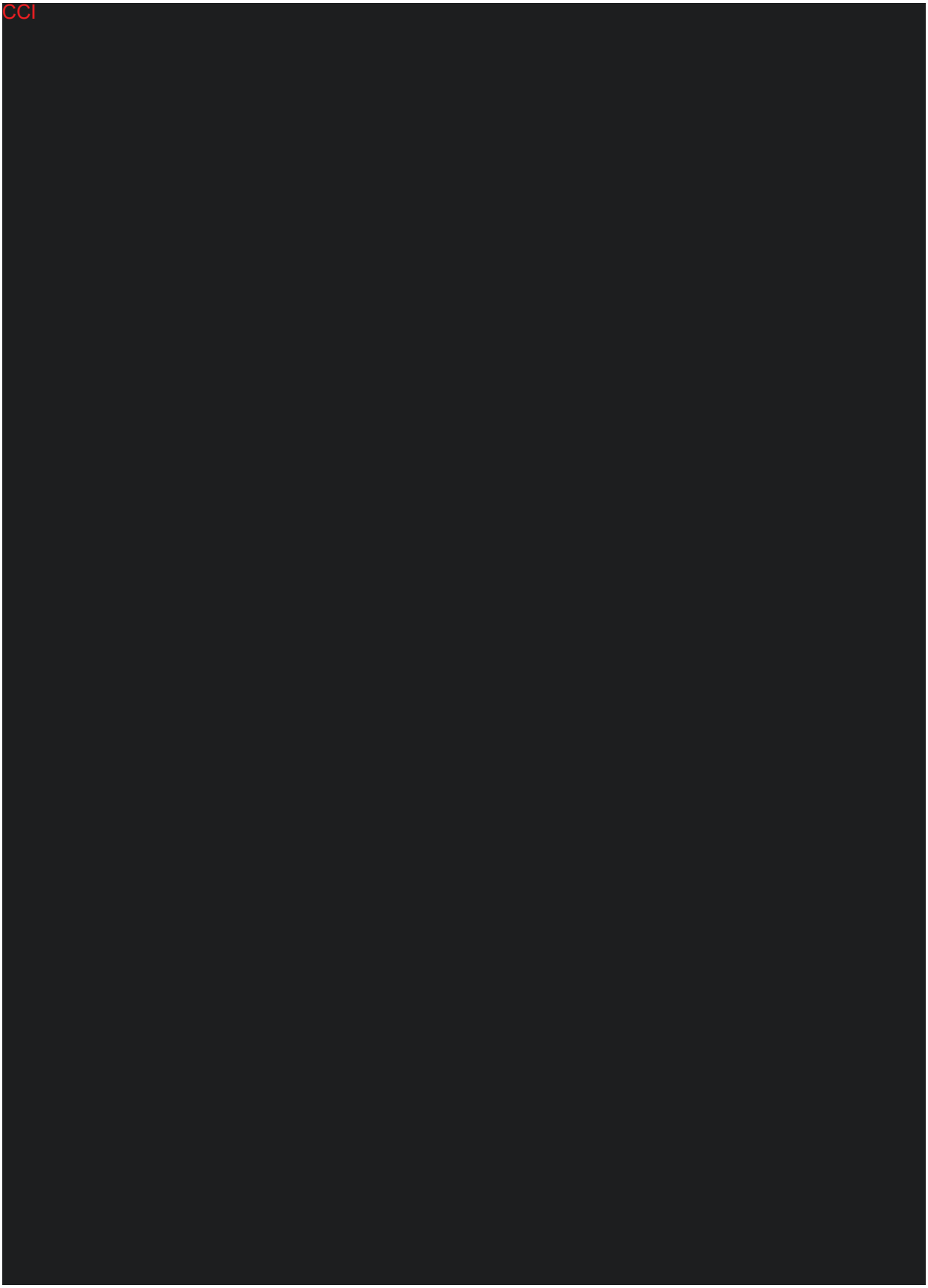

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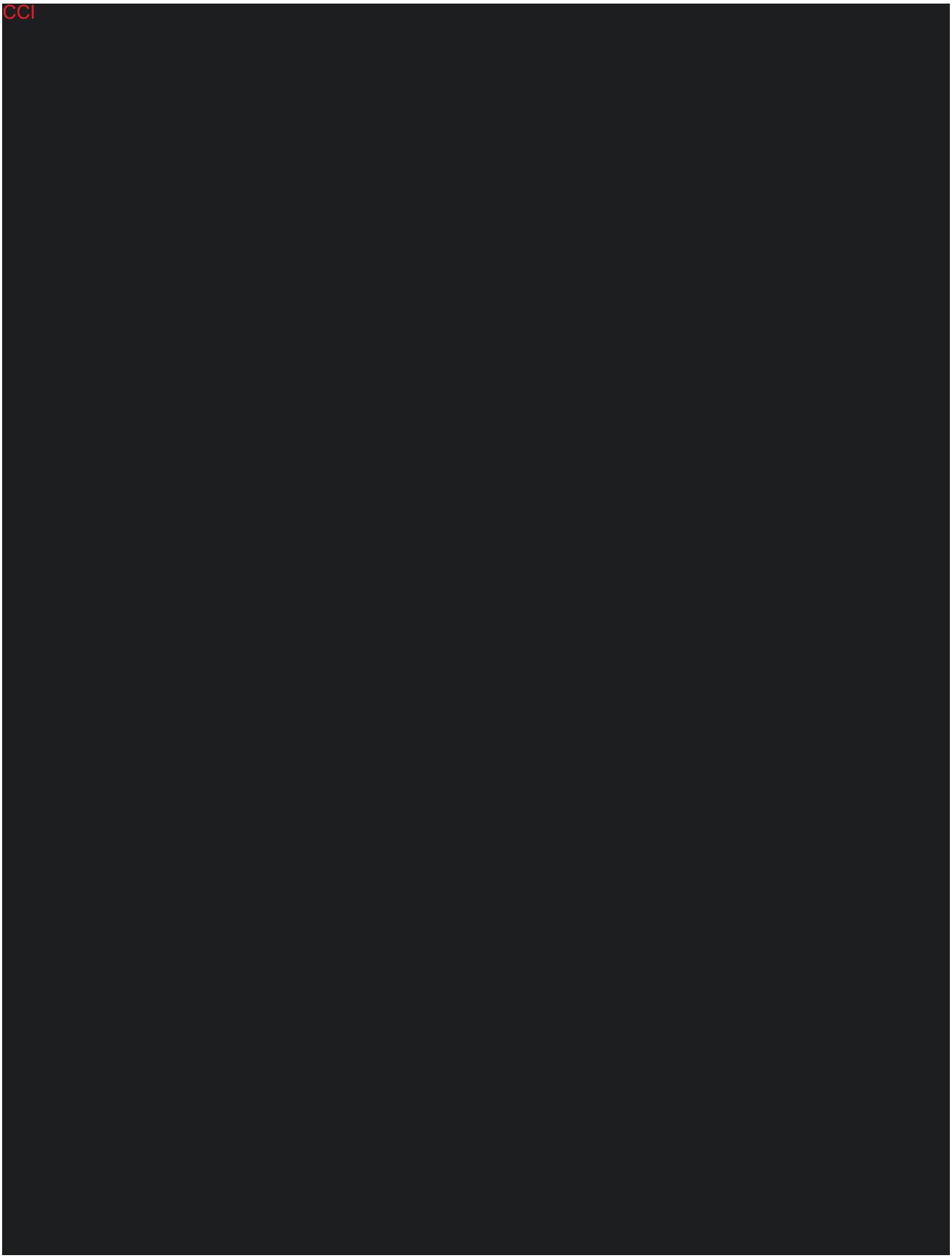

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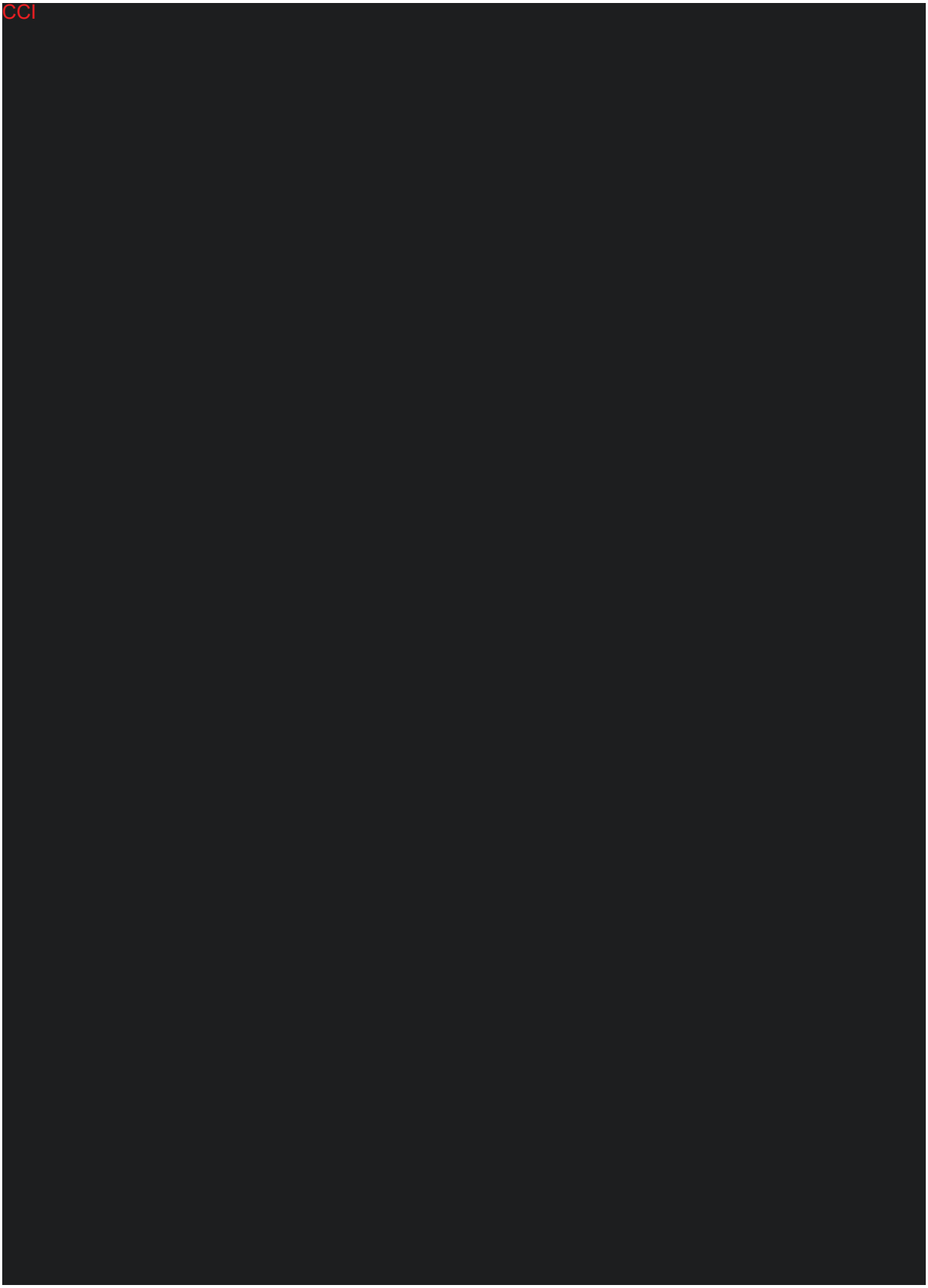

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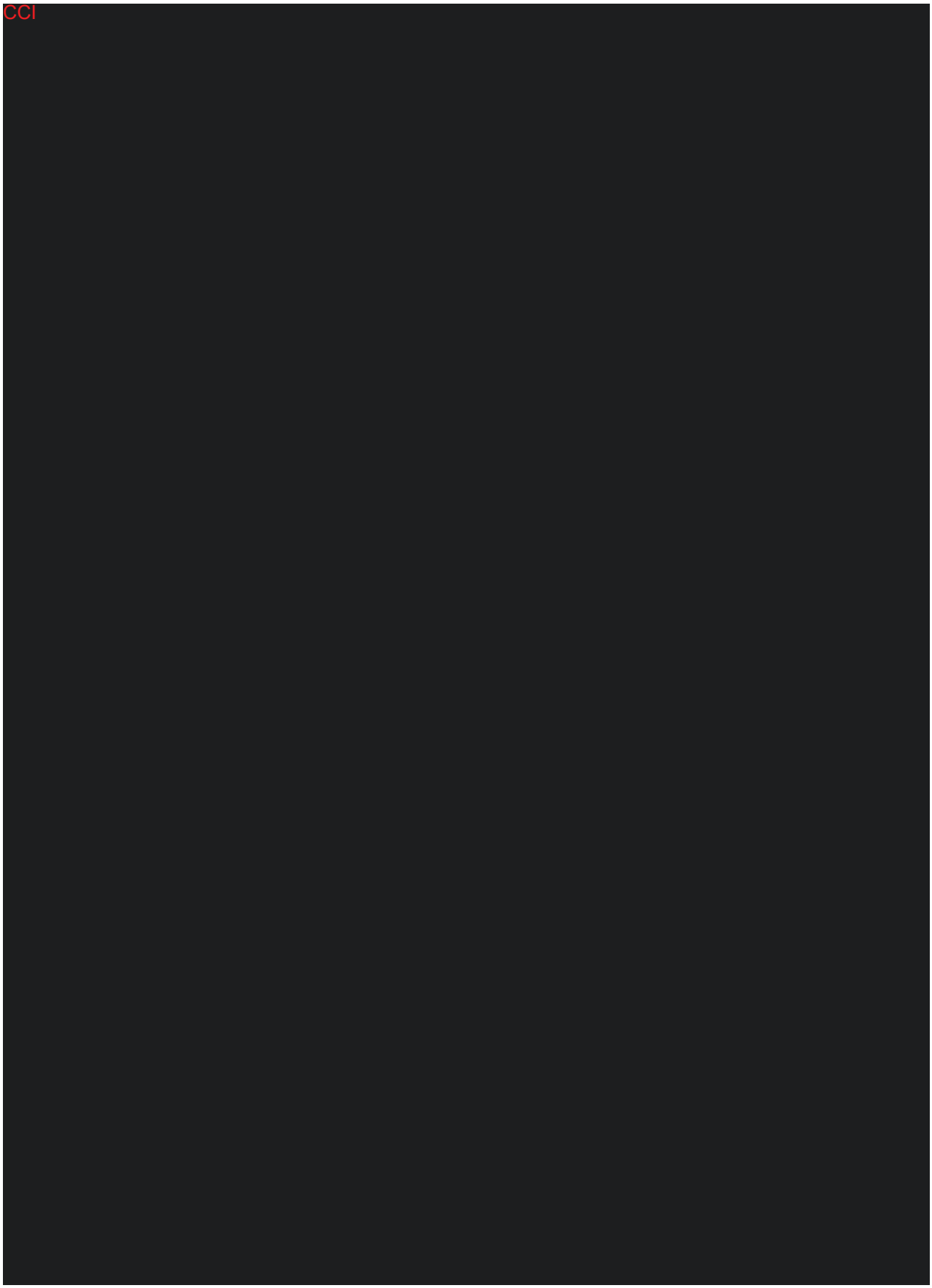

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