Protocol C5091001

COVID-19: A MULTIPART, PHASE 1 STUDY WITH RANDOMIZED, DOUBLE-BLIND, SPONSOR-OPEN, PLACEBO-CONTROLLED, SINGLE- AND MULTIPLE-DOSE ESCALATION TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF PF-07817883 AND OPTIONAL OPEN-LABEL, RANDOMIZED STUDY TO EVALUATE RELATIVE BIOAVAILABILITY AND FOOD EFFECT OF SOLID ORAL FORMULATION AND OPTIONAL OPEN-LABEL, NON-RANDOMIZED STUDY TO EVALUATE METABOLISM AND EXCRETION OF PF-07817883 AND OPTIONAL RANDOMIZED, OPEN-LABEL STUDY TO ASSESS THE EFFECT OF PF-07817883 ON PHARMACOKINETICS OF MIDAZOLAM IN HEALTHY ADULT PARTICIPANTS

Statistical Analysis Plan
(SAP)

Version: **v2.0**

Date: 24 May 2023

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1.0 27 Oct 2022	Original 14 Sep 2022 Protocol Amendment 1 21 Oct 2022	N/A	N/A
2.0 24 May 2023	Protocol Amendment 2 31 Jan 2023 Protocol Amendment 3 9 Mar 2023	Updates based on SAP template update, protocol amendments, A&R plan review and Blinded Data Reviews.	Rationale: the protocol has been amended to • Remove '(Optional)' for PART 3: RBA/FE, PART 4: ME and PART 5: DDI • Added PART-6: SE Cohort and Optional Cohort to PART-5: DDI The following sections were revised as part of this rationale: • Updated protocol title • Sections 2, 2.3, 3, 4 and 6 – updated to match protocol amendments • Section 2.2 – added objectives and endpoints for PART-6 • Section 3.3 – added moxifloxacin PK endpoints; updated Tables 5 and 6 for clarity • Section 3.6 – added microsampling PK blood samples for PART-2 • Section 6.3.1 – moved food effect analysis in PART-1 as exploratory endpoint • Section 6.3.2 added analysis for PK biomarkers in PART-2 • Section 6.3.3 – moved taste assessment analysis in PART-3 as exploratory endpoint

			• Section 6.3.4 – moved metabolic profiling in PART-4 as exploratory endpoint • Section 6.3.5 – added analysis for PK microsampling in PART-2 • Section 6.3.6 – added cQT analyses and assay sensitivity for PART-6 • Section 8 – added references • Appendix 3 – updated list of abbreviations • Appendix 4 – added example SAS code for MMRM of QTcF Rationale: Changes to reflect current SAP template: • Added links to Figures in Table of Contents • Section 2.2: added "Type" and "Estimand" columns to objective/endpoint/estimand table • Section 6.3 – added sections for exploratory endpoints Rationale: Changes to reflect updates based on ongoing review of tables etc: • Section 3.5.4 – changed definition of PART-1 baseline to match that used in PART-6 • Section 6 – clarified reporting of Japanese and Chinese in PART-2 and PART-5. • Sections 6.6.2, 6.6.3 and 6.6.4 – added individual participant profiles for participants meeting the sponsor abnormality criteria • Section 6.6.3 – removed temperature as only collected during screening and unplanned visits

2. INTRODUCTION

*The current study is the FIH study of PF-07817883 in healthy adult participants. It is a 6-part study combining **PART-1: SAD, PART-2: MAD, PART-3: RBA/FE, PART-4: ME, PART-5: DDI and PART-6: SE**. **PART 1: SAD and -2: MAD** will evaluate safety, tolerability and PK of single and multiple escalating oral doses of PF 07817883 in healthy adult participants. **PART 2: MAD** of the study may also evaluate the safety, tolerability and PK in Japanese and Chinese participants. **PART-3: RBA/FE** will evaluate relative bioavailability and food effect of up to 2 new PF-07817883 oral formulations. **PART 4: ME** will evaluate the metabolism and excretion of PF-07817883. **PART-5: DDI** will evaluate the effect of steady-state PF 07817883 on PK of midazolam in healthy participants. **PART-6: SE** will assess safety, tolerability, and PK of PF-07817883 at SE in healthy participants.*

Results from this study will inform the study design of the Phase 2/3 studies in COVID-19 patients.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C5091001. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Endpoints, and Estimands

There are no estimands for this study.

PART-1: SAD

Type	*Objectives*	*Endpoints*	Estimand
	Primary:	*Primary:*	
Safety	• *To assess the safety and tolerability following single ascending doses of PF-07817883.*	• *Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.*	N/A
	Secondary:	*Secondary:*	

PK	• *To assess the plasma PK profile of PF-07817883 following single ascending doses of PF-07817883.*	• *Plasma PK parameters of PF-07817883:*
		  • *C_{max}, T_{max}, AUC_{last}, C_{max}(dn), AUC_{last}(dn).*
		  • *If data permit, AUC_{inf}, AUC_{inf}(dn), $t_{½}$, V_z/F, and CL/F.*
			N/A

	Tertiary/Exploratory:	*Tertiary/Exploratory:*	
PK	• *To explore metabolites in plasma, urine, and feces, if data permit.*	• *Qualitative characterization of metabolites of PF-07817883 in pooled plasma, urine, and feces if data permit.*	N/A
PK	• *To determine the extent of excretion of drug related material in urine and feces after a single oral administration of PF-07817883.*	• *Total recovery of drug related material in urine and feces separately, and both routes combined, expressed as a percent of total dose administered.*	N/A
PK	• *To evaluate the effect of food (high fat meal) on the exposure of PF-07817883 following a single oral dose of PF-07817883, if evaluated (Optional).*	• *The ratio of AUC_{last}, AUC_{inf} (if data permit) and C_{max} under fed condition and fasted condition.*	N/A

PART-2: MAD (including optional Japanese and Chinese cohort)

Type	*Objectives*	*Endpoints*	Estimand
	Primary:	*Primary:*	
Safety	• *To assess the safety and tolerability following multiple ascending doses of PF-07817883.*	• *Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.*	N/A
	Secondary:	*Secondary:*	
PK	• *To assess the plasma PK profile of PF-07817883 on Days 1, 5 and 10 following multiple ascending doses of PF-07817883.*	• *Plasma PK parameters of PF-07817883:* • *C_{max}, T_{max}, AUC_{tau}, C_{12}, $C_{max}(dn)$, $AUC_{tau}(dn)$, C_{av}, R_{ac}, $R_{ac,Cmax}$, PTR, CL/F and V_z/F.* • *If data permit, $t_{½}$.*	N/A
PK	• *To assess the renal excretion of PF-07817883 on Day 10 following multiple ascending doses of PF-07817883.*	• *PF-07817883 urinary PK parameters:* • *Ae_{tau} and Ae_{tau}%, CL_r.*	N/A
	Tertiary/Exploratory:	*Tertiary/Exploratory:*	
PK	• *To explore PK by microsampling technique(s), if evaluated (Optional).*	• *Concentration of PF-07817883, if evaluated.*	N/A
PK	• *To explore RBC partitioning of PF-07817883 (Optional).*	• *Ratio of PF-07817883 concentration in plasma to that in blood.*	N/A
Biomarkers	• *To explore the effect of PF-07817883 on endogenous plasma biomarkers. (Optional)*	• *Ratio of plasma concentrations of endogenous biomarkers on Day 10 to those before PF-07817883 dose.*	N/A

PART-3: RBA/FE

Type	*Objectives*	*Endpoints*	Estimand
	Primary:	*Primary:*	
PK	• *To determine the oral bioavailability of oral formulation(s) of PF-07817883 relative to suspension.*	• *The ratio of AUC_{last}, AUC_{inf} and C_{max} of oral formulation(s) and suspension.*	N/A
	Secondary:	*Secondary:*	
PK	• *To evaluate the effect of food (high-fat high-calorie meal) on the exposure of PF-07817883 following a single oral dose of PF-07817883 tablet formulation(s).*	• *The ratio of AUC_{last}, AUC_{inf} and C_{max} of tablet formulation under fed condition and fasted condition.*	N/A
PK	• *To determine the pharmacokinetics of PF-07817883 following oral administration of tablet formulation(s) and suspension of PF-07817883.*	• *Plasma PK parameters of PF-07817883: T_{max}, C_{max}, AUC_{last}, if data permit AUC_{inf}, $t_{½}$, CL/F, V_z/F.*	N/A
PK	• *To determine the safety and tolerability of PF-07817883 following oral administration of tablet formulation(s) and suspension of PF-07817883.*	• *Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.*	N/A
	Tertiary/Exploratory:	*Tertiary/Exploratory:*	
Other	• *To evaluate the taste attributes of the PF-07817883 following oral administration of oral formulation(s) and suspension of PF-07817883, if evaluated.*	• *Taste Assessment Survey Scoring Metrics: mouth feel, bitterness, tongue/mouth burn, throat burn, overall liking.*	N/A

PART-4: ME

Type	*Objectives*	*Endpoints*	Estimand
	Primary:	*Primary:*	
Other	• *To determine the extent of excretion of drug related material in urine and feces after a single oral administration of PF-07817883.*	• *Total recovery of drug related material in urine and feces separately, and both routes combined, expressed as a percent of total dose administered.*	N/A
	Secondary:	*Secondary:*	
PK	• *To determine the pharmacokinetics of PF-07817883 following a single oral administration of PF-07817883.*	• *Plasma PK parameters of PF-07817883: T_{max}, C_{max}, AUC_{last}, if data permit AUC_{inf}, $t_{½}$, CL/F, V_z/F.*	N/A
Safety	• *To determine the safety and tolerability of PF-07817883 after a single oral administration of PF-07817883.*	• *Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.*	N/A
	Tertiary/Exploratory:	*Tertiary/Exploratory:*	
Other	• *To characterize the metabolic profile and identify circulating and excreted metabolites following administration of a single oral dose of PF-07817883, if possible.*	• *Metabolic profiling/identification and determination of relative abundance of PF-07817883 and the metabolites of PF-07817883 in plasma, urine, and feces, if possible.*	N/A

PART-5: DDI

Type	*Objectives*	*Endpoints*	Estimand
	Primary Objective:	***Primary Endpoint:***	
PK	• *To estimate the effect of PF-07817883 on the PK of midazolam.*	• *Midazolam plasma PK parameters: C_{max} and AUC_{inf} (if data permit, otherwise AUC_{last}) with PF-07817883 (test) versus without PF-07817883 (reference).*	N/A
	Secondary Objective:	***Secondary Endpoints:***	
Safety	• *To evaluate the safety and tolerability of PF-07817883 in healthy participants in the absence and presence of midazolam.*	• *Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.*	N/A
PK	• *To evaluate the effects of PF-07817883 on additional PK parameters of midazolam in healthy participants.*	• *Midazolam plasma PK parameters: T_{max}, AUC_{last}, and if data permit $t_{½}$, CL/F, and V_z/F for midazolam with and without coadministration of PF-07817883.*	N/A
	Tertiary/Exploratory Objectives:	***Tertiary/Exploratory Endpoints:***	
PK	• *To assess the plasma PK profile of PF-07817883 on Days 1, 5 (optional) and 10 following multiple ascending doses of PF-07817883.*	• *Plasma PK parameters of PF-07817883:* • *C_{max}, T_{max}, AUC_{tau}, C_{12}, C_{max}(dn), AUC_{tau}(dn), C_{av}, R_{ac}, $R_{ac,Cmax}$, PTR, CL/F and V_z/F.* • *If data permit, $t_{½}$.*	N/A
PK	• *To assess the plasma PK profile of PF-07817883 on Days 1, 5 (optional) and 10 following multiple ascending doses of PF-07817883 in Chinese and Japanese participants (Optional).*	• *Plasma PK parameters of PF-07817883:* • *C_{max}, T_{max}, AUC_{tau}, C_{12}, C_{max}(dn), AUC_{tau}(dn), C_{av}, R_{ac}, $R_{ac,Cmax}$, PTR, CL/F and V_z/F.* • *If data permit, $t_{½}$.*	N/A

PART-6: SE

Type	*Objectives*	*Endpoints*	Estimand
	Primary Objective:	***Primary Endpoint:***	
Safety	• *To assess the safety and tolerability of a SE of PF-07817883 administered as split dosing.*	• *Assessment of TEAEs, clinical laboratory abnormalities, vital signs, and 12-lead ECGs.*	*N/A*
	Secondary Objective:	***Secondary Endpoints:***	

PK	• *To assess the plasma PK of PF-07817883 at an SE of PF-07817883 administered as split dosing.*	• *Plasma PK parameters of PF-07817883:*
		  • *C_{max}, T_{max}, AUC_{last}*
		  • *If data permit, AUC_{inf}, $t_{½}$.*
			N/A

	Tertiary/Exploratory Objectives:	***Tertiary/Exploratory Endpoints:***	
PK	• *To assess the plasma PK of moxifloxacin*	• *Plasma moxifloxacin parameters C_{max}, T_{max} and AUC_{last}.*	*N/A*
Other	• *To determine assay sensitivity by comparing the effect of moxifloxacin 400 mg on QTcF interval with placebo at historical moxifloxacin T_{max} of 3 hours.*	• *Time matched mean differences in QTcF between moxifloxacin and placebo at the historical moxifloxacin T_{max} of 3 hours.*	*N/A*
Other	• *To determine assay sensitivity by exposure-response analysis of moxifloxacin*	• *Baseline corrected QTcF*	*N/A*
Other	• *To determine exposure response analysis of PF-07817883*	• *Baseline corrected QTcF*	*N/A*

2.3. Study Design

2.3.1. Overall Design

This 6-part, Phase 1, FIH study will combine PART-1: SAD, PART-2: MAD (including optional Japanese and Chinese Cohorts), PART-3: RBA/FE, PART-4: ME, PART-5: DDI and PART-6: SE. PART-1 and PART-2 are a randomized, double-blind, sponsor -open, placebo-controlled study to evaluate safety, tolerability, and PK of single and multiple escalating oral doses of PF-07817883 in healthy adult participants, respectively. PART-2 of the study may also evaluate the safety, tolerability, and PK in Japanese and Chinese participants. PART-3 is a randomized, open-label, cross-over, study to evaluate RBA and FE of 2 new PF-07817883 oral formulations. PART-4 is an open-label, non-randomized, single period to evaluate the ME of PF-07817883. PART-5 is an open-label, randomized, cross-over study to evaluate the effect of steady-state PF-07817883 on PK of midazolam in healthy adult participants. PART-6: SE is a sponsor-open, randomized, 3-treatment, 3-period, 6-sequence, cross-over, placebo-and positive-controlled study to evaluate safety, tolerability, and PK at SE in healthy participants.

2.3.2. PART-1: SAD

SAD will include 2 interleaving cohorts with a total of approximately 16 participants planned (approximately 8 participants in each cohort – 6 active: 2 placebo), with 3-period, cross-over in each cohort. Period 3 is an optional period which may be used to further explore PK at additional doses or assess food effect (high-fat high-calorie meal), based on emerging safety, tolerability and PK assessments. There will be a washout interval of ⩾5 days between dosing to a given participant.

2.3.3. PART-2: MAD

*The first MAD cohort may start after a total daily dose, which provides comparable or higher total daily exposure (24h) in SAD to the projected total daily steady-state exposure (over 24h) at the starting dose in MAD, is found safe and well tolerated in the **PART-1** of the study. The proposed MAD study design will be parallel cohorts, with 10 days of dosing. **PART-2** will consist of approximately 2 to 6 cohorts including up to 4 optional cohorts (Cohorts 5, 6, 7 and 8) with approximately 6 participants in each cohort (4 active: 2 placebo). Cohorts 7 and 8 are optional Japanese and Chinese participants, respectively. Dose escalation to subsequent dose levels in MAD cohorts will be based on a minimum of 6 days safety data and PK over approximately ⩾6 hours on Day 5 in a minimum of 4 participants (3 active and 1 placebo) at previous dose levels.*

2.3.4. PART-3: RBA/FE

This cohort will be an open-label, randomized, 4-period, 6-sequence cross-over single dose *cohort evaluating the RBA of 2 new PF-07817883 oral formulation(s) compared to PF-07817883 oral suspension and to evaluate the effect of food on the bioavailability of the PF-07817883 oral formulation(s) in healthy adult participants. An exploratory assessment of the taste may be conducted. Approximately 12 participants may be enrolled in PART-3 of the study with approximately equal number of participants randomized to 1 of 6 sequences.*

In this part, there will be a washout interval of at least 3 days between dosing to a given participant in each period.

Table 2. Treatment Sequences in PART-3: RBA/FE

Sequence	*Period 1*	*Period 2*	*Period 3*	*Period 4*
1	*A*	*B*	*C*	*D*
2	*B*	*C*	*A*	*D*
3	*C*	*A*	*B*	*D*
4	*B*	*A*	*C*	*E*
5	*A*	*C*	*B*	*E*
6	*C*	*B*	*A*	*E*

Treatment A = PF-07817883 600 mg oral suspension SD Fasted;
Treatment B = PF-07817883 600 mg Formulation 1 CCI Fasted
Treatment C = PF-07817883 600 mg Formulation 2 Fasted
Treatment D = PF-07817883 600 mg Formulation 1 Fed (high-fat meal)
Treatment E = PF-07817883 600 mg Formulation 2 Fed (high-fat meal)

2.3.5. PART-4: ME

This part will include a single cohort of approximately 6 male participants. The dose of this cohort will be decided based on the emerging PK and safety data. The selected dose will not exceedthe highest dose deemed safe in PART-1. Each participant will receive a single dose of PF-07817883 at 0 hr on Day 1 after at least 10 hr of fasting. The participants will be discharged on Day 11.

2.3.6. PART-5: DDI

This part may consist of up to 2 cohorts (Cohort 11 and optional Cohort 12). Based on the data from the Cohort 11, an optional Cohort 12 may be initiated at a dose lower than the 600 mg BID. Both cohorts will have 2 treatments, 2 sequences, and 2 periods with a cross-over design to evaluate the effect of steady-state PF-07817883 on the PK of midazolam in healthy adult participants. The dose of PF-07817883 in Cohort 11 is 600 mg BID and the dose of Cohort 12 will be decided based on the emerging PK data from Cohort 11. Each enrolled participant will be randomly assigned to 1 of 2 sequences to receive 2 treatments in 2 periods. The 2 treatments in this part will be: single oral dose of 5 mg midazolam alone (Treatment A) and multiple oral doses of PF-07817883 in combination with a single oral dose of 5 mg midazolam (Treatment B). A total of approximately 14 healthy participants will be enrolled in each cohort to ensure at least 12 participants will complete that cohort.

Table 3. Treatment Sequences in PART-5: DDI

	Period 1	*Period 2*
Sequence 1 (n=7)	*Treatment A*	*Treatment B or Treatment C*
Sequence 2 (n=7)	*Treatment B or Treatment C*	*Treatment A*

- *Treatment A: Single oral dose of 5 mg midazolam with at least 2-day washout (Treatment A period duration: Day 1 to Day 3).*
- *Treatment B: PF-07817883 administered orally for 10 days: Day 1 morning to Day 10 morning. On Day 10 morning, participants will receive a single oral dose of 5 mg midazolam administered with PF-07817883, followed by a 7-day washout (Treatment B period duration: Day 1 to Day 17).*
- *Treatment C: PF-07817883 administered orally for 10 days: Day 1 morning to Day 10 morning. On Day 5 morning and Day 10 morning, participants will receive a single oral dose of 5 mg midazolam administered with PF-07817883. A 7-day washout to follow after last PF-07817883 administration (Treatment C period duration: Day 1 to Day 17).*

2.3.7. PART-6: SE

This is a single-dose, randomized, 3-treatment, 3-period, cross-over, 6-sequence, sponsoropen, placebo-and positive-controlled study to be conducted in approximately 24 adult healthy participants. Each participant will be randomly assigned to one of the reatment sequences shown in Table 4. The participants randomized to treatment will receive 6000 mg as 2 split doses of PF-07817883 3000 mg administered at 0 and 1 h. The participant randomized to placebo will receive placebo at 0 and 1h. The participants randomized to moxifloxacin will receive moxifloxacin 400 mg and placebo at 0 and 1h, respectively. Treatment assignments to PF-07817883 and placebo will be blinded to the participants, investigator and CRU staff (except pharmacy staff) but open to the sponsor. Administration of moxifloxacin and placebo in participants randomized to moxifloxacin treatment will be open label. Each period will be separated by at least 7 days of wash-out interval. Sentinel dosing will be implemented in this cohort.

Table 4. Treatment Sequences in PART-6: SE

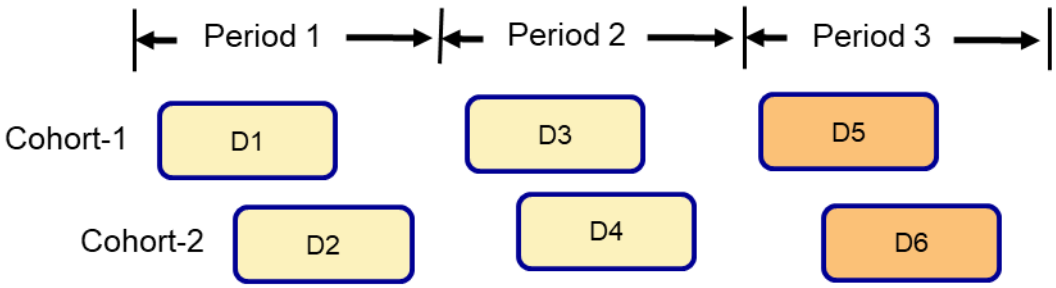
	Period 1	**Period 2**	**Period 3**
Sequence 1 (n=4)	A	B	C
Sequence 2 (n=4)	B	C	A
Sequence 3 (n=4)	C	A	B
Sequence 4 (n=4)	B	A	C
Sequence 5 (n=4)	A	C	B
Sequence 6 (n=4)	C	B	A

Treatment A: PF-07817883 6000 mg oral suspension administered as 2 split-doses of 3000 mg at 0 and 1h in fasted state.
Treatment B: Placebo oral suspension.
Treatment C: Moxifloxacin 400 mg SD at 0h and placebo at 1h in fasted state.

2.3.8. Number of Participants

A total of up to 122 participants (16 in PART-1: SAD, up to 36 [with 2 cohorts and 4 optional cohorts] in PART-2: MAD, 12 in PART-3: RBA/FE cohort, 6 in PART-4: ME, up to 28 [with 2 cohorts of 14 each] in PART-5: DDI and 24 in PART-6: SE) are planned to be enrolled in this study.

Figure 1. PART-1: SAD



Optional

Optional dose levels may be used to explore high doses or food effect. Dosing with food may be done based on the emerging PK/safety data

Figure 2. PART-2: MAD

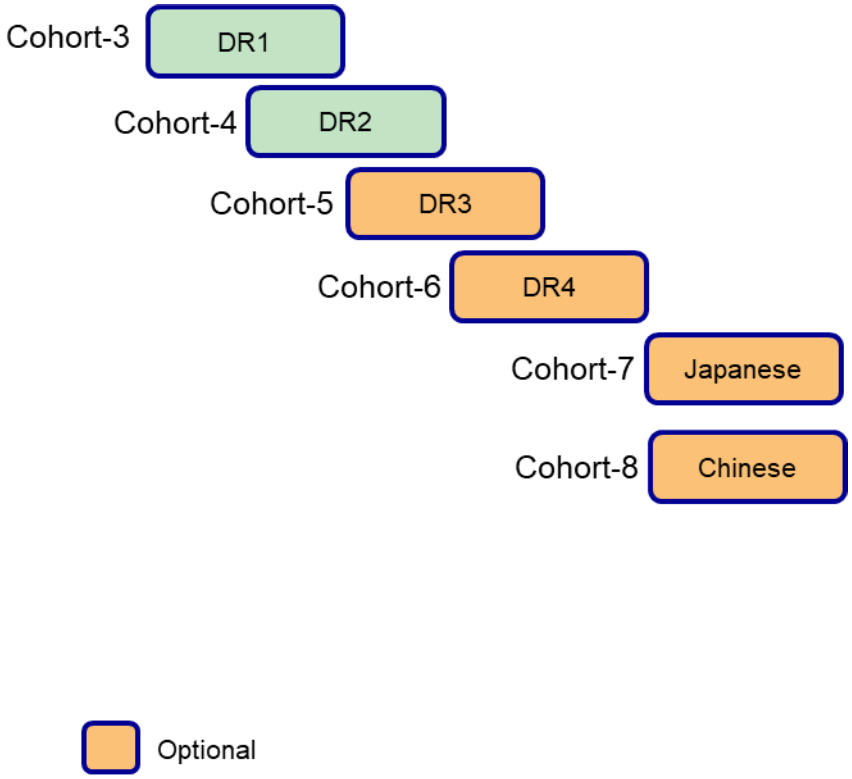
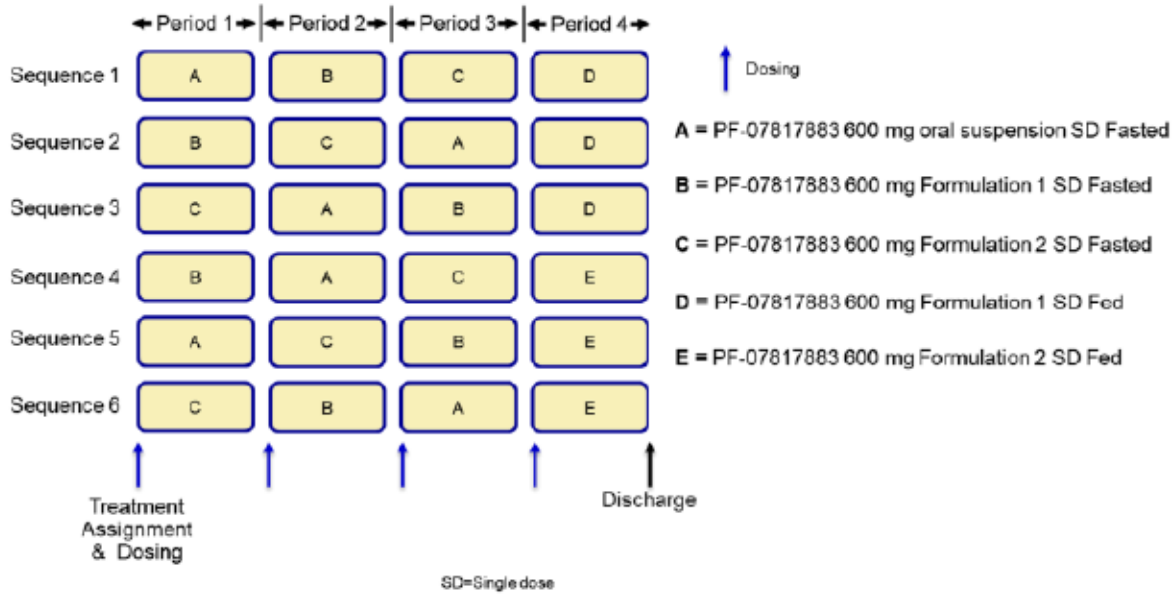


Figure 3. PART-3: RBA/FE

Cohort 9:

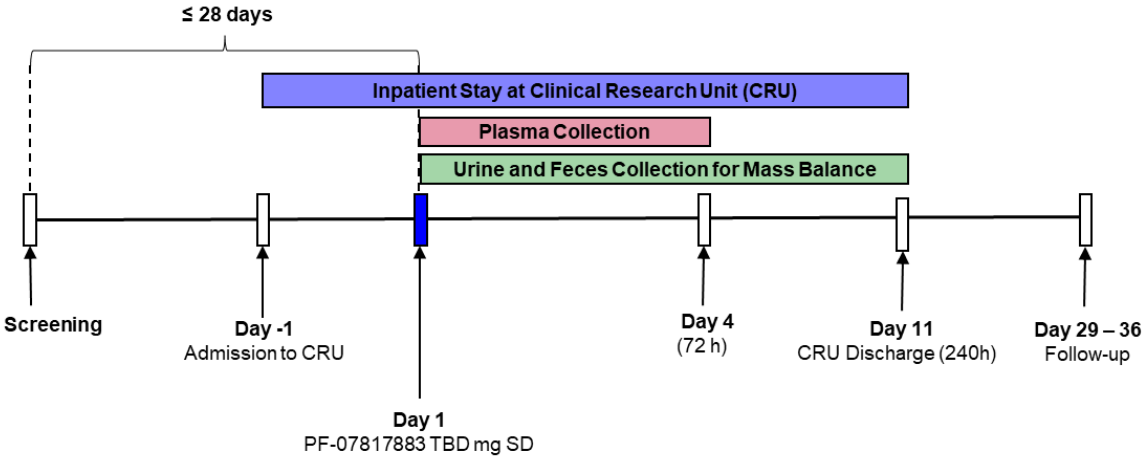


Formulation 1: CCI [redacted]

Formulation 2: CCI [redacted]

Figure 4. PART-4: ME

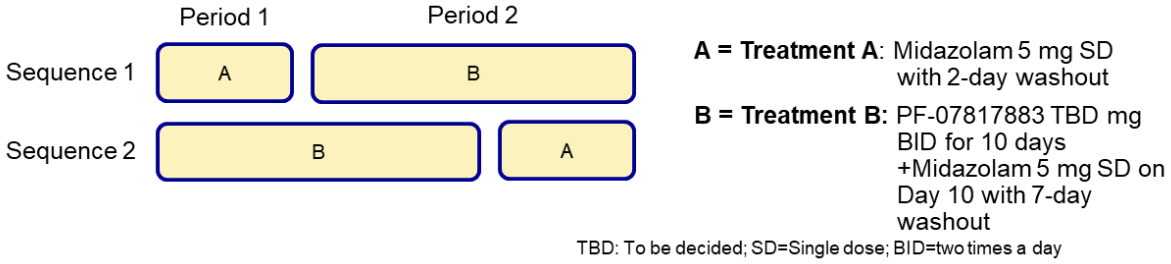
Cohort 10:



TBD: To be decided; SD=Single dose

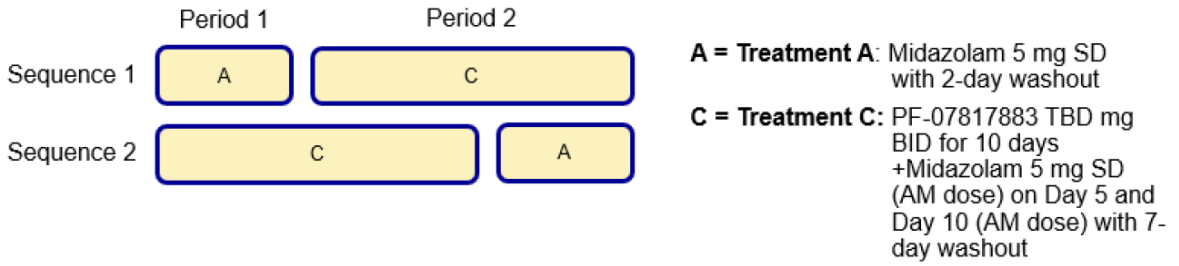
Figure 5. PART-5: DDI

Cohort 11:



TBD: To be decided; SD=Single dose; BID=two times a day

Cohort 12 (Optional):

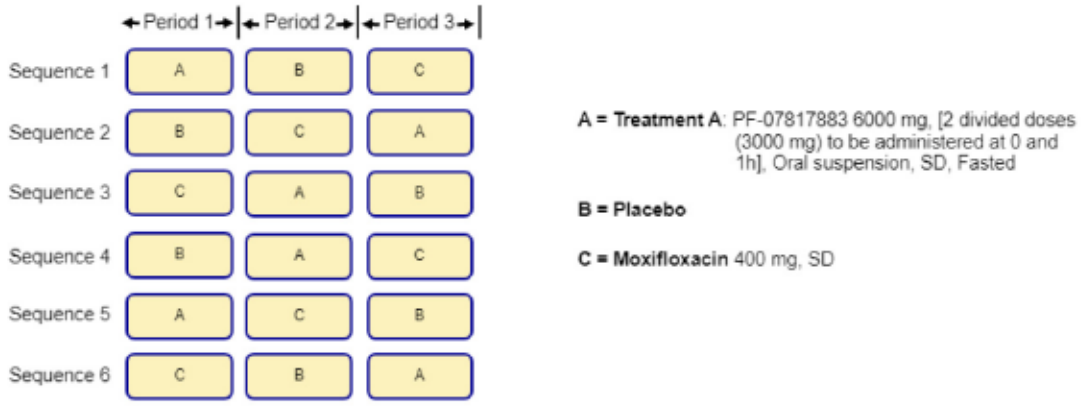


TBD: To be decided; SD=Single dose; BID=two times a day

Washout duration may be modified based on emerging data.

Figure 6. PART-6: SE

Cohort 13:



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

As listed in Section 2.2 the primary endpoints in **PART-1**, **PART-2** and **PART-6** are related to safety/tolerability and are described in Section 3.5.

The primary endpoints in **PART-3** are the PF-07817883 plasma PK endpoints which are described in Section 3.3.

The primary endpoints in **PART-4** are total recovery of drug-related material in urine, feces and both routes combined, determined based on total administered dose. Percent recovery of drug-related material in urine and feces will be determined based on total administered dose.

The primary endpoints in **PART-5** are Midazolam plasma PK endpoints: C_{max} and AUC_{inf} (if data permit, otherwise AUC_{last}) with PF-07817883 (test) versus without PF-07817883 (reference).

3.2. Secondary Endpoint(s)

The secondary endpoints in **PART-1**, **PART-2** and **PART-6** are related to PK are described in Section 3.3. The secondary endpoints in **PART-3**, **PART-4** and **PART-5** are related to PK described in Section 3.3 and safety/tolerability are described in Section 3.5.

3.3. Other Endpoint(s)

3.3.1. Pharmacokinetic (PK) Endpoints

Blood and urine samples for the PK analysis of PF-07817883/midazolam/moxifloxacin will be taken according to the SoA given in the protocol.

The PK parameters of PF-07817883, midazolam (**PART-5**) and moxifloxacin (**PART-6**) will be derived (if data permit) from the concentration-time data using standard noncompartmental methods defined in Table 5 (single oral dose) and Table 6 (multiple oral doses). Urine PF-07817883 PK parameters are described in . Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 5. Plasma PF-07817883 PK Parameters for PART-1: SAD, PART-3: RBA/FE, PART-4: ME and PART-6: SE, Midazolam PK Parameters in PART-5: DDI, and Moxifloxacin PK Parameters in PART-6: SE

Parameter	Part of the Study	Analysis Scale	PF-07817883/ Midazolam/Moxifloxacin
AUC_{last}†[a]	1, 3, 4, 5, 6	ln	D, A
AUC_{inf}*¶	1, 3, 4, 5, 6	ln	D, A
C_{max}[a]	1, 3, 4, 5, 6	ln	D, A
T_{max}[a]	1, 3, 4, 5, 6	R	D
$t_{½}$*¶	1, 3, 4, 5, 6	R	D
CL/F*	1, 3, 4, 5, 6	ln	D
V_z/F*	1, 3, 4, 5, 6	ln	D
AUC_{last}(dn)‡	1	ln	D
AUC_{inf}(dn)*‡	1	ln	D
C_{max}(dn)‡	1	ln	D

Key: D=displayed with descriptive statistics,
ln=natural-log transformed, R=raw (untransformed), A=analysed
*=if data permits, dn = normalized to a 1mg PF-07817883 dose,
†=In PART-3, pre-dose (0h) sample from Periods 2 and 3 will also be considered as 48h PK sample for Periods 1 and 2, respectively,
‡=Not required except PART-1,
[a] Only selected PK parameters to be calculated for moxifloxacin in PART-6

In **PART-3**, pre-dose (0h) sample from Periods 2 and 3 will also be considered as 48h PK sample for Periods 1 and 2, respectively. In PART-5, Sequence 1, Day 1, 0h sample of midazolam in Period 2 will be considered as 48h PK for Period 1.

T_{last} will also be provided as a support parameter for AUC_{last}. T_{last} values will only be listed and not summarized.

Table 6. Noncompartmental PK Parameters for PART-2: MAD and PART-5: DDI (for PF-07817883)

Parameter	Day(s)[a]	Analysis Scale	PF-07817883
Plasma			
AUC_τ	1, 5, 10	ln	D
C_{max}	1, 5, 10	ln	D
T_{max}	1, 5, 10	R	D
C_{12}	5, 10	ln	D
PTR	5, 10	ln	D

Table 6. Noncompartmental PK Parameters for PART-2: MAD and PART-5: DDI (for PF-07817883)

Parameter	Day(s)[a]	Analysis Scale	PF-07817883
R_{ac}	5, 10	ln	D
$R_{ac,Cmax}$	5, 10	ln	D
CL/F	5, 10	ln	D
$t_{½}$*	10	R	D
V_z/F*	10	ln	D
AUC_τ(dn)	1, 5, 10	ln	D
C_{max}(dn)	1, 5, 10	ln	D
C_{av}	1, 5, 10	ln	D
Urine[b]			
Ae_τ	10	ln	D
Ae_τ%	10	ln	D
CL_τ	10	ln	D

Key: D=displayed with descriptive statistics,
ln=natural-log transformed, R=raw (untransformed),
*=if data permits, dn = normalized to a 1mg PF-07817883 dose.
a. Day 5 optional for PART-5.
b. Urine parameters are not applicable for PART-5.

3.4. Baseline Variables

Baseline for laboratory data, vital signs and ECG are defined in Sections 3.5.2, 3.5.3 and 3.5.4 respectively.

3.5. Safety Endpoints

3.5.1. Adverse Events

An adverse event is considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that start on or after the first dosing day and time/start time, if collected, but before the end of the study will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date.

3.5.2. Laboratory Data

Safety laboratory tests will be performed as described in the protocol.

For **PART-1, PART-3**, **PART-5** and **PART-6**, baseline will be the last pre-dose measurement prior to administration of PF-07817883, placebo, midazolam or moxifloxacin (as applicable) in each study period. For **PART-2**, baseline will be the last pre-dose measurement. For **PART-4**, baseline will be the last pre-dose measurement prior to administration of PF-07817883.

To determine if there are any clinically significant laboratory abnormalities, the hematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take

into account whether each participant's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

For **PART-1**, **PART-2, PART-5** and **PART-6** change from baseline and percent change from baseline will be calculated for each post-baseline timepoint. This will be for all hematology and chemistry safety labs will be included plus aPTT, PT, INR, Amylase and Lipase.

3.5.3. Vital Signs

Single supine blood pressure, respiratory rate and pulse measurements will be taken at times detailed in the SoA given in the protocol.

For **PART-1**, **PART-3 PART-5** and **PART-6**, baseline will be defined as the last pre-dose measurement immediately prior to first administration of study intervention in each study period. Unplanned measurements will be used where applicable.

For **PART-2**, baseline will be the last pre-dose measurement.

For **PART-4** baseline will be the last pre-dose measurement prior to administration of PF-07817883.

The following vital signs endpoints will be determined:

- Change from baseline in supine systolic and diastolic blood pressure, pulse rate and respiratory rate.
- The maximum decrease from baseline over all measurements taken post-dose for supine systolic and diastolic blood pressures and respiratory rate.
- The maximum increase from baseline over all measurements taken post-dose for supine pulse rate.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each post-dose measurement to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken.

Similarly, the maximum decrease from baseline will be determined by selecting the minimum value of the changes from baseline. In cases where a participant does not show a decrease, the minimum increase should be taken.

If 3 of more participants have an unplanned measurements at the same timepoint these may be summarized in addition to the planned timepoints.

3.5.4. ECG

A 12-lead ECG will be obtained on all participants at screening. 12-lead ECGs will be recorded on all participants at times detailed in the SoA given in the protocol. Triplicate measurements will be performed in **PART-1**, **PART-2** and **PART-6**, and single measurements in **PART-3**, **PART-4** and **PART-5**. The QT, heart rate, QTcF, PR and QRS will be recorded at each assessment time.The average of the triplicate readings collected (where applicable) at each assessment time will be calculated for each ECG parameter.

For **PART-1** and **PART-6** baseline will be defined as the average of the triplicate measurements at 3 timepoints (-1 hour, -0.5 hour, and 0 hours) prior to administration of study treatment in each study period.

For **PART-2**, baseline will be defined as the average of the triplicate measurements prior to administration of study treatment.

For **PART-3** and **PART-5**, baseline will be defined the last measurement prior to administration of study treatment in each study period.

For **PART-4**, baseline will be defined as the last measurement prior to administration of PF-07817883.

The following ECG endpoints will be determined:

- Change from baseline in QT interval, heart rate, QTcF interval, PR interval, and QRS complex.
- The maximum absolute value (post-dose) will be calculated for QTcF, PR and QRS.
- The maximum increase from baseline over all measurements taken post-dose will be calculated for QTcF.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each triplicate-average post-dose measurement to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a participant does not show an increase. In such an instance, the minimum decrease should be taken.

3.6. Other Endpoint(s)

If done, the data collected for taste assessment (in **PART-3**) *using the sponsor-provided taste questionnaire will be numerically derived by measuring length (using a scale with gradations of at least 0.1 centimeter) of the "x" marked by the participant relative to the "good trait".*

If performed, blood samples for the measurement of 4β-hydroxycholesterol, cholesterol, ratio of 4β-hydroxycholesterol:cholesterol and other PK biomarkers will be collected at times specified in the SoA given in the protocol in **PART-2**. Baseline will be the sample on Day 1, prior to morning dosing and the ratios of Day 10 to Day 1 will be calculated.

In PART-2: MAD portion of the study conducted at NH CRU only, exploratory microsampling PK blood samples for the measurement of PF-07817883 concentrations maybe collected.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

The study part referred to below can be either **PART-1: SAD**, **PART-2: MAD**, **PART-3: RBA/FE**, **PART-4: ME**, **PART-5: DDI**, or **PART-6: SE**.

Population	Description
Enrolled	*"Enrolled" means a participant's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.*
Evaluable	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention for the given part of the study.*
Safety	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.*
PK Concentration Set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 concentration value is reported for the given part of the study.*
PK Parameter Set	*All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the PK parameters of interest are reported for the given part of the study.*

Population	Description
PK Biomarker Set	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention and in whom at least 1 of the PK biomarkers of interest and both pre and post PF-07817883 dose measurements are reported for PART-2: MAD.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There is no statistical hypothesis testing planned for this study and no statistical decision rules will be applied.

5.2. General Methods

Unless otherwise stated, all summaries and plots will be presented by treatment.

5.2.1. Analyses for Continuous Endpoints

Continuous variables will be presented using summary statistics: number of observations, arithmetic mean, standard deviation, cv%, median, minimum and maximum values.

Log transformed continuous variables will be presented using summary statistics: number of observations, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.

5.2.2. Analyses for Categorical Endpoints

Categorical variables will be presented using summary statistics: number of observations and percentages.

5.3. Methods to Manage Missing Data

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

In all PK data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero.

In listings, BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification (LLQ).

For PK summary tables and plots of mean/median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie not done) or NS (ie no sample),
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist/statistician.

If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (ie not calculated). (Note that NC values will not be generated beyond the day that a participant discontinues). In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular dose with ≥3 evaluable measurements.

If an individual participant has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

6. ANALYSES AND SUMMARIES

Separate tables will be produced for **PART-1: SAD, PART-2: MAD, PART-3: RBA/FE**, **PART-4: ME**, **PART-5: DDI,** and **PART-6: SE** unless otherwise specified. Placebo will be a separate treatment group. In **PART-2**, Japanese and Chinese will be separate treatment groups. *If the number of Chinese or Japanese participants in **PART-5** are ≥3, the plasma concentration, PK parameters of PF-07817883* and safety data *may also be summarized separately for Chinese, Japanese and Western population.* Tables in PART-5 will be paged by population e.g. Japanese, Non-Japanese and All.

6.1. Primary Endpoint(s)

The primary endpoints in **PART-1**, **PART-2** and **PART-6** are related to safety/tolerability and their analyses are described Section 6.6.

The primary endpoints in **PART-3** and **PART-5** are the plasma PK endpoints whose analyses are described in Section 6.2.

The primary endpoints in **PART-4** are percent recovery and cumulative recovery of drug-related material in urine, feces and both routes combined based on total administered dose. This may be calculated and reported separately.

6.2. Secondary Endpoint(s)

The secondary endpoints in **PART-1**, **PART-2**, **PART-4** and **PART-6**, as well as the primary endpoints in **PART-3** and **PART-5**, are related to PK and are described herein.

*No formal inferential statistics will be applied to the plasma PK data apart from the comparisons of formulation and food effect in either **PART-1** or **PART-3** and the estimation of the effect of steady-state PF-07817883 on the PK of midazolam in **PART-5**. The PK data for PF-07817883 and Midazolam (**PART-5**) will be reported separately.*

The PK parameters detailed in Section 3.3.1 will be listed and summarized for participants in the PK Parameter Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3. Each PK parameter will be summarized by matrix (plasma or urine), treatment and dose. Each summary will include the set of summary statistics as

specified in Table 7. Summaries will be performed separately for **PART-1**, **PART-2**, **PART-3**, **PART-4**, **PART-5** and **PART-6**.

Table 7. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC_{last}, AUC_{inf}, C_{max}, , AUC_{last}(dn), AUC_{inf}(dn), C_{max}(dn), AUC_{τ}, CL/F, V_z/F , C_{av}, C_{12}, R_{ac}, $R_{ac,Cmax}$, PTR, AUC_{τ}(dn), Ae_{τ}, Ae_{τ}%, and CL_r	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{1/2}$,	N, arithmetic mean, median, standard deviation, minimum, maximum.

To assess the relationship between the PK parameters and dose, dose normalized C_{max}, AUC_{last}, and AUC_{inf} (**PART-1**) and C_{max} and AUC_{τ} (**PART-2**) of PF-07817883 will be plotted against dose (using a logarithmic scale), and will include individual participant values and the geometric means for each dose. Geometric means will have a different symbol than the individual values. In **PART-2**, the data from the Japanese and Chinese subjects will be identified by different symbols/colours. The values will be dose normalized (to a 1 mg dose) by dividing the individual values and raw geometric means by dose. A footnote will be added to the plots to indicate that geometric means are presented. All dose normalized parameters will be listed along with other individual PK parameters.

For **PART-5**, box and whisker plots for individual participant parameters (AUC_{inf}, AUC_{last} and C_{max}) will be presented by treatment and overlaid with geometric means.

Supporting data from the estimation of $t_{½}$ will be listed by treatment and dose where applicable: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation ($AUC_{extrap\%}$); and the first, last, and number of time points used in the estimation of k_{el}. These data may be included in the CSR.

Presentations for PF-07817883/midazolam concentrations will be presented using participants in the PK Concentration Set (as defined in Section 4) and will include:

- a listing of all concentrations sorted by participant ID, dose, matrix and nominal time post-dose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

- a summary of concentrations by dose and nominal time post-dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- individual concentration-time plots by dose (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each dose per scale).

- individual concentration-time plots by participant (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each dose per scale).

- median concentration-time plots (on both linear and semi-log scales) against nominal time post-dose by dose (all doses on the same plot per scale, based on the summary of concentrations by dose and time post-dose).

- mean concentration-time plots (on both linear and semi-log scales) against nominal time post-dose by dose (all doses on the same plot per scale, based on the summary of concentrations by dose and time post-dose).

The scale used for the x-axis (time) of these plots will be decided on review of the data, and will depend on how long PF-07817883/midazolam concentration is quantifiable in the matrix.

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used.

For **PART-2** and **PART-5**, urine amounts of PF-07817883 as listed in Table 6 will be listed and summarized descriptively, if data permit.

*For **PART-3**, natural log transformed AUC_{last}, C_{max}, and AUC_{inf} (if data permit) for PF-07817883 will be analyzed using a mixed effect model with sequence, period, and treatment included as fixed effects and participant nested within sequence as a random effect.* The Kenward-Roger adjustment for the degrees of freedom will be used. *Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for these differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for these ratios. Only the first 3 periods will be used in this analysis (ie, Fed formulations excluded).*

To compare the Fed and Fasted formulations, natural log transformed AUC_{last}, C_{max}, and AUC_{inf} (if data permit) for PF-07817883 from these two formulations will be analyzed separately using a paired t-test. Resulting estimates of the mean differences (Test - Reference) and corresponding 90% CIs from the t-test will be exponentiated to provide estimates of the ratio of geometric means (Test/Reference) and 90% CIs for the ratios. Formulation Fasted is the Reference treatment and Formulation Fed is the Test treatment.

The following comparisons will be made (where applicable):

Comparison	*Test*	*Reference*
Formulation	*PF-07817883 Oral Formulation 1 in Fasted state*	*PF-07817883 Oral Suspension in Fasted state (A)*
	PF-07817883 Oral Formulation 2 in Fasted state	*PF-07817883 Oral Suspension in Fasted state (A)*
Food Effect	*PF-07817883 Oral Formulation 1 in Fed (high fat high-calorie meal) state*	*PF-07817883 Oral Formulation 1 in Fasted state*
	PF-07817883 Oral Formulation 2 in Fed (high fat high-calorie meal) state	*PF-07817883 Oral Formulation 2 in Fasted state*

*For **PART-5**, natural log transformed AUC_{last}, C_{max} and AUC_{inf} (if data permit) of midazolam will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant nested within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. Midazolam alone is the Reference treatment whilst midazolam + PF-07817883 is the Test treatment.*

*If the number of Chinese or Japanese participants in **PART-5** are ≥3, the plasma concentration and PK parameters of PF-07817883 may also be summarized separately for Chinese, Japanese and Western population.*

6.3. Other Endpoints

6.3.1. Food Effect in PART-1: SAD

If performed, to assess any effect of food/formulation in **PART-1**, natural log transformed AUC_{last}, C_{max}, and AUC_{inf} (if data permit) for PF-07817883 will be analyzed using a mixed effects model with treatment as a fixed effect and participant as a random effect using participants with data from relevant periods only.

6.3.2. PK Biomarker in PART-2: MAD

Absolute values and the ratios of Day 10 to Day 1 for PK biomarkers including plasma 4β-hydroxycholesterol/cholesterol ratio will be summarized descriptively by treatment and timepoint, as described in Section 5.2.1. The PK biomarker analysis set (as defined in Section 4) will be used. Individual plots will be created by participant against actual time post-dose (there will be separate spaghetti plots for each treatment) overlaid with the median.

6.3.3. Taste Assessment in PART-3: rBA/FE

In **PART-3**, *the taste attributes from the taste questionnaires (Appendix 1) will be listed and descriptively summarized and appropriate plots may be generated. The summary and analysis of the taste assessments may not be reported in the CSR.* The mean value for each taste assessment score calculated at each time point will be reported in a radial plot (eg 1 radial plot including all time points, with separate radial plots for each treatment). Paired t-tests will be performed comparing treatments by time.

6.3.4. Metabolic Profiling in PART-4: ME

Qualitative characterization of metabolites of PF-07817883, quantitative excretion of drug related material using ^{19}F-NMR spectroscopy, metabolic profiling/identification and determination of relative abundance of PF-07817883 and its metabolites will be analysed separately and maybe included in the CSR in an appendix.

6.3.5. PK by Microsampling in PART-2: MAD

At each nominal time point with concurrent microsampling and venipuncture plasma sample, blood to plasma (B/P) ratio will be calculated by dividing whole blood PF-07817883 concentration with the plasma PF-07817883 concentration. A geometric mean B/P ratio of all samples will be calculated for each individual as well for the population. The plasma PF-07817883 concentration by microsampling (referred as Tasso PK) will be calculated by dividing whole blood concentration with individual geometric mean B/P ratio. As a sensitivity analysis, the Tasso PK will also be calculated using population geometric mean B/P ratio. Summary statistics (N, geometric mean, geometric CV, median, arithmetic mean, CV, minimum, maximum) of the whole blood concentrations, plasma concentrations by microsampling using individual B/P ratio and plasma concentration by microsampling using geometric mean B/P ratio at nominal time of collection as defined in SoA for each treatment arm will be calculated.

The concordance analyses between plasma PK sample and both sets of Tasso PK sample (calculated using individual or population) as described below will be performed.

Bland-Altman plots will be produced to look at the consistency between PK sample and Tasso PK sample. Plots of the difference between the two samples (on Y-axis) as a function of the average of the two samples (on X-axis). These plots will be coloured by participant in addition to by timepoint. In addition, a correlation plot of the PK sample (on X-axis) and Tasso PK sample (on Y-axis) will be created including a line of equality Y = X.

6.3.6. Exploratory Analysis from PART-6: SE

6.3.6.1. PK of Moxifloxacin

The Moxifloxacin PK parameters detailed in Section 3.3.1 will be listed and summarized for participants in the PK Parameter Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3. Each summary will include the set of summary statistics as specified in Table 7.

For PART-6 - presentations for moxifloxacin concentrations will be presented using participants in the PK Concentration Set (as defined in Section 4) and will include:

- a listing of all concentrations sorted by participant ID, nominal time post-dose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.

- a summary of concentrations by nominal time post-dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.

- median concentration-time plots (on both linear and semi-log scales) against nominal time post-dose .

The scale used for the x-axis (time) of these plots will be decided on review of the data, and will depend on how long moxifloxacin concentration is quantifiable in the matrix.

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used.

6.3.6.2. Concentration-QTc Models (PART-6: SE only)

PK/PD model will be established to characterize the relationship between analyte (either PF-07817883 or moxifloxacin) plasma concentration and change from baseline in heart rate-corrected QT interval (ΔQTc) in this study. Change from baseline in Fridericia's heart-rate corrected QT interval (ΔQTcF) will be default dependent variable. Based on the recommendation in the White Paper[2] published recently on concentration-QTc (C-QTc) modeling, the linear mixed effect model is preferred, it is pre-specified as

$$\Delta QTc_{ijk} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + (\theta_2 + \eta_{2,i}) C_{ijk} + \sum_{k=1}^{K} \theta_{3k} TIME_k + \theta_4 \left(QTc_{ij0} - \overline{QTc_0}\right) + \varepsilon_{ijk}$$

ΔQTc_{ijk} is the change from baseline in QTc for participant i, in treatment j, at time k; j=1 for active drug/ moxifloxacin and 0 for placebo; C_{ijk} is 0 for placebo; θ_0 is the population mean intercept in the absence of a treatment effect; $\theta_{0,i}$ is the random effect associated with the intercept term θ_0; θ_1 is the fixed effect associated with treatment TRT_j; θ_2 is the population mean slope of the assumed linear association between concentration and ΔQTc_{ijk}; $\eta_{2,i}$ is the random effect associated with the slope θ_2; θ_{3k} is the fixed effect associated with time k and $TIME_k$ is an indicator variable for the nominal time k (k=1,2,…K); and θ_4 is the fixed effect associated with baseline QTc_{ij0}; $\overline{QTc_0}$ is overall mean of QTc_{ij0}, ie, mean of all the baseline (= time 0) QTc values; Assumptions for random effect terms and residuals: $(\eta_{0,i}, \eta_{2,i})' \sim$ normal distribution with mean (0,0) and unstructured covariance matrix, whereas the residuals ε_{ijk} are normally distributed with mean 0 and variance σ^2.

It follows from the White Paper[2] on concentration-QTc modeling that four basic assumptions will be evaluated using simple graphics. Details of these graphics are described in Section 6.6.4.1.2.

6.3.6.3. Evaluation of Assumptions - Linear Mixed Effect Model (PART-6: SE only)

According to the White Paper[3] on concentration-QTc modeling, the following assumptions for the linear mixed effect model will be evaluated using exploratory plots.

- **Assumption 1**: no drug effect on HR.

  The time course of mean change from baseline in HR and/or placebo-adjusted change from baseline HR by treatment will be plotted to evaluate the potential effect of PF-07817883/moxifloxacin on HR.

- **Assumption 2**: QTcF interval is independent of HR.

  A scatterplot of QTcF vs. RR intervals by treatment and a QTcF-RR quantile plot will be generated to confirm the appropriateness of Fridericia's heart-rate correction method.

- **Assumption 3**: No time delay between drug concentration and ΔQTcF. PK/PD hysteresis will evaluated using following exploratory plots:

  Longitudinal plot of mean and 90% CI for ΔQTcF and/or placebo-adjusted ΔQTcF (ΔΔQTcF) and concentration of PF-07817883/ moxifloxacin.

  Plot of mean ΔΔQTc and concentration connected in temporal order for PF-07817883/ moxifloxacin.

  Scatter plot of paired ΔΔQTcF and concentration of PF-07817883/ moxifloxacin.

- **Assumption 4**: Linear Concentration-ΔQTcF relationship.

  The linearity will be assessed by a scatter plot of paired ΔΔQTcF and concentration by treatment incorporating a trend line (e.g. loess smooth or linear regression).

If exploratory plots indicate the modeling assumptions for the linear model are not met, additional modeling steps will be performed to determine an appropriate C-QTc model.

- If there is a potential delay between PF-07817883/moxifloxacin concentration and the effect on QTcF, an alternative model with a delayed effect will be considered to account for the delay.

- If a linear relationship between PF-07817883 concentration and the effect on QTcF is not supported by exploratory plots, or linear models cannot describe the observed data well, nonlinear models will be adapted. Emax models described in Section 0

may be used, however, other types of PD models may be explored to optimize the model fit.

- o If apparent relationship between QTcF and RR interval and/or differences distribution of HR between on- and off-drug conditions are observed in exploratory plots, other approaches to evaluate QT/QTc may be considered as summarized in the methodology paper by Garnett et al[3].

6.3.6.4. Concentration-QTc Quantile Plot (PART-6: SE only)

A concentration- ΔQTc quantile plot of observed data overlaid with the model predictions is a visual assessment of how well the model fits the data. In this plot, the observed PF-07817883/ moxifloxacin concentrations are categorized into their deciles (e.g. 10 bins of equal size) and the mean change from baseline QTcF intervals (ΔQTcF) are calculated for each bin, along with their 5th and 95th percentiles, as well as the 90% confidence interval for the mean.

6.3.6.5. Model Selection and Evaluation (PART-6: SE only)

The drug effect models routinely tested are the linear and Emax models. If the linear model clearly does not capture the trend of the data in the concentration-QTcF quantile plot, the Emax model specified below will be fitted and assessed:

$$\Delta QTc_{ijk} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + \frac{(\theta_{22} + \eta_{2,i})C_{ijk}}{\theta_{21} + C_{ijk}} + \sum_{k=1}^{K} \theta_{3k} TIME_k + \theta_4\left(QTc_{ij0} - \overline{QTc_0}\right) + \varepsilon_{ijk}$$

The parameter θ_{21} is the population mean of EC50. The parameter θ_{22} is the population mean of maximum effect (Emax) with an associated random effect of $\eta_{2,i}$. The treatment effect (θ_1) may or may not be included in the Emax model. Assumptions for random effect terms and residuals: $(\eta_{0,i}, \eta_{2,i})' \sim$ normal distribution with mean (0,0) and unstructured covariance matrix, whereas the residuals ε_{ijk} are normally distributed with mean 0 and variance σ^2. The goodness-of-fit of the Emax model will be compared with the linear mixed effect model through review of the AIC criteria, the parameter estimates, residual plots, concentration-ΔQTc quantile plots and other diagnostic plots.

6.3.6.6. Model-based Estimation of ΔΔQTcF at Concentration of Interest (PART-6: SE only)

The final C-QTc model will be used to compute the ΔΔQTcF at concentrations of interest. The placebo adjusted change from baseline QTcF (ΔΔQTcF) is the difference between the model-estimated ΔQTcF at concentration of interest and the model-estimated ΔQTcF for placebo (eg. concentration=0).

The final C-QTc model parameters will be presented in tabular format showing the estimate, standard error of the estimate, p-value and 95% confidence interval. Goodness-of-fit plots will be presented for the final C-QTc model. A visualization displaying the model

predicted mean and the 90% confidence interval for the mean for placebo-adjusted mean change from baseline QTcF intervals (ΔΔQTcF) will also be created.

Results of the model-based C-QTc analyses and exploratory plots (as listed in Secions 6.3.6.2 through 6.3.6.6), model selection and evaluations, and model fitting statistics, will be documented in a separate report and may be included as an Appendix to the CSR.

6.3.6.7. Assay Sensitivity (PART-6: SE only)

Change from baseline in QTcF will be modelled using a repeated measures mixed effect (MMRM) model. All planned post-dose time points from the safety analysis set up to 120h will be included in the model. The model will include treatment, period, time (as a factor), treatment-by-time interaction and individual baseline (for each period) as fixed effects, subject as a random effect, and time repeated within each participant*period as a repeated effect. The Kenward-Roger adjustment for the degrees of freedom will be used. A compound symmetry covariance matrix will be fitted to the repeated times within participant (other covariance matrices will be considered if necessary, e.g. if the model does not converge).

The Least Squares (LS) means (and standard errors, 90% confidence intervals and 2-sided p-values) will be obtained for each treatment at each timepoint. Differences (and standard errors, 90% confidence intervals and 2-sided p-values) between LS means will also be obtained, comparing each treatment versus placebo.

The study will be deemed adequately sensitive to detect QT/QTc prolongation if the lower bound of the 2-sided 90% CI for the LSmean difference between moxifloxacin and placebo is greater than 5 ms at 3 hours post-dose of moxifloxacin (historic population T_{max}).

Additionally, exposure-response analysis of baseline corrected QTcF of moxifloxacin will be conducted in a separate report and may not be included in the the CSR.

Example SAS code is provided in Appendix 4.

Statistical Model Diagnostics

The presence of outliers will be investigated for this model. An outlier will be defined as any response data value with a studentized (conditional) residual greater than 3, or less than 3. A listing will be presented of any participants meeting these criteria and will be included with standard SAS output. The assumptions of normality will be verified graphically using residual plots. For each fitted model, a set of conditional studentized residual plots will be produced, including residual plot, histogram of normality, quartile-quartile (QQ) plot and summary of fit statistics. The residual plots will not be included in the CSR.

If there are outliers or major deviations from normality, then the effect of these on the conclusions may be investigated through alternative transformations and/or analyses excluding outliers. Justification for any alternative to the planned analysis will be given in the report of the study.

6.4. Subset Analyses

No subset analyses will be performed.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Study Conduct and Participant Disposition

Participant evaluation groups will show participant disposition by treatment. Frequency counts and percentages will be supplied for participant discontinuation(s) by treatment. Data will be reported in accordance with the sponsor reporting standards.

6.5.2. Demographic Data

Demographic data (age, biological sex, race, ethnicity, weight, body mass index and height) will be summarised by cohort for **PART-1**, **PART-3, PART-5 and PART-6**, by treatment for **PART-2** and **PART-4** and overall (if applicable) in accordance with the sponsor reporting standards.

6.5.3. Concomitant Medications and Nondrug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be reported according to current sponsor reporting standards.

6.5.4. Other Screening Data

These data will not be recorded in the study database, and therefore will not be listed.

6.6. Safety Summaries and Analyses

In all 5 parts of the study, all safety analyses will be performed on the Safety Analysis Set.

6.6.1. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards.

6.6.2. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. Baseline is as defined in Section 3.5.2.

Individual participant profiles will be created for those participants meeting the sponsor abnormality criteria – including absolute values, change from baseline and percent change from baseline.

For **PART-1**, **PART-2, PART-5 and PART-6**, change from baseline and percent change from baseline will be summarized descriptively by treatment and timepoint, as described in Section 5.2.1. The safety analysis set (as defined in Section 4) will be used. Mean change from baseline and percent change from baseline will be plotted against time post-dose. On each plot there will be one line for each treatment and 90% CIs.

6.6.3. Vital Signs

Absolute values and changes from baseline in supine systolic and diastolic blood pressure, pulse rate and respiratory rate will be summarized by treatment and time post-dose, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.5.3.

Mean changes from baseline for supine systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate will be plotted against time post-dose. Each part will have its own output with 1 line for each treatment. Placebo will be pooled in the plots for **PART-1** and **PART-2**, although the Fed, Japanese and Chinese placebo in **PART-2** (if applicable) will be treated as separate treatment groups. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum decrease from baseline for supine systolic and diastolic blood pressures and respiratory rate and maximum increase from baseline for supine pulse rate and temperature will be summarized by treatment, according to sponsor reporting standards.

Minimum and/or maximum absolute values and changes from baseline for supine vital signs will also be summarized descriptively by treatment using categories as defined in Appendix 2. Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post-dose time points will be counted in these categorical summaries.

Individual participant profiles will be created for those participants meeting the sponsor abnormality criteria – including absolute values, change from baseline and percent change from baseline.

6.6.4. ECG

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized by treatment and time post-dose using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.5.4.

Mean changes from baseline in QT, heart rate and QTcF will be plotted against time post-dose. Each part will have its own output with 1 line for each treatment. Placebo will be pooled in the plots for **PART-1, PART-6** and **PART-2**, although the Fed, Japanese and Chinese placebo in **PART-2** (if applicable) will be treated as separate treatment groups. Corresponding individual plots of changes from baseline will also be produced for each treatment.

Maximum increase from baseline for QTcF will be summarized by treatment, according to sponsor reporting standards.

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by treatment using categories as defined in Appendix 2 (for QTcF these correspond to the Pfizer Guidance[1] in Section 8). Numbers and percentages of participants

meeting the categorical criteria will be provided. All planned and unplanned postdose time points will be counted in these categorical summaries.

Individual participant profiles will be created for those participants meeting the sponsor'sabnormality criteria – including absolute values, change from baseline and percent change from baseline.

7. LISTINGS OF PARTICIPANTS WITH ANY SINGLE POST-DOSE VALUE >500 MSEC WILL ALSO BE PRODUCED FOR QTCF.INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study. As this is a sponsor open study, the sponsor will conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, facilitating PK modeling, and/or supporting clinical development. Unblinded results will be reviewed by a designated limited number of sponsor colleagues within the study team.

7.2. Interim Analyses and Summaries

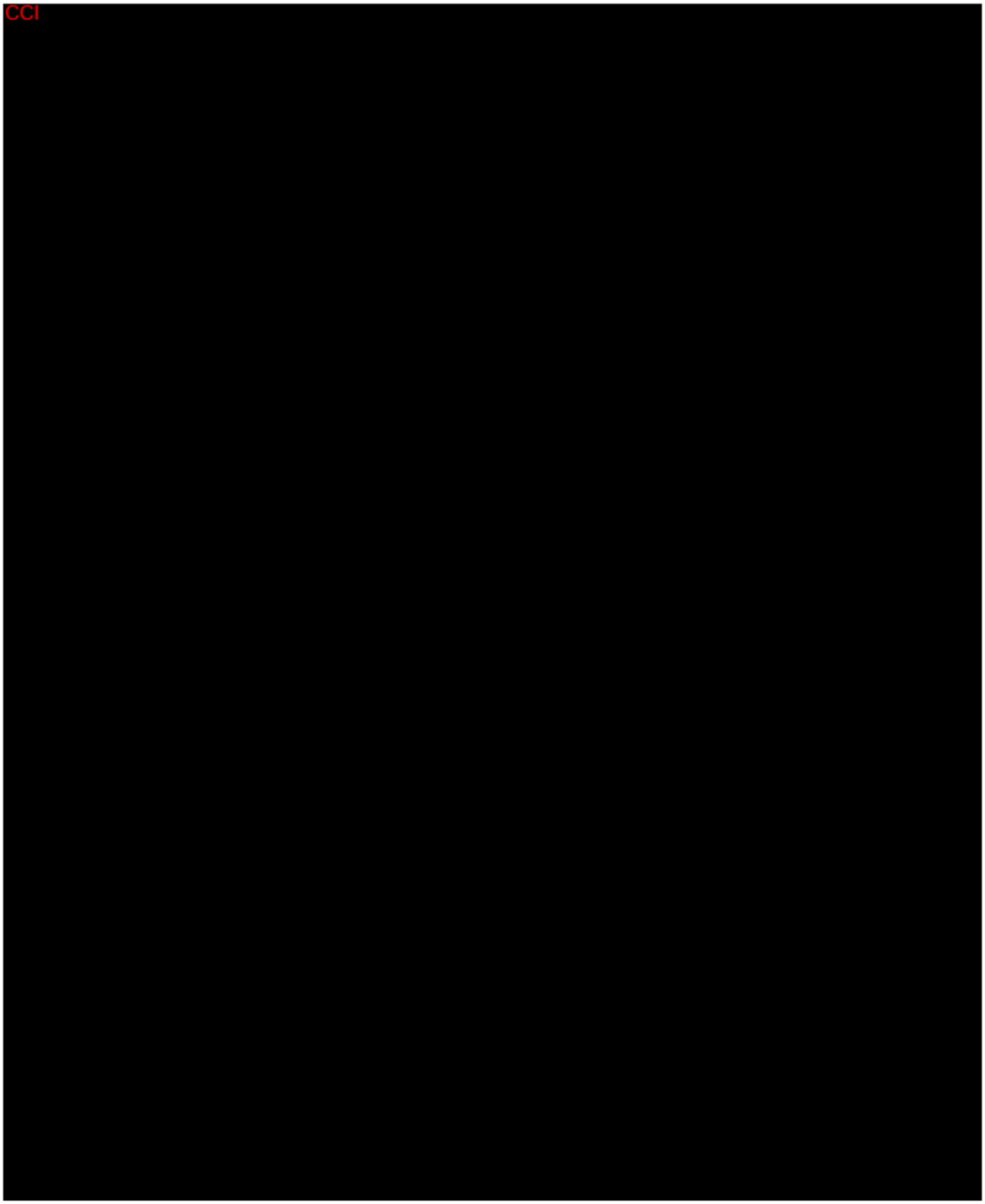
N/A

8. REFERENCES

1. Pfizer Guidance for Evaluation of QT / QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs; Members of the Cardiovascular Safety & Advisory Council (CVSAC); January 26, 2018
2. Garnett C., et al. Scientific white paper on concentration-QTc modeling. Journal of Pharmacokinet and Pharmacodyn December 2017; https://doi.org/10.1007/s10928-017-9558-5
3. Garnett C., et al. Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic effects. Am Heart J 163(6): 912-30

APPENDICES

CCI



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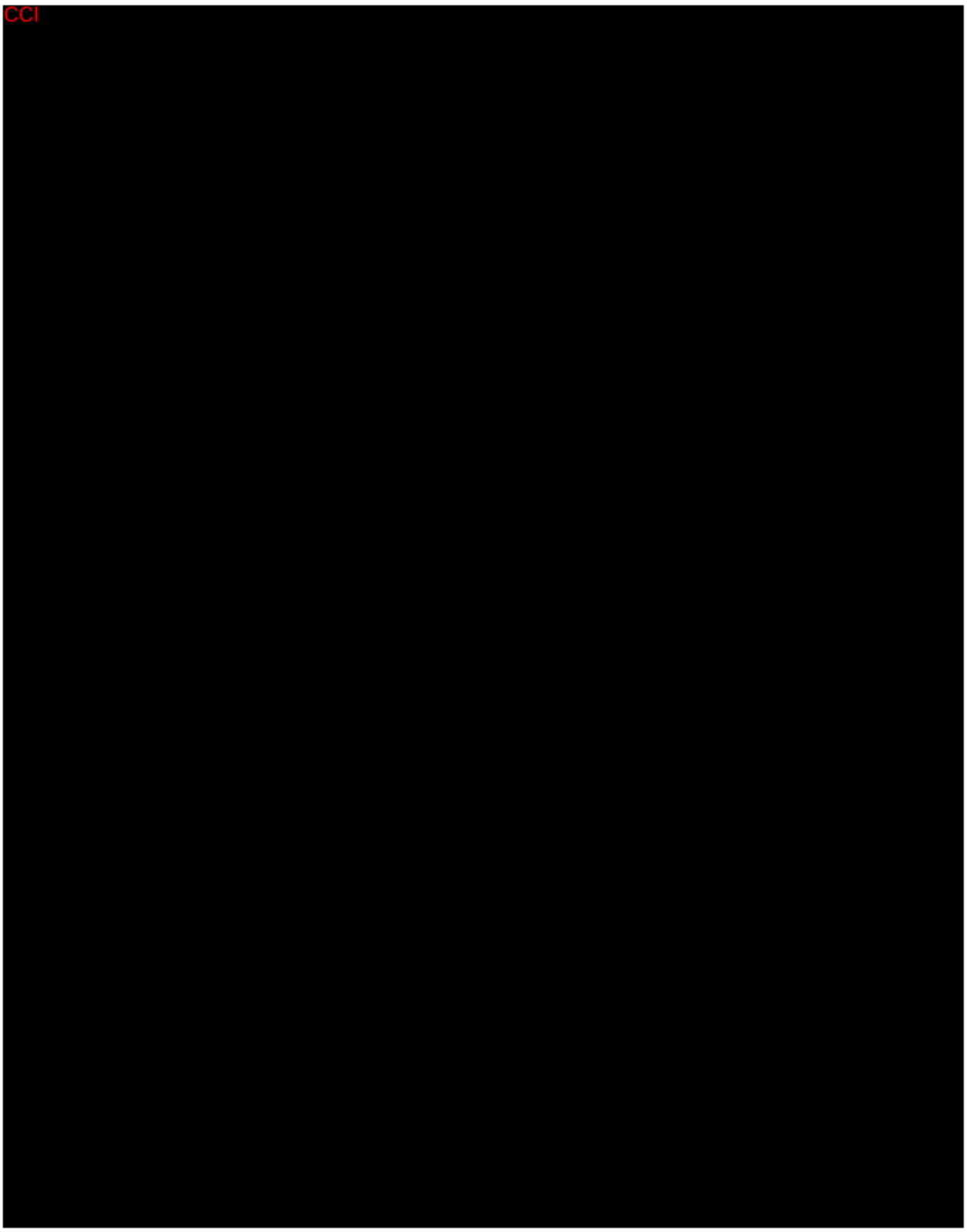

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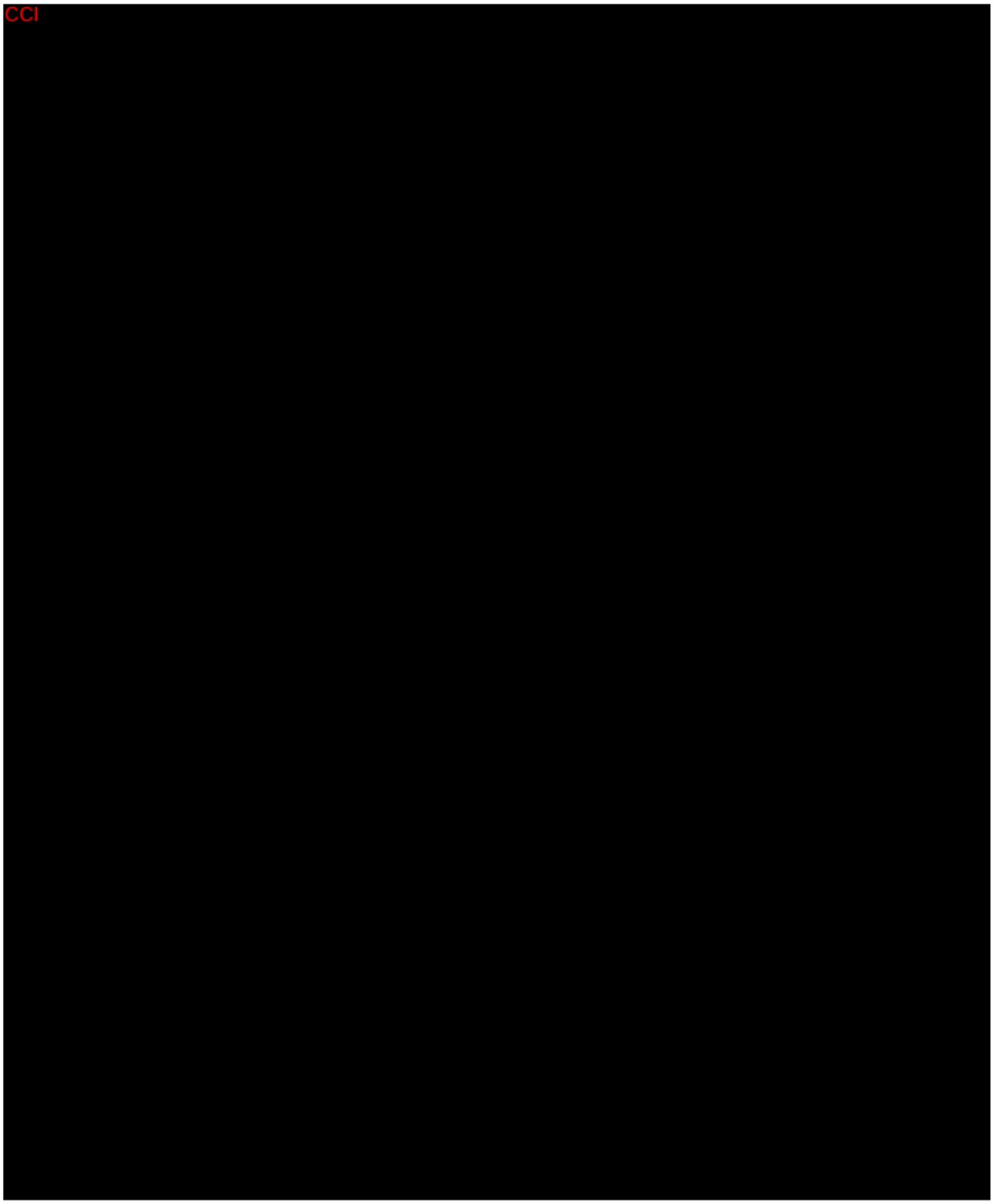

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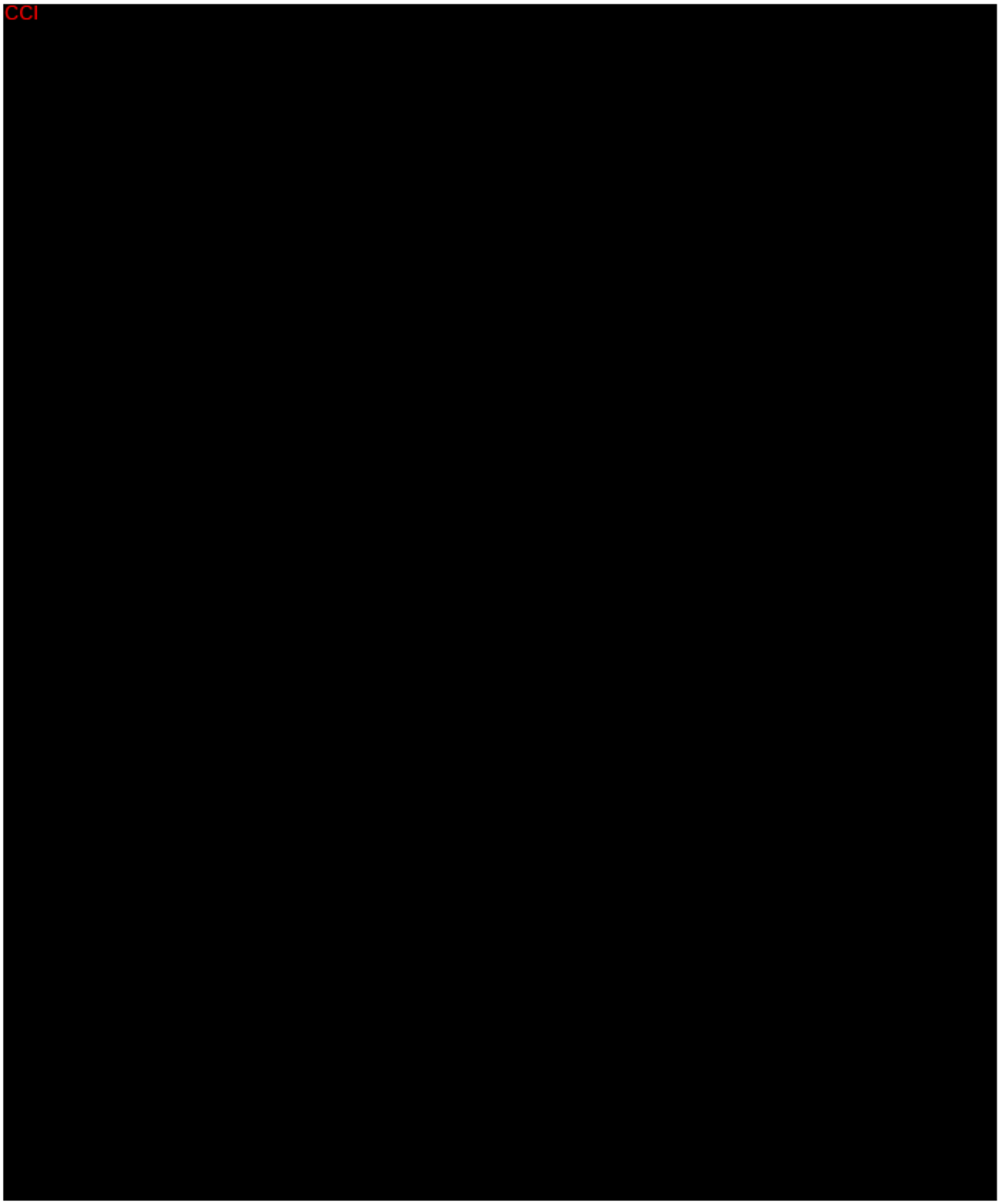

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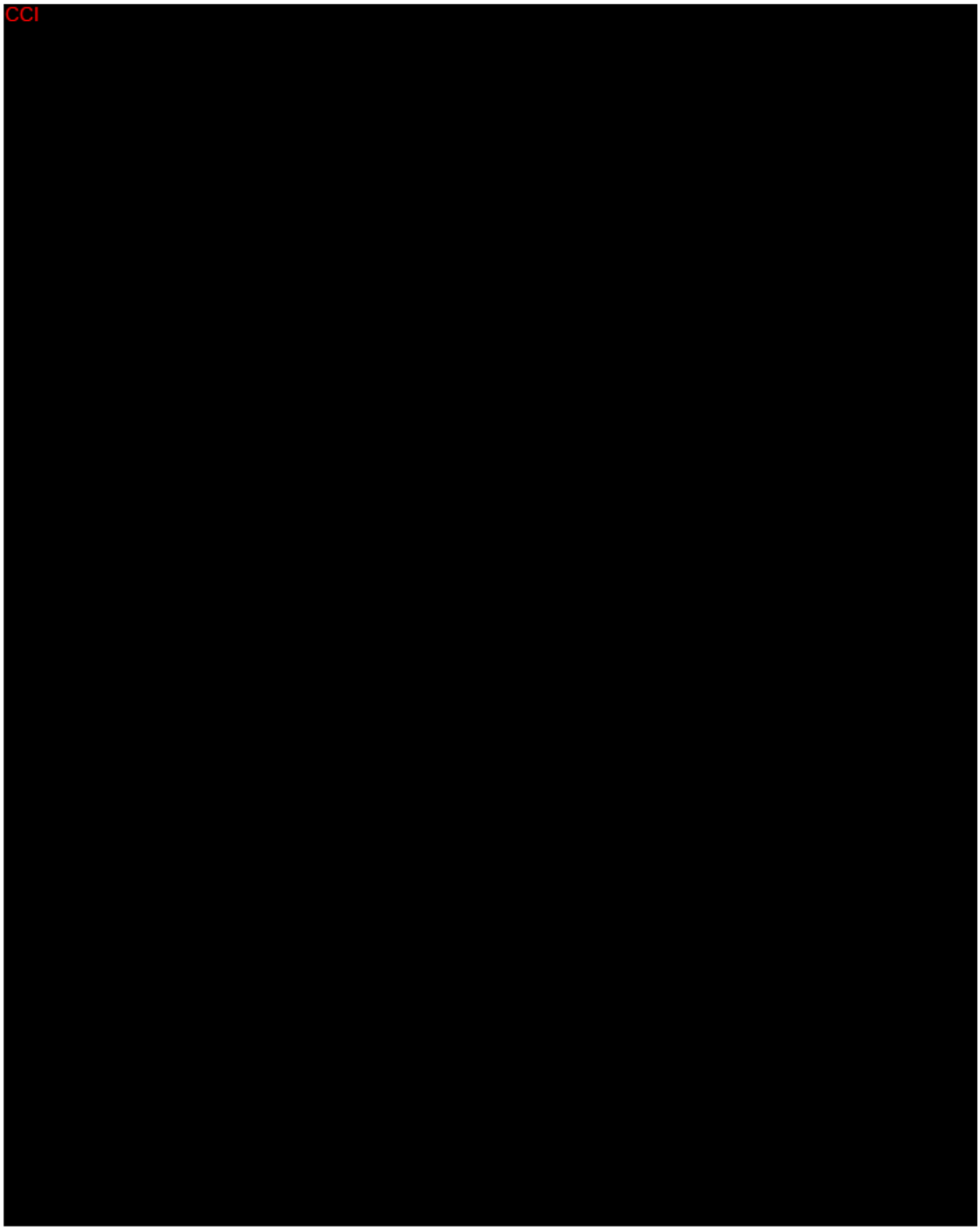

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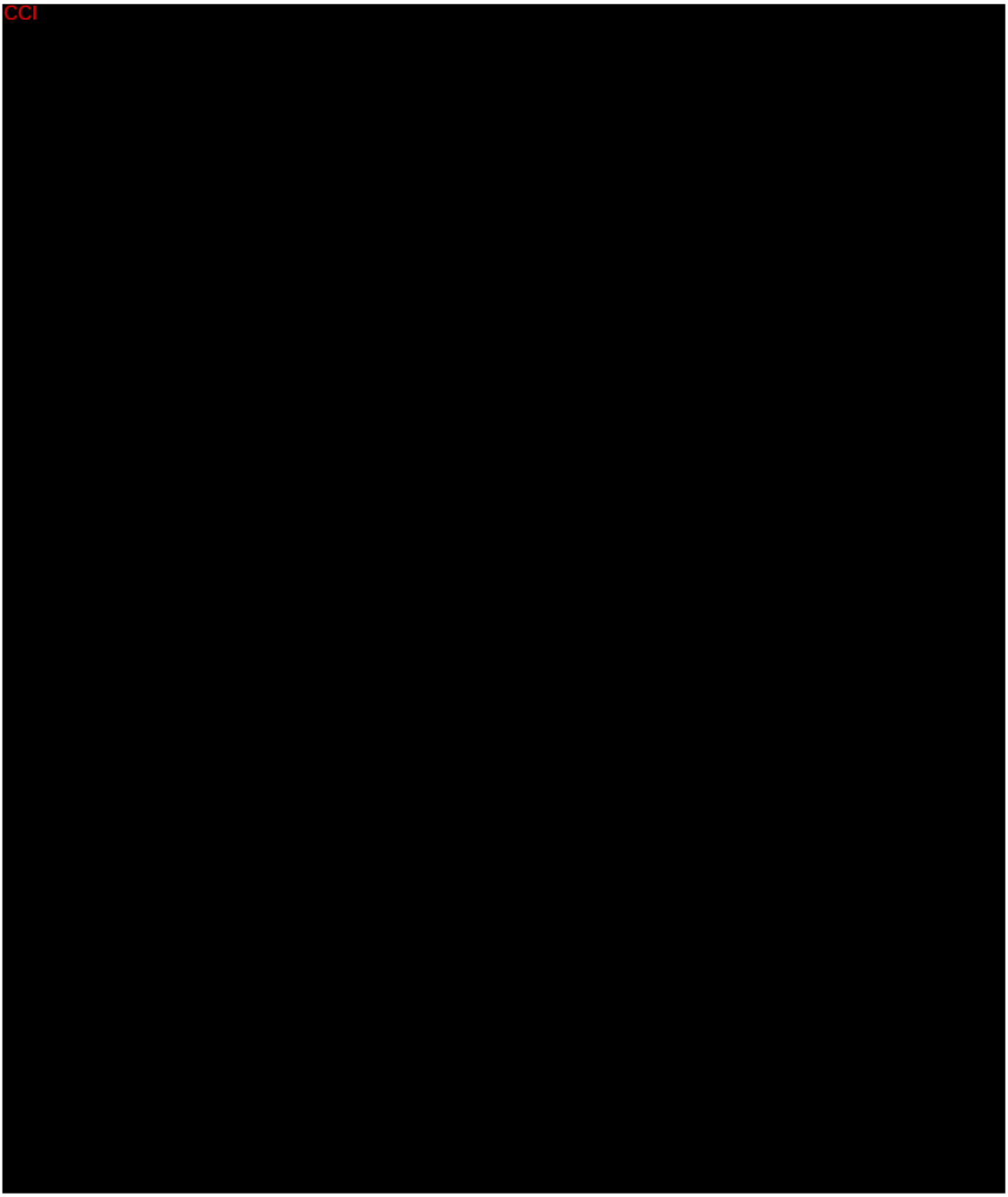

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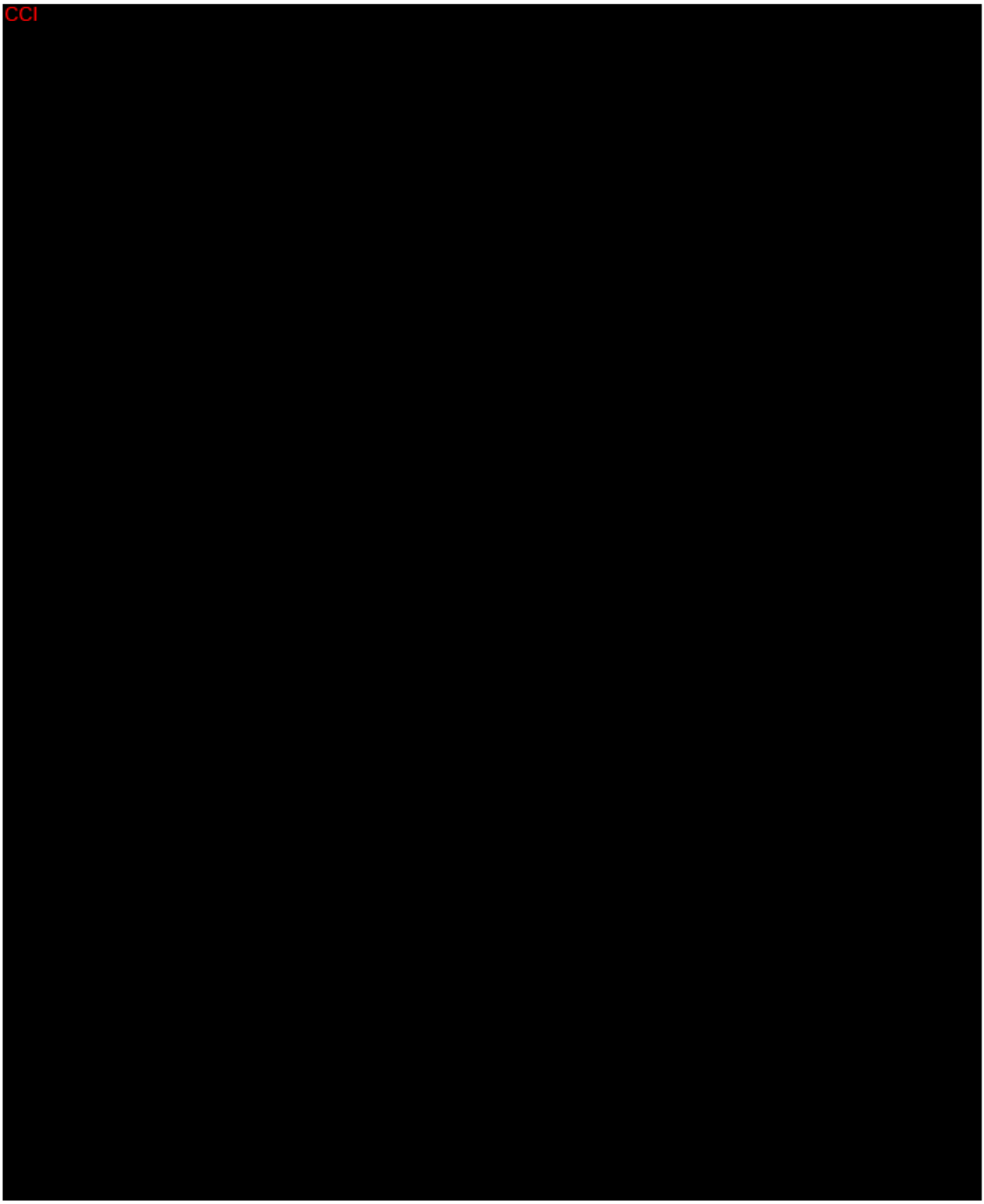

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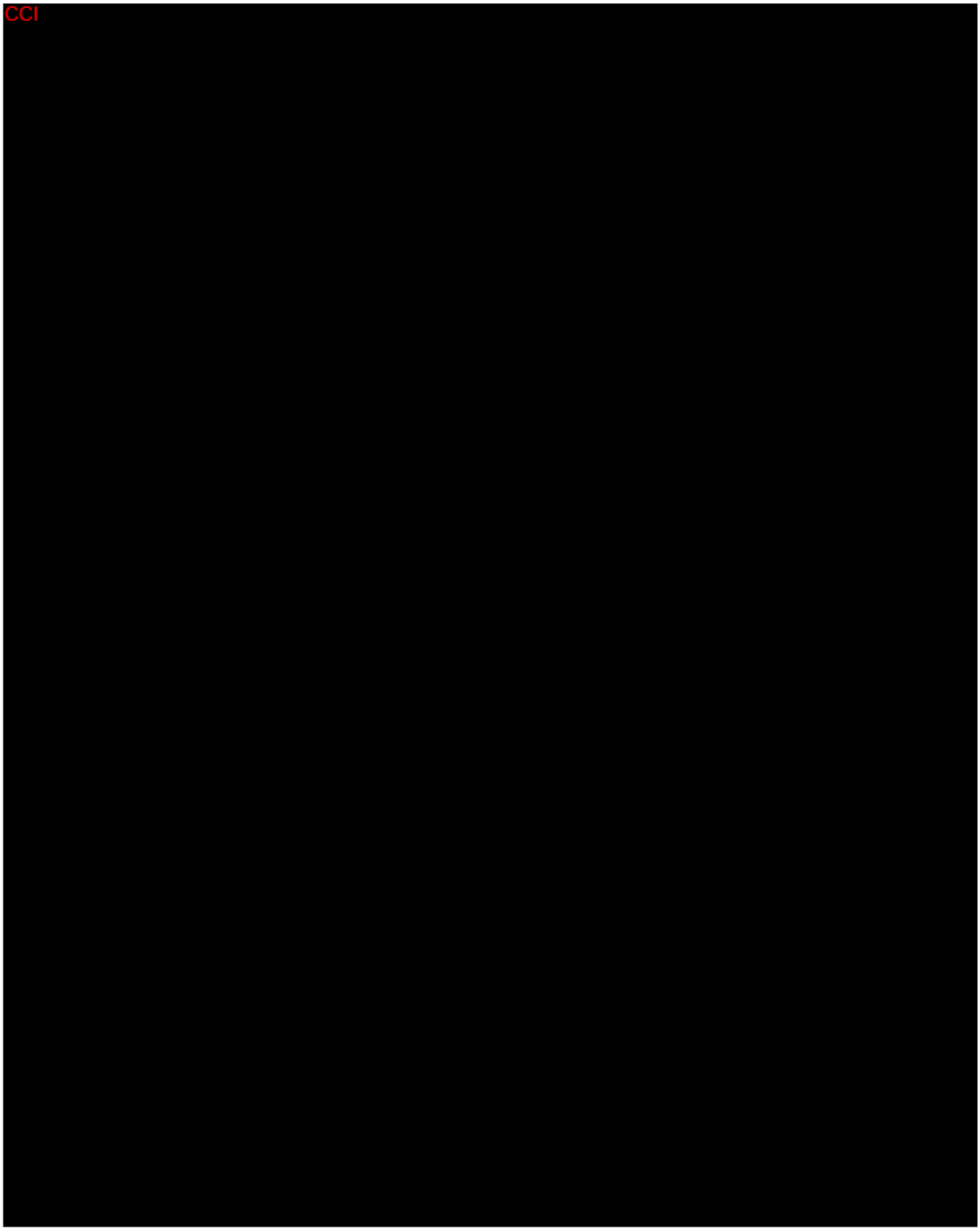

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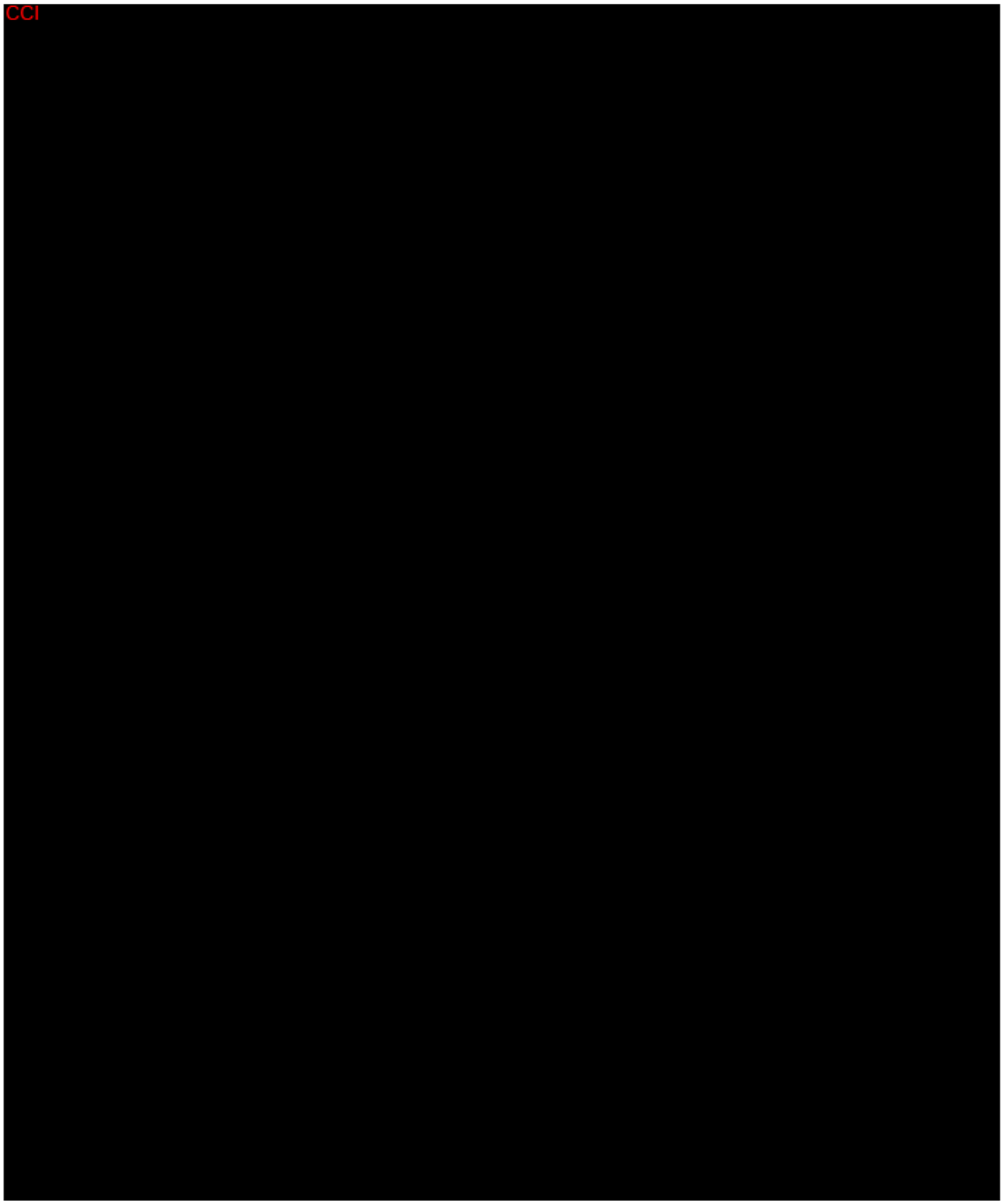

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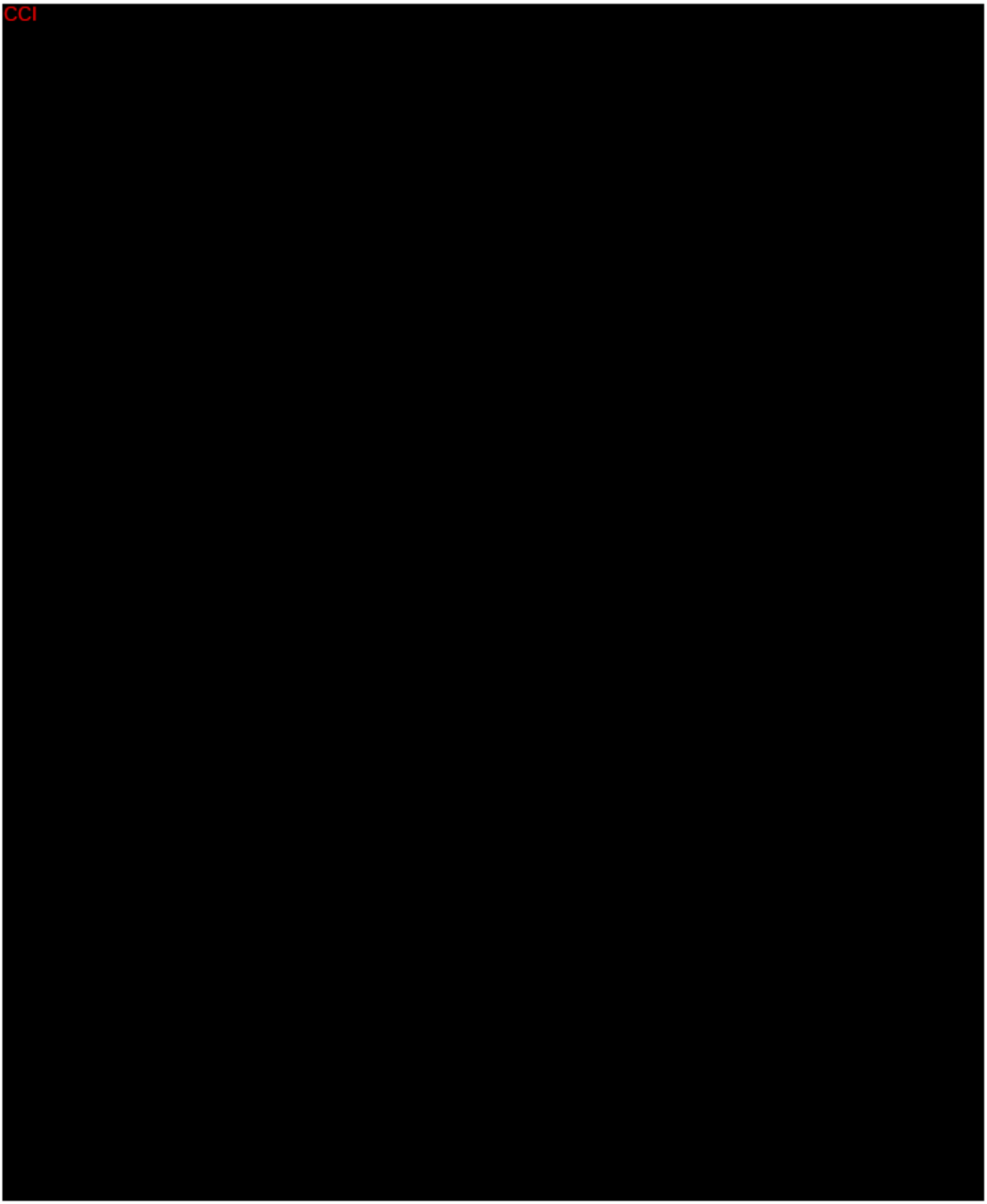

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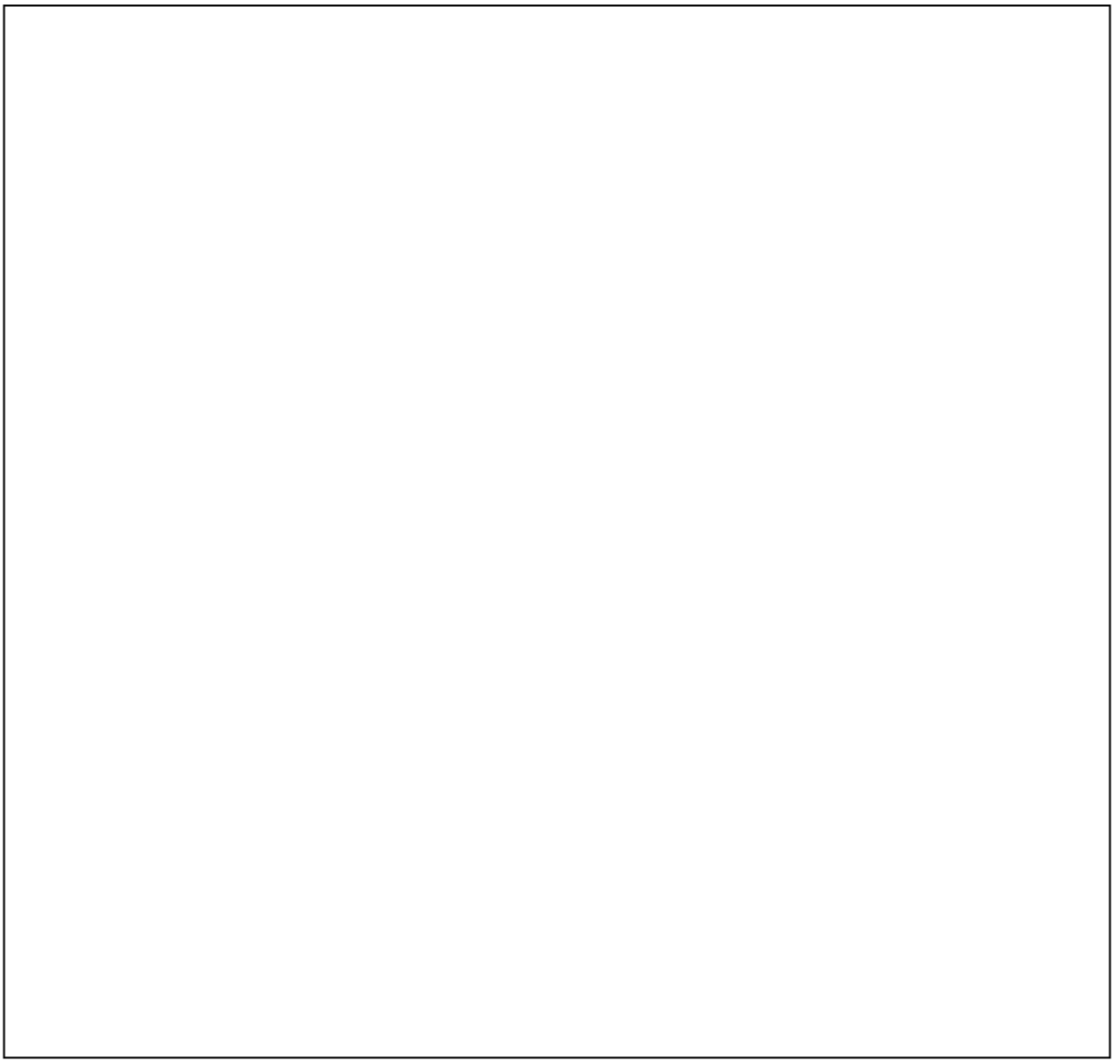

Appendix 2. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value of QTcF (msec)	>450 and ≤480	>480 and ≤500	>500
Increase from baseline in QTcF (msec)	>30 and ≤60	>60	

Categories for PR and QRS

PR (ms)	max. ≥300	
PR (ms) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max. ≥140	
QRS (ms) increase from baseline	≥50% increase	

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120

Appendix 3. List of Abbreviations

Abbreviation	Term
AE	adverse event
AUC	area under the curve
BA	Bioavailability
BLQ	below the limit of quantitation
BP	blood pressure
CI	confidence interval
C_{max}	maximum observed concentration
CRF	case report form
CSR	clinical study report
DDI	drug-drug interaction
ECG	electrocardiogram
FE	food effect
GCP	Good Clinical Practice
ICD	informed consent document
ICH	International Council for Harmonisation
LLOQ	lower limit of quantitation
LS	least-squares
MAD	multiple ascending dose
ME	Metabolism and Excretion
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
N/A	not applicable
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PT	preferred term
QTcF	corrected QT (Fridericia method)
RBA	relative bioavailability
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	supratherapeutic exposure
TEAE	treatment-emergent adverse event

Appendix 4. Example SAS code for Statistical Analyses

MMRM for QTcF analyses:

Base1 is the average baseline for each participant, base2 is the period-adjusted baseline.

```
proc mixed data=pd method=reml order=data;
     title1 "SAS output MMRM Endpoint = &endpoint_name";
     class subjid treattxt time period;
     model &var=base1 base2 period treattxt time
     treattxt*time / ddfm=kr residual;
     repeated time / subject=subjid*period type=un;
     lsmeans treattxt /diff cl ;
     lsmeans treattxt*time /diff cl alpha = 0.1;
run;
```