Protocol *C0341001*

A PHASE 1, RANDOMIZED, DOUBLE-BLIND, THIRD-PARTY OPEN, PLACEBO-CONTROLLED, DOSE ESCALATING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF SINGLE AND MULTIPLE INTRAVENOUS AND SUBCUTANEOUS DOSES OF PF-06817024 IN HEALTHY SUBJECTS WHO ARE MILDLY ATOPIC AND OF SINGLE DOSES OF PF-06817024 IN PATIENTS WITH CHRONIC RHINOSINUSITIS WITH NASAL POLYPS, AND SUBJECTS WITH MODERATE-SEVERE ATOPIC DERMATITIS

Statistical Analysis Plan (SAP)

Version: **Version 2 (Amendment** 1)

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Date: 06 MAY 2019

Revision History

Version	Date	Author(s)	Summary of Changes/Comments
Version 1.0	19 Dec 2018	PPD	None
Version 2.0	06 May 2019	PPD	Added longitudinal analysis of percent change from baseline CCI scores. Updated sections 6 and 8 to include analysis. CCI [redacted]

NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

PF-06817024 is a humanized antibody against interleukin-33 (IL-33). IL-33 is a member of the IL-1 family of cytokines.

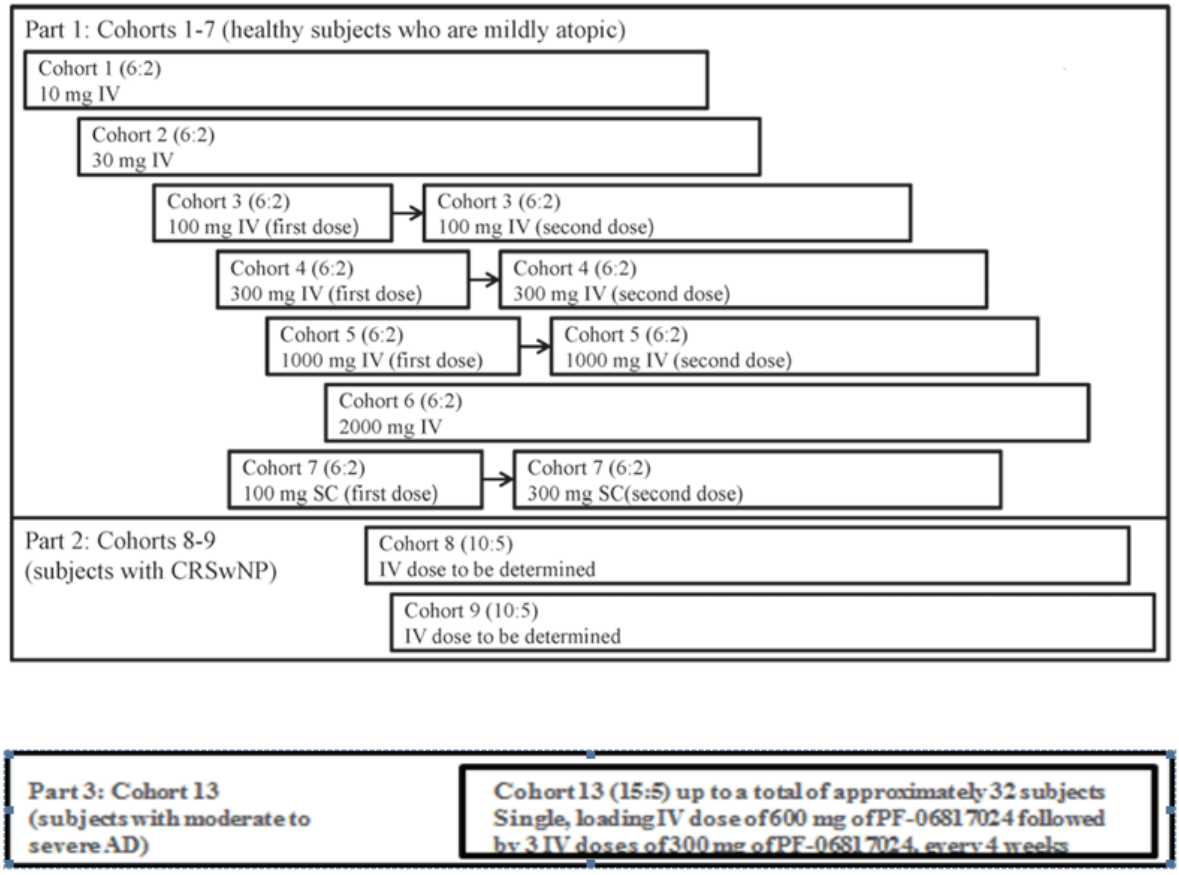
This is a first-in-human, placebo-controlled, double blind (pharmacist and sponsor open), single and multiple IV and SC dose study that will be conducted in three parts. Part 1 is conducted in healthy subjects who may be mildly atopic. Parts 2 and 3 are conducted in patients with chronic rhinosinusitis with nasal polyps (part 2) and patients with moderate to severe atopic dermatitis (part 3).

The study was originally designed to be a two-part Phase 1, randomized, double-blind (sponsor and pharmacist open), placebo-controlled, dose escalating clinical study with single and multiple doses of PF-06817024 in healthy subjects who may be mildly atopic (Part 1: Cohorts 1-7) and of one or two single doses of PF-06817024 in patients with chronic rhinosinusitis with nasal polyps (Part 2: Cohorts 8 and 9).

Amended protocol *added Part 3, consisting of a single cohort (Cohort 13) of subjects with moderate – severe AD. Cohort 13 is a randomized, double-blind (sponsor and pharmacist unblinded), placebo-controlled, multiple dose evaluation of PF-06817024.*

The study schematic is shown on Figure 1. The gap in the cohort numbers (cohort 13 follows cohort 9) is caused by the elimination of the initially planned optional cohorts 10 through 12 during the study.

Figure 1. Study Design Schematic



Cohorts 3-5 and Cohort 7: second dose occurs at a minimum of 4 weeks and maximum of 12 weeks after the first dose. Second dose is only administered if protocol safety criteria are met. Except for the starting dose, the actual doses for other cohorts may be changed but will follow dose escalation and stopping rules

2.1. Part 1:

Approximately 56 healthy subjects who may be mildly atopic will be enrolled into the proposed cohorts listed below. This study starts with a single ascending dose (SAD) escalation design, with selected cohorts rolling into a multiple dose component. Up to approximately 80 healthy subjects who may be mildly atopic will be enrolled if separate multiple dose cohort(s) are required. Subjects may only participate in 1 cohort.

Figure 1 demonstrates the study design with the select SAD cohorts rolling over into the multiple dose component. Depending on the safety, CCI [redacted] *and pharmacokinetic data available, dose escalation may be adjusted to doses other than those planned in the study. Intermediate doses can be evaluated instead of or in addition to the planned dose levels. A possible dosing scenario is included in the schematic.*

- *Cohort 1 (n=8): 10 mg active (n=6) or placebo (n=2), IV.*

- *Cohort 2 (n=8): 30 mg active (n=6) or placebo (n=2), IV.*
- *Cohort 3 (n=8): 100 mg active (n=6) or placebo (n=2), IV x 2 doses.* [n=4 in MAD cohort].
- *Cohort 4 (n=8): 300 mg active (n=6) or placebo (n=2), IV x 2 doses.* [no MAD].
- *Cohort 5 (n=8): 1000 mg active (n=6) or placebo (n=2), IV x 2 doses.* [no MAD].
- *Cohort 6 (n=8): 2000 mg active (n=6) or placebo (n=2), IV.* [dose escalation stopped before 2000 mg dose group].
- *Cohort 7 (n=8): 100 mg (first dose) followed by 300 mg (second dose) active (n=6) or placebo (n=2), SC.* [Second dose not given, 100 mg dose changed to 30 mg].

2.2. Part 2:

One or more cohorts of CRSwNP patients will receive a single dose of PF-06817024. Randomization will occur after safety data from Day 8 and PK data through at least Day 5 of the same or higher dose in Part 1 of the study has been reviewed and deemed safe.

- *Cohorts 8 and 9: Subjects in each cohort will be randomized in either a 1:1 or 2 : 1 (PF-06817024: placebo) ratio, depending on the number of cohorts and the emerging data. Up to approximately 10 active (per dose) and approximately 15 placebo (overall) subjects will be enrolled in Part 2 for a planned total of up to approximately 35 subjects.*

2.3. Part 3

- *Part 3 will consist of a single cohort of subjects with moderate to severe AD*
- *Cohort 13: Approximately 20 subjects in this cohort will be randomized to receive PF-06817024 or placebo in a 3:1 ratio (PF-06817024: placebo). Additional subjects up to a total of approximately 32 [28 actually enrolled] may be enrolled in a 3: 1 ratio (PF-06817024: placebo)* CCI [redacted] *Subjects in this cohort randomized to PF-06817024 will receive a planned dosing regimen consisting of a 600 mg IV loading dose followed by 3 doses of 300 mg IV every 4 weeks.*

Note that subjects were randomized 2:1 by site under protocol amendment 4 and then randomized centrally in a 3:1 ratio under amendment 5.

2.3.1. Primary Objectives

Part 1

- *For the SAD component, the objective is to determine the safety and tolerability of single IV infusions and single SC doses of PF-06817024 in healthy subjects who may be mildly atopic.*

- *For the multiple dose component, the objective is to determine the safety and tolerability following administration of multiple IV and SC doses of PF-06817024 inhealthy subjects who may be mildly atopic.*

Part 2

- *To determine the safety and tolerability of single IV infusions of PF-06817024 in patients with chronic rhinosinusitis with nasal polyps.*

Part 3

- To determine the safety and tolerability of repeat IV doses of PF-06817024 in subjects with moderate to severe AD.

2.3.2. Secondary Objectives

Part 1

- *To characterize the PK profile of PF-06817024 following single IV infusions and single SC doses of PF-06817024 in healthy subjects who may be mildly atopic.*

- *To characterize the PK profile of PF-06817024 following multiple SC and IV doses of PF-06817024 in healthy subjects who may be mildly atopic.*

- *To evaluate immunogenicity of PF-06817024 in healthy subjects who may be mildly atopic.*

Part 2

- *To characterize the PK profile of PF-06817024 following single IV infusions of PF-06817024 in patients with chronic rhinosinusitis with nasal polyps.*

- *To evaluate immunogenicity of PF-06817024 in patients with chronic rhinosinusitis with nasal polyps.*

Part 3

- To characterize the PK profile of PF-06817024 following repeat IV doses in subjects with moderate to severe AD.

- To evaluate immunogenicity of PF-06817024 in subjects with moderate to severe AD.

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3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

This is a third party open study, with the investigator and subject blinded to study treatment. Specific Pfizer personnel (analytical staff, medical monitor, clinician, statistician, and clinical pharmacologist) will be unblinded to subject treatments in order to permit real-time interpretation of the safety and pharmacokinetic data, and to provide information necessary to potentially alter the dose escalation sequence. To minimize the potential for bias, treatment randomization information will be kept confidential by Pfizer personnel and will not be released to the investigator/study staff until the conclusion of the study. Unblinding will not be performed until the final database has been locked for all cohorts. Final analysis will follow the official database release.

No formal interim analysis will be conducted for this study. However, as this is a sponsor-open study, the Sponsor may 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 to support clinical development. Unblinded results will be reviewed by a designated limited number of Sponsor colleagues within the study team.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No statistical hypotheses will be tested in this study.

4.2. Statistical Decision Rules

No statistical decision rules will be used for this study.

5. ANALYSIS SETS

5.1. Full Analysis Set

The full analysis set is comprised of all randomized subjects.

5.2. Pharmacokinetic Analysis Sets

5.2.1. Concentration Analysis Set

The PK concentration set is defined as all enrolled subjects treated who have at least 1 measurement of PF-06817024 concentration.

If PK concentrations from placebo treated subjects were measured, the results will only be included in the listing, but will not be included in the concentration analysis set.

5.2.2. Parameter Analysis Set

The PK parameter analysis set is defined as all enrolled subjects treated who have at least 1 of the PK parameters of interest measured.

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5.4. Safety Analysis Set

All subjects who receive at least 1 dose of study medication will be included in the safety analyses set.

5.5. Immunogenicity Analysis Set

The immunogenicity analysis set is defined as all enrolled subjects who receive at least 1 dose of investigational product and have at least 1 post-treatment measurement of immunogenicity parameters of interest (ie, ADA [anti-PF-06817024 antibody] or NAb [Neutralizing anti-PF-06817024 antibody]).

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5.7. Treatment Misallocations

All analyses will be performed on an "as-treated" basis and will not include data from subjects who are randomized but not treated.

If a subject takes a treatment that is not consistent with the treatment they are randomized to, for example takes a treatment out of sequence or takes the same treatment twice, then they will be reported under the treatment that they actually receive for all safety, PK and CCI [redacted] analyses, where applicable.

5.8. Protocol Deviations

Subjects who experience events that may affect their PK profile (eg, vomiting) may be excluded from the PK analysis. At the discretion of the pharmacokineticist, a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

CCI [redacted] At the discretion of the clinical team, a value may also be excluded if the deviation collection / procedure time is of sufficient concern or if the concentration is anomalous for any other reason.

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A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure.

5.8.1. Deviations Assessed Prior to Randomization

At screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 4.1 and 4.2 of the protocol.

5.8.2. Deviations Assessed Post-Randomization

Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

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6.2. Safety Endpoints

In this section, the safety endpoints that will be measured during the study are detailed. Where applicable, details of the endpoints to be derived and definition of baseline are also provided.

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- *Adverse events;*

- *Laboratory data;*
- *Vital signs data;*
- *ECG results.*

6.2.1. Adverse Events

Any events occurring following start of treatment or increasing in severity after randomization will be counted as treatment emergent.

Events that occur in a non-treatment period (for example, washout or follow-up) will be counted as treatment emergent and attributed to the previous treatment taken.

6.2.2. Laboratory Safety Tests

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

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 subject's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

Baseline will be the last pre-dose measurement of Day 1.

6.2.3. Vital Signs

Single supine blood pressure, pulse measurements and temperature will be taken at times detailed in the Schedule of Activities given in the protocol.

The last pre-dose measurement at Day 1 will be used as the baseline, subjects with a second dose will not be re-baselined. 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 subject 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 subject does not show a decrease, the minimum increase should be taken.

6.2.4. ECG

A single or triple 12-lead ECG will be obtained on all subjects at times detailed in the Schedule of Activities given in the protocol. The average of the triplicate readings collected in Part 1 at each assessment time will be calculated for each ECG parameter. Baseline will be defined as the average of the triplicate pre-dose recordings at Day 1, for Parts 2 and 3, the last measurement prior to first dose will be used as the baseline.

The QT, QTc, PR, RR, QRS and heart rate will be recorded at each assessment time.

If not supplied, QTcF will be derived using Fridericia's heart rate correction formula:

$$QTcF = QT / (RR)^{1/3} \qquad \text{where RR = 60/HR (if not provided)}$$

If not supplied, QTcB will be derived using Bazett's heart rate correction formula:

$$QTcB = QT / (RR)^{1/2} \qquad \text{where RR = 60/HR (if not provided)}$$

The maximum increase from baseline will be calculated by first subtracting the baseline value from each postdose 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 subject does not show an increase. In such an instance, the minimum decrease should be taken.

6.2.5. Other Safety Data

Additional safety data will be collected as described in the protocol and will be listed if collected in the sponsor's database.

6.3. Pharmacokinetic Endpoints

Blood samples for PK analysis of PF-06817924 will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for PF-06817024 (if possible) from the concentration-time values using standard non-compartmental methods for Parts 1, 2 and 3.

Table 1 Non-compartmental PK Parameters

Parameter	Analysis Scale	PF-06817024
Single Dose †		
AUC_{last}	ln	D
AUC_{inf} *	ln	D
AUC_{inf} (dn) *	ln	D
C_{max}	ln	D
C_{max}(dn)	ln	D
T_{max}	R	D
$t_{1/2}$ *	R	D
CL (IV only) *	ln	D
V_{ss} (IV only) *	ln	D
CL/F (SC only) *	ln	D
Vz/F (SC only) *	ln	D
Multiple Dose ‡		
AUC_{tau}	ln	D
AUC_{tau} (dn)	ln	D
C_{av}	ln	D
C_{max}	ln	D
C_{max}(dn)	ln	D
T_{max}	R	D
$t_{1/2}$ *	R	D
C_{min}	ln	D
R_{ac} AUC_{tau}	ln	D
R_{ac} C_{max}	ln	D

D = displayed with descriptive statistics, ln = natural-log transformed, R = raw (untransformed), * = if data permit, † = single dose subjects in Part 1 and all subjects in Part 2, ‡ = multiple dose subjects in Part 1 and all subjects in Part 3, tau = dosing interval for multiple dosing.

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6.5. Immunogenicity Endpoints

Blood samples for immunogenicity (ADA and NAb) will be collected at the time points described in the Schedule of Activities given in the protocol. Samples will be tested for ADA first, only confirmed ADA positive samples and the corresponding baseline samples will be tested in the NAb assay.

Incidence of the development of anti-drug antibodies (ADAs)/neutralizing antibodies (NAbs) will be summarized by descriptive statistics presented separately for SAD and MAD. The treatment dose will be characterized by the total dose and routes of exposure (SC and IV).

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7. HANDLING OF MISSING VALUES

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied. Longitudinal modeling will use available data only, no imputation will be done.

7.1. Concentrations Below the Limit of Quantification

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).

In all biomarker data presentations (except listings), biomarker values below the limit of quantification (BLQ) will be set to LLQ/2. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification).

7.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of 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.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

7.3. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject'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 subject 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 subject 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.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

As this is an exploratory study, no formal hypothesis testing will be performed. CCI [redacted]

Statistical Analyses

All efficacy data from parts 1, 2 and 3will be listed and summarized separately. Safety data will also be summarized combining all three parts as well as separately. Percentages will be presented to one decimal place in all summaries. Minimum and maximum values will be presented to the same number of decimal places as collected on the CRF or with the laboratory screening panel; mean and median will be presented to one further decimal place; standard deviations will be presented to two further places.

In data presentations, results will be sorted by increasing dose level and by study part (SAD/MAD, Nasal Polyps, or Atopic Dermatitis) as appropriate.

Binary variables will be summarized by the number of responders and the number of subjects with data. Percentages will be presented for both observed cases (number of subjects with data at the time point for the denominator) and by non-response imputation (NRI) (number of subjects with data at baseline in the denominator).

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Pharmacokinetic Analysis

To assess the pharmacokinetics of PF-06817024, the PK parameters detailed in Section 6.3 will be listed and summarized for subjects in the PK analysis set (as defined in Section 5.2.2). Missing values will be handled as detailed in Section 7. Each PK parameter will be summarized by cohort and will include the set of summary statistics as specified in the table below:

Table 2. PK Parameters to be Summarized Descriptively

Type of Dosing	Parameter	Summary Statistics
Single Dose†	AUC_{last}, AUCinf, AUCinf (dn), C_{max}, Cmax(dn), CL, Vss, CL/F, Vz/F	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, cv%, standard deviation, minimum, maximum.
Multiple Dose‡	AUC_{tau}, AUCtau (dn), C_{av}, C_{max}, C_{max}(dn), Cmin, Rac AUCtau, Rac C_{max}	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, cv%, standard deviation, minimum, maximum.

† = single dose subjects in Part 1 and all subjects in Part 2, ‡ = multiple dose subjects in Part 1 and all subjects in Part 3.

There will be 1 summary table for each Part presenting all PK parameters. Each table will include data from all cohorts in the Part and will be paged by cohort. The treatment subheading will include the cohort number and dose information.

To assess the relationship between the PK parameters and dose, dose normalized AUC_{inf} and C_{max} will be plotted against dose (using a logarithmic scale), and will include individual subject values and the geometric means for each dose from Part 1 only. Geometric means will have a different symbol than the individual values. The values will be dose normalized (to a 1mg 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 and that data from both cohorts are presented on the plot.

Supporting data from the estimation of $t_{½}$ and AUC_{inf} will be listed by analyte 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}. This data may be included in the clinical study report.

Presentations for PF-06817024 concentrations will include:

- A listing of all concentrations sorted by subject ID, cohort, dose and nominal time post first 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 cohort, dose and nominal time post first 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 concentrations time plots (on both linear and semi-log scales) against nominal time post first dose by cohort and dose (all cohorts on the same plot per scale, based on the summary of concentrations by cohort, dose and time post-dose).

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

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

- Individual concentration time plots by subject (on both linear and semi-log scales) against actual time post first dose (there will be separate plots for each subject).

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long the PF-06817024 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 subject plots by time, the actual PK sampling time will be used.

NOTE: Cohort 3 in Part 1 had subjects receiving both single and multiple doses. Therefore all listings, PK parameter summaries, concentration-time profile plots and any other PK data summarizations or analyses should separate single and multiple dose subjects from Cohort 3 treating them as two distinct sub-groups.

8.1.1. Immunogenicity Analysis

Immunogenicity analysis will be conducted on the immunogenicity analysis set as defined in Section 5.5.

ADA and NAb results will be listed and summarized by cohort and time post first dose for samples collected. ADA listing will include ADA testing results and the titer for positive ADA samples. In addition, the PF-06817024 concentration at the matching time point may also be included in the listing to help the interpretation of the ADA results.

An ADA immune response following study drug administration for each subject is defined as:

- A confirmed post-treatment positive ADA result in combination with a negative baseline ADA result; or
- A confirmed post-treatment positive ADA result in combination with at least one dilution factor increase in titer relative to a positive baseline ADA result.

The number of ADA and NAb positive samples will be summarized by cohort and nominal time post-dose. The number of subjects with negative or positive ADA immune response and NAb response will be summarized by cohort in tabular format.

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8.1.3. Treatment and Disposition of Subjects

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics, immunogenicity, CCI [redacted] as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by treatment.

Data will be presented by study part (SAD/MAD, Nasal Polyps and Atopic Dermatitis) and cumulatively across all study parts. Data will be reported in accordance with the sponsor reporting standards.

8.1.4. Demographic and Clinical Examination Data

A breakdown of demographic data will be provided for age, race, weight, body mass index and height. Each will be summarized by sex at birth and 'All Subjects' for each cohort separately and overall in accordance with the sponsor reporting standards. Data will be presented by study part (SAD/MAD, Nasal Polyps and Atopic Dermatitis) and cumulatively across all study parts.

8.1.5. Discontinuation(s)

Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized by treatment. Data will be presented by study part (SAD/MAD, Nasal Polyps and Atopic Dermatitis) and cumulatively across all study parts.

Data will be reported in accordance with the sponsor reporting standards.

8.1.6. Adverse Events

Data will be presented by study part (SAD/MAD, Nasal Polyps and Atopic Dermatitis) and cumulatively across all study parts. Adverse events will be reported in accordance with the sponsor reporting standards.

8.1.7. Laboratory Data

Laboratory data will be listed and summarized by treatment in accordance with the sponsor reporting standards. Baseline is as defined in Section 6.2.2.

8.1.8. Vital Signs Data

Absolute values and changes from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by study part (SAD/MAD, Nasal Polyps, Atopic Dermatitis). They will be further summarized by cohort, treatment and time postdose, according to sponsor reporting standards as appropriate. Tables will be paged by parameter. Baseline is as defined in Section 6.2.3.

Mean changes from baseline for supine systolic and diastolic blood pressure and pulse rate will be plotted against time postdose. On each plot there will be 1 line for each cohort. Data from all cohorts will be plotted on the same figure using separate lines for the 2 placebos. Corresponding individual plots of changes from baseline will also be produced for each cohort and treatment.

For supine systolic and diastolic blood pressure and pulse rate, the differences between each dose and placebo (dose – placebo) will be summarized (N, mean, 90% confidence interval) and plotted (mean) for each cohort, dose and timepoint (including baseline).

Maximum absolute values and changes from baseline for vital signs will also be summarized descriptively by treatment using categories as defined in Appendix 1. Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned postdose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

8.1.9. ECG Data

Absolute values and changes from baseline in QT, heart rate, QTcF, PR and QRS will be summarized by study part (SAD/MAD, Nasal Polyps, Atopic Dermatitis). They will be further summarized by cohort, treatment and time postdose using sponsor reporting standards as appropriate. Tables will be paged by parameter. Baseline is as defined in Section 6.2.4. All triplicate measures will be averaged prior to summarization. Telemetry data will not be summarized along with other ECG data but listed in adverse events as appropriate.

Mean changes from baseline in QT, heart rate and QTcF will be plotted against time postdose. On each plot there will be 1 line for each treatment. Data from all cohorts will be plotted on the same figure using separate lines for the 2 placebos. Corresponding individual plots of changes from baseline will also be produced for each cohort and treatment.

Changes from baseline in QTcF will also be plotted separately against drug concentrations. This will be a scatter plot for all observations where QTcF and drug concentration are recorded. Placebo data will also be included (with drug concentration set to zero). Different symbols will be used for each cohort. There will be 1 plot for each of the parts of the study (Part 1, 2, 3), for Part 1 the SAD and MAD data will be plotted separately.

Maximum increase from baseline (0 to 12 hours) for QTcF, heart rate, QT, PR and QRS will be summarized by cohort and treatment, according to sponsor reporting standards for the first two parts (SAD/MAD and Nasal Polyps) of the study.

In addition for QTcF, heart rate and QT, and change from baseline for each subject will be summarized and plotted (N, mean, 90% confidence interval) for each cohort, dose and timepoint (including baseline).

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by cohort and treatment using categories as defined in Appendix 1 (for QTc these correspond to ICH E141).[1] Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned postdose timepoints will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Listings of subjects with any single postdose value ≥500 msec will also be produced for QTcF.

QTcB will be listed only and not summarized.

8.1.10. Other Safety Data

None.

8.1.11. Concomitant Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be summarized and listed. Summaries will be done by study part and and cohort, as well as across the entire study.

8.1.12. Screening and Other Special Purpose Data

Prior medication(s) and non-drug treatment(s), serum FSH concentrations, urine drug screen, serum or urine B-hCG for all females of childbearing potential, and urine or blood cotinine concentration will be obtained at Screening.

These data will not be brought in-house, and therefore will not be listed.

9. REFERENCES

1. ICH E14 - The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. CHMP/ICH/2/04.

Appendix 1. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

QTcF (ms)	450≤ max. <480	480≤ max.<500	max. ≥500
QTcF (ms) increase from baseline	30≤ max. <60	max. ≥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
Standing pulse rate (bpm)	min. <40	max. >140

Measurements that fulfill these criteria are to be listed in report.

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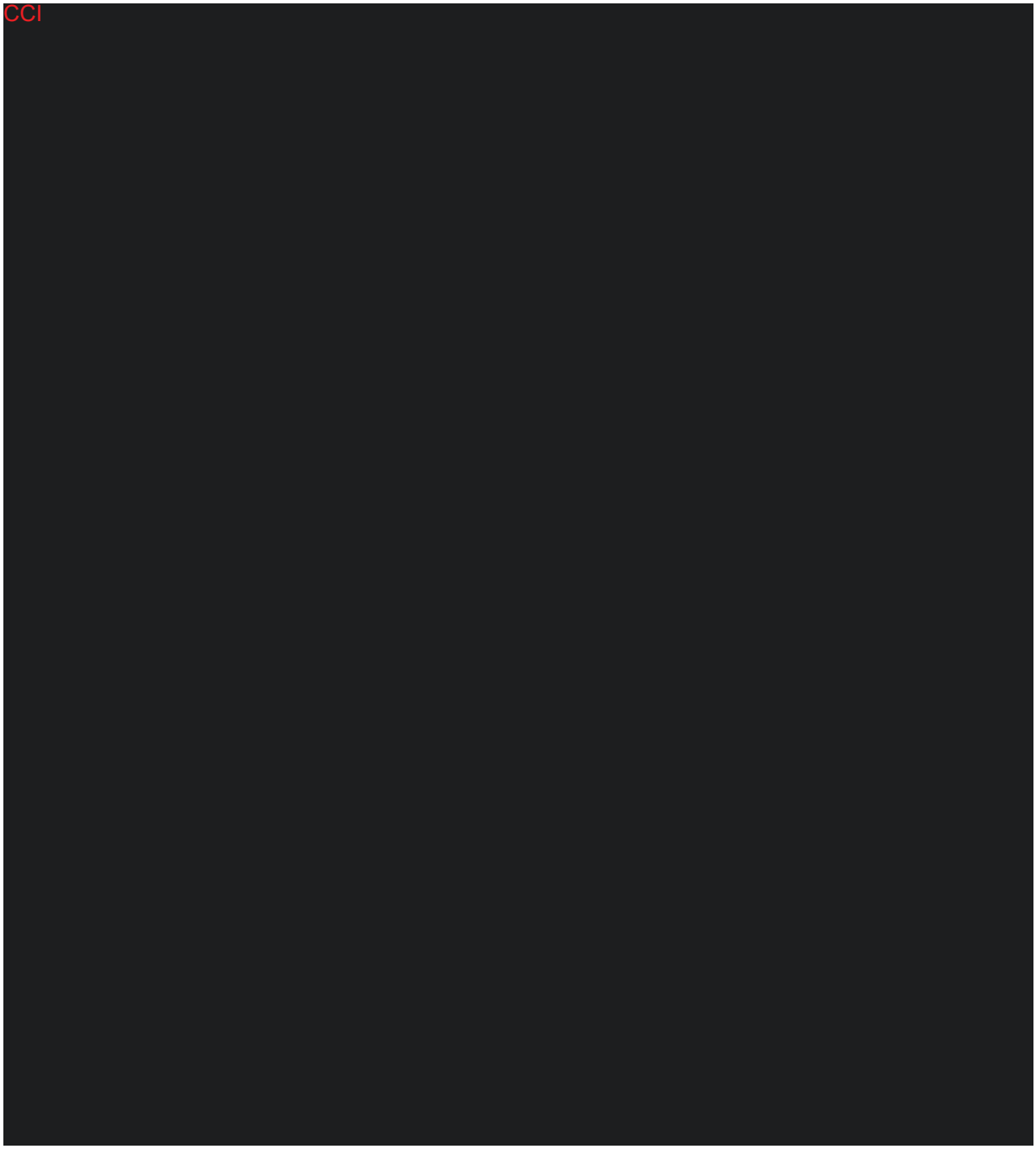

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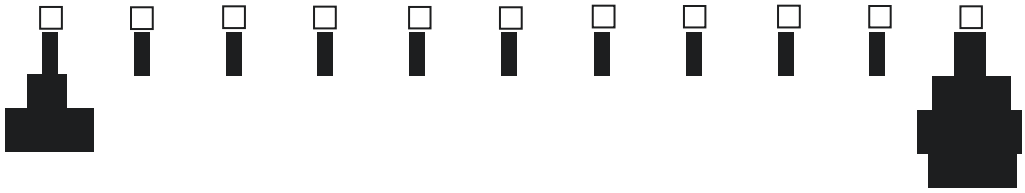

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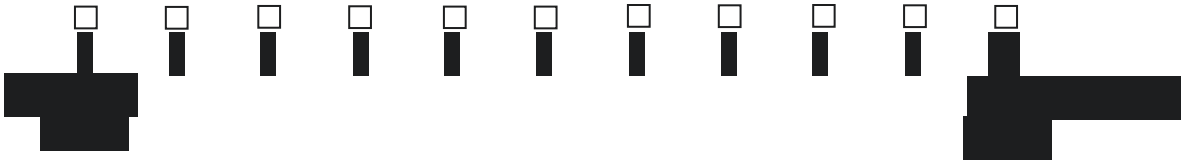

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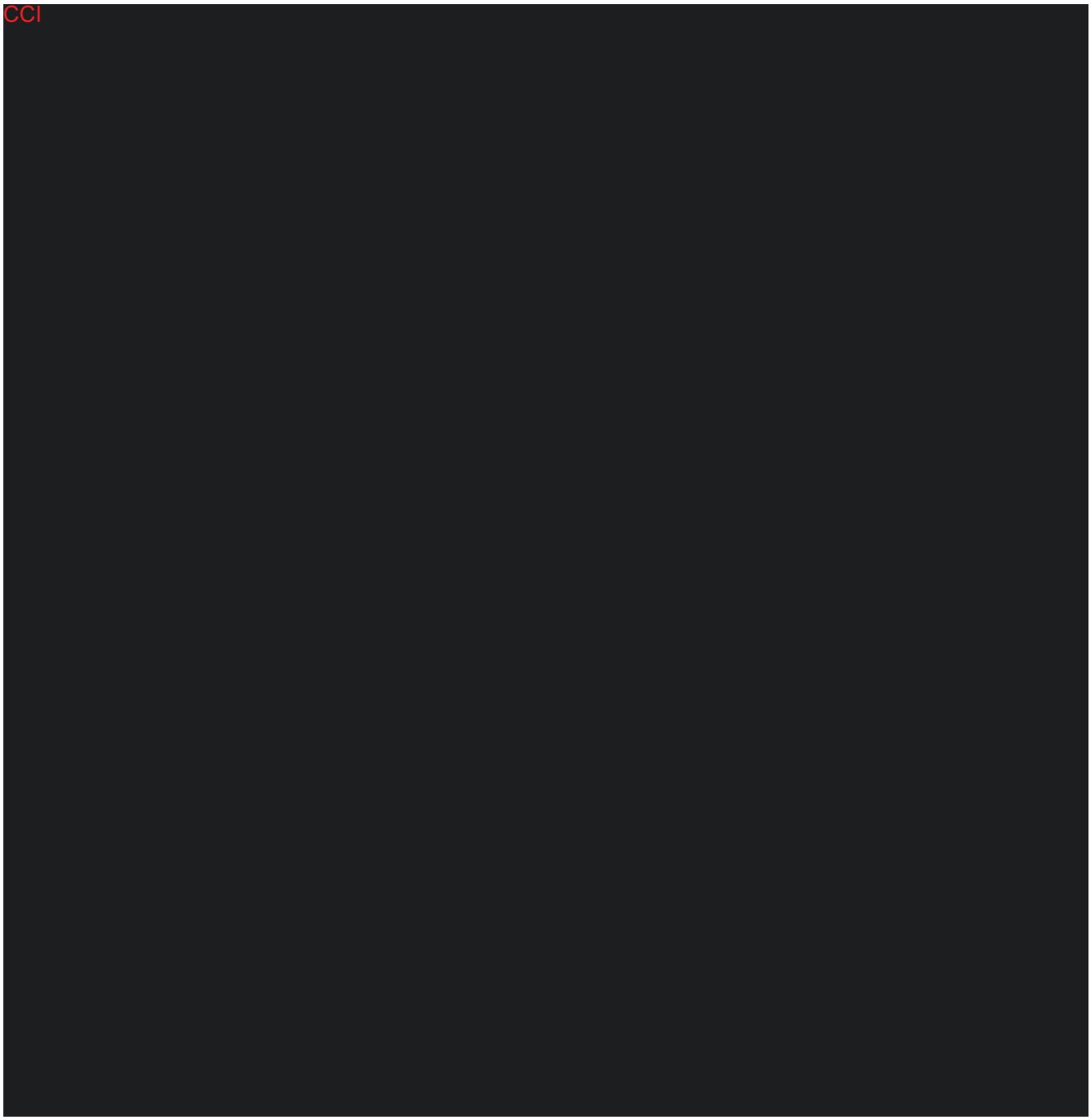

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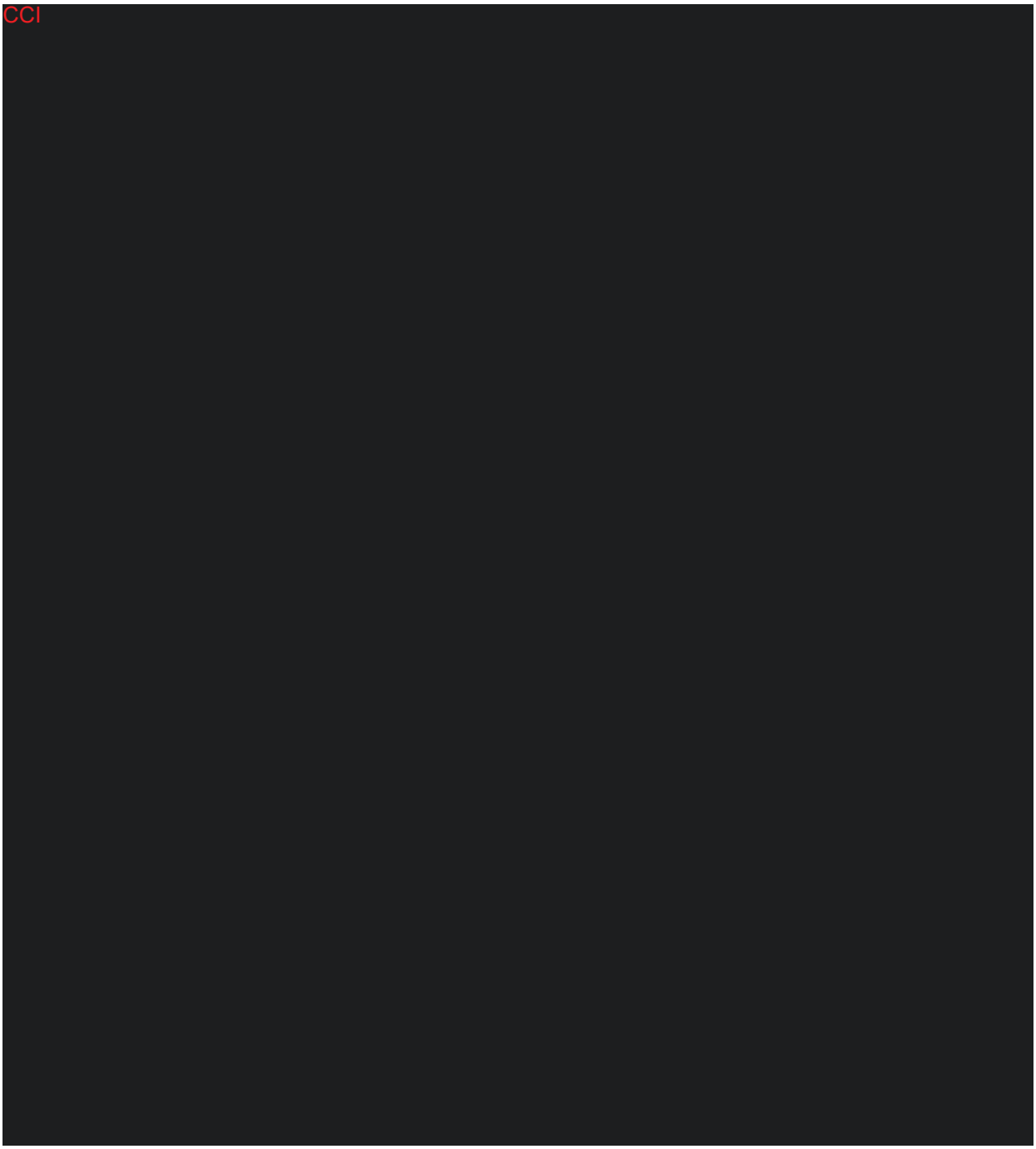

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