



Title: A Phase 1, Open-Label, Randomized, Parallel Group Pilot Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Needle Safety Device in Healthy Subjects

NCT Number: NCT03949621

SAP Approve Date: 05 June 2018

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: VedolizumabSC-1017

CCI [REDACTED] STUDY NUMBER: CA23614

A Phase 1, Open-Label, Randomized, Parallel Group Pilot Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Needle Safety Device in Healthy Subjects

Vedolizumab SC PFS+NSD Pilot Pharmacokinetic Study

PHASE 1

Version: Amendment 1

Date: 05 June 2018

Prepared by:

PPD

Based on:

Protocol Dated: 11 December 2017

Protocol Clarification Letter Dated: 14 February 2018

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1.1 Amendment Revision History

Study Number: VedolizumabSC-1017

CCI Study Number: CA23614

Statistical Analysis Plan (SAP) Amendment Revision History

SAP Version	Date	Description
Final	03-Apr-2018 (version from CCI) 11-Apr-2018 (version entered into Mosaic)	Initial document – Final SAP
Amendment 1	05-Jun-2018 (version from CCI)	<p>This SAP amendment was written to be consistent with the Final SAP for study VedolizumabSC-1021 (CCI study number CA23618).</p> <p>As a result of the amendment, the following sections of the protocol were updated:</p> <ol style="list-style-type: none"> 1. Section 3.0, List of Abbreviations: Updated. 2. Section 5.2.2, PK Endpoints: Added apparent clearance after extravascular administration (CL/F) and apparent volume of distribution during the apparent terminal phase after extravascular administration (V_z/F). 3. Section 7.1, General Principles: Specified how concentration values below the limit of quantitation (BLQ) will be presented in the concentration table listings, and how they will be treated in the calculation of summary statistics, the generation of concentration plots, and the calculation of pharmacokinetic (PK) parameters. This section now specifies that if actual times are missing, nominal times will be used instead for the calculation of PK parameters, and also includes criteria for which PK parameter data will be excluded from the descriptive statistics and statistical evaluation. 4. Section 7.3, Disposition of Subjects: Updated to indicate that a separate listing

		<p>will be generated for screen failures.</p> <ol style="list-style-type: none">5. Section 7.4, Demographic and Other Baseline Characteristics: Updated to indicate that for height, the screening measurement will be reported, but for weight and body mass index, the check-in value will be reported.6. Section 7.5, Medical History and Concurrent Medical Conditions: Updated to indicate that medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before signing of informed consent.7. Section 7.6, Medication History and Concomitant Medications: Updated to clarify that medication history to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 14 days prior to signing of informed consent, and that concomitant medications are recorded on the CRF and include any medication other than study drug taken at any time between time of signing the informed consent through the end of the study (including follow-up visit).8. Section 7.9.1, Pharmacokinetic Analysis: Table 7.a was updated to indicate the nominal sampling times in hours from Day 10 onwards. The text was updated to indicate that the actual date and time of sample collection will be recorded on the source document and electronic case report form (eCRF), and that if actual sample times are missing, nominal times may be used in the calculation of PK parameters.9. Section 7.11, Safety Analysis: Updated to indicate that percentages will also be reported for categorical data when appropriate. The level of precision with
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		<p>which continuous variables will be presented was removed.</p> <p>10. Section 7.11.1, Adverse Events: Corrected the last sentence to indicate that the end of the study is <u>127</u> days after the last dose of study drug. Clarified that treatment-emergent adverse events (AEs) will be coded using MedDRA[®] Version 20.1. Clarified how AEs would be summarized. Added Table 7.b Adverse Events of Special Interest.</p> <p>11. Section 7.11.2, Clinical Laboratory Evaluations: Clarified how change from baseline will be summarized. Added that all clinically significant lab tests and the corresponding values will be listed by subject.</p> <p>12. Section 7.11.3, Vital Signs: Clarified how vital sign results and change from baseline will be summarized.</p> <p>13. Section 7.11.4, 12-Lead ECGs: Clarified how ECG results and change from baseline will be summarized.</p> <p>14. Section 7.11.5.1, Standardize immunogenicity analysis for AVA data: Updated the definition of persistently positive antivedolizumab antibody status. Deleted “Responses to drug-induced liver injury questionnaires will be listed but not summarized.”</p> <p>15. Section 7.12, Interim Analysis: Indicated that an interim analysis was not applicable for this study and created Section 7.13, Analysis of Pharmacokinetic Data up to 2 Weeks Postdose.</p> <p>16. Section 7.14, Changes in the Statistical Analysis Plan: Section renumbered from 7.13 to 7.14. Indicated that CL/F and V_z/F were included as additional endpoints.</p> <p>17. Section 9.1, In-text Summary Tables and Figures: Updated titles of Tables 10-1 and 11-1.</p>
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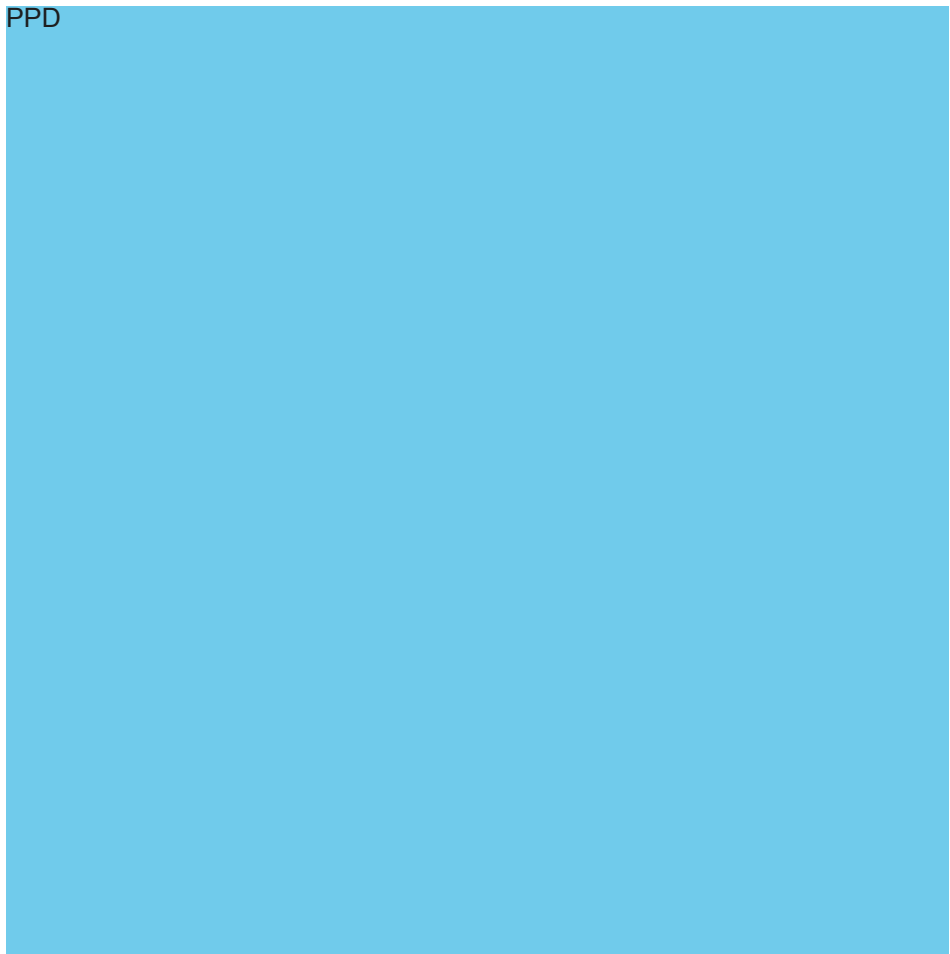
		<p>18. Section 9.2, Section 15 Summary Tables and Figures: Updated titles of Tables 15.1.1 to 15.1.3, 15.2.1.8, 15.3.1.5 to 15.3.1.12, and Figures 15.2.2.3 to 15.2.2.5.</p> <p>19. Section 9.3, Section 16 Data Listings: Renumbered the subappendices in Appendix 16.2.5. Renumbered the listing for Appendix 16.2.6.2 to 16.2.8.10. Added Appendix 16.2.8.3.</p> <p>20. Section 10.1, In-Text Summary Table Shells: Minor modifications were made to Tables 11-2 to 11-4. Corrected the source in the shell for Table 12-2.</p> <p>21. Section 10.3, Section 15 Summary Table Shells: Corrected shells for Tables 15.2.1.1 and 15.2.1.2. Modified shells for Tables 15.3.1.1 to 15.3.1.10 to include system organ class and preferred terms. Modified the shells for Tables 15.3.1.11 and 15.3.1.12 to only include AEs related to injection site reaction, hypersensitivity reactions, progressive multifocal leukoencephalopathy, and liver injury, and to include preferred terms. Added a footer to Tables 15.3.5.1.2, 15.3.5.1.4, and 15.3.5.1.6.</p> <p>22. Section 11.0, Listing Shells: Corrected shells for Appendices 16.2.4.1.1 and 16.2.4.1.2. Corrected and renumbered shells for Appendix 16.2.5. Renumbered the shell for immunogenicity response results from Appendix 16.2.6.2 to 16.2.8.10.</p> <p>In addition, other minor clarifications and typographical and formatting changes were incorporated into the SAP.</p>
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1.2 Approval Signatures

Study Title: A Phase 1, Open-Label, Randomized, Parallel Group Pilot Study to Compare the Pharmacokinetics of Single Subcutaneous Injections of Vedolizumab Administered in Prefilled Syringe Versus Prefilled Syringe in Needle Safety Device in Healthy Subjects - Vedolizumab SC PFS+NSD Pilot Pharmacokinetic Study

Approvals:

PPD



Date

Date

Date

Date

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
AUC	area under the curve
AUC _∞	area under the serum concentration-time curve from time 0 to infinity
AUC _{last}	area under the serum concentration-time curve from time 0 to time of the last quantifiable concentration.
AUC _{Week2}	area under the serum concentration-time curve from time 0 to Week 2.
AVA	antivedolizumab antibodies
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
C _{max}	maximum observed serum concentration
CPAP	Clinical Pharmacology Analysis Plan
CRF	case report form
CS	clinically significant
CSR	clinical study report
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
GCV	geometric coefficient of variation
Geo. Mean	geometric mean
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
ln	natural log
LSM	least-square means
LTFU	long-term follow-up
Mean	arithmetic mean
MedDRA	Medical Dictionary for Regulatory Activities
PFS	prefilled syringe
PFS+NSD	prefilled syringe in needle safety device
PI	Principal Investigator
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy

RAMP	Risk Assessment and Minimization for PML
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SEM	standard error of the mean
SOC	system organ class
$t_{1/2}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
TFL	tables, figures and listings
t_{max}	time to first occurrence of C_{max}
VNS	Visual Numeric Scale
WHO	World Health Organisation

4.0 OBJECTIVES

4.1 Primary Objectives

- To compare the pharmacokinetics (PK) of single dose of vedolizumab subcutaneous (SC) 108 mg administered as prefilled syringe (PFS) vs prefilled syringe in needle safety device (PFS+NSD).

4.2 Secondary Objectives

Not applicable.

4.3 Additional Objectives

- To evaluate the safety and tolerability of single dose of vedolizumab SC 108 mg administered as PFS and PFS+NSD.
- To evaluate the development of antivedolizumab antibodies (AVA) and neutralizing AVA following single dose of vedolizumab SC 108 mg administered as PFS and PFS+NSD.

4.4 Study Design

This is an open-label, randomized, parallel-group study to compare the PK of a single dose of vedolizumab SC 108 mg for injection administered in 2 different device delivery presentations (2 treatments) in healthy subjects. A minimum of 24 subjects (12 per group) will be randomized to 1 of 2 device presentations (Group A or B).

A summary of the treatment groups is presented in [Table 4.a](#).

Table 4.a Summary of Treatment Groups

Group	Approximate Number of Subjects	Treatment (a)
A	12	Single dose of vedolizumab SC 108 mg delivered by PFS (reference)
B	12	Single dose of vedolizumab SC 108 mg delivered by PFS+NSD (test)

(a) Subjects randomized to each device (1:1 ratio) were also randomized for the site of administration (abdomen, thigh, or arm) (1:1:1 ratio). Thus, within each treatment group, there are 3 sites of administration (abdomen, thigh, or arm) randomly assigned, for a total of 6 treatment combinations.

Subjects were randomized to each Group in a 1:1 ratio using 12 blocks of 2. Within each Group subjects were randomized to injection site in a 1:1:1 ratio using 4 blocks of 3. No stratification factors were used in the randomization. However, at least 40% of each sex will be enrolled. Subjects will be screened up to 28 days prior to dosing, to determine eligibility before randomization. Eligible subjects will return to the clinic at Check-in (Day -1). On Day 1, all doses will be administered by a health care professional. A schematic of the study design is included as [Figure 4.a](#).

Figure 4.a Schematic of Study Design

Screening		Treatment	Follow-up				
Days -28 to -2	Day -1 (Check-in)	Day 1	Day 2	Days 3-8	Days 10, 15, 29, 43, 64, 85, 106	Final Visit/ Early Termination Day 127 (a)	Day 168 Follow-up Phone Call (b)
		Dosing, PK, and safety	PK and safety assessments				
		←-----Confinement -----→					

(a) In the case that abnormal, clinically significant findings are observed upon discharge, subjects may be brought back to the clinic for re-evaluation per investigator's discretion.

(b) Subjects will be followed poststudy by telephone to administer a questionnaire, which will include progressive multifocal leukoencephalopathy (PML) questions at Day 168 (± 3 days).

Subjects for all treatment groups will be kept in the study unit from Day -1 Check-in until at least 24 hours after dosing (Day 2) for safety and PK assessments before discharge. The minimum confinement will be 2 nights (Days -1 to 2, inclusively). Subjects can stay longer at the discretion of the investigator. Subjects will return to the study unit periodically according to the schedule for PK sampling and safety assessments. Subjects will be required to participate in a long-term follow-up (LTFU) safety survey by telephone on Day 168.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The following serum PK parameters will be analyzed for each treatment (PFS and PFS+NSD) following a single dose of vedolizumab SC:

- Maximum observed serum concentration (C_{max}).
- Area under the serum concentration-time curve (AUC) from time 0 to time of the last quantifiable concentration (AUC_{last}).
- AUC from time 0 to infinity (AUC_{∞}).

5.2 Additional Endpoints

5.2.1 Safety Endpoints

The following safety variables will be used to characterize the safety and tolerability of vedolizumab SC:

- Physical examination findings, treatment-emergent adverse events (TEAEs), clinical laboratory test results, vital sign measurements, and 12-lead electrocardiograms (ECGs).
- Percentage of subjects who are positive for AVA during the study.
- Percentage of subjects who have positive neutralizing AVA during the study.

5.2.2 PK Endpoints

- AUC from time 0 to Week 2 (AUC_{Week2}).
- Terminal disposition phase half-life ($t_{1/2}$).
- Time to first occurrence of C_{max} (t_{max}).
- Apparent clearance after extravascular administration (CL/F).
- Apparent volume of distribution during the apparent terminal phase after extravascular administration (V_z/F).

6.0 DETERMINATION OF SAMPLE SIZE

The sample size of 12 subjects per group is considered to be sufficient for exploratory purposes. The study is not powered for statistical hypothesis testing.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All PK analyses will be conducted using CCI or higher. All statistical analyses will be conducted using CCI or higher.

Arithmetic mean (mean), median, and geometric mean (Geo. Mean) values will be presented to 1 more level of precision than the individual values. Standard deviation (SD) and standard error of the mean (SEM) will be presented to 2 more levels of precision than the individual values. Minimum and maximum values will be presented to the same precision as the individual values. Arithmetic percent coefficient of variation (CV%) and geometric percent coefficient of variation (GCV%) will be presented to 1 decimal place.

Geometric least-squares means (LSMs) will be presented with 1 more level of precision than the recorded data. Geometric LSMs are least-squares means derived from analysis of covariance model with weight as a covariate, and then exponentiated to provide estimates on the original scale. Ratios of geometric LSMs (presented as a %) and 90% confidence intervals (CIs) about a parameter estimate will be reported as 2-sided and presented using 2 decimal places.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment group, site of injection, and overall, where applicable. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

Concentration values below the limit of quantitation (BLQ) will be presented as 'BLQ' in the concentration table listings and footnoted accordingly. BLQ values will be treated as zero for the calculation of summary statistics, the generation of concentration plots, and the calculation of PK

parameters, unless they are obvious outliers (e.g. BLQ value between 2 measurable values), in which case they will be treated as missing.

For the calculation of PK parameters, if actual times are missing, nominal times will be used instead.

A subject's PK parameter data will be included in the listings but excluded from the descriptive statistics and statistical evaluation if one or more of the following criteria are met:

- A predose (0 hr) concentration is greater than 5% of that subject's C_{max} value in that period (e.g. single dose BE studies).
- A subject did not meet inclusion/exclusion criteria that may have an effect on the PK (as determined by the Takeda Clinical Pharmacology Lead and CCI pharmacokineticist).
- A subject deviates substantially from the protocol defined study procedures including but not limited to dosing, dose timing, sample collection, meal timing, etc. (as determined by the Takeda Clinical Pharmacology Lead and CCI pharmacokineticist).

See Clinical Pharmacology Analysis Plan (CPAP) for details on the PK parameter calculations and data presentation including specifics on the following:

- Insufficient data to determine a reliable t_{1/2} value and other terminal elimination rate constant dependent parameters.
- PK parameters presented by treatment and by site of administration within each treatment, including the units, precision, and summary statistics that will be presented in in-text and end-of-text tables.
- Concentration data presented by treatment, including the units, precision, and summary statistics that will be presented in end-of-text tables.
- Concentration data file used for PK analysis.
- PK parameter CCI output file used to generate the tables, figures, and listings (TFLs).
- Analysis of covariance (ANCOVA) results including all subjects and excluding AVA-positive subjects (sensitivity analysis) presented in in-text and end-of-text tables.
- Arithmetic mean concentration-time figures presented as in-text and end-of-text figures.
- Individual concentration-time figures presented in Appendix 16.2.6.
- AUC and C_{max} scatter plots presented by treatment and by site of administration within each treatment as in-text and end-of-text figures.

7.1.1 Study Definitions

7.1.2 Definition of Study Days

Day 1 is defined as the date on which a subject is administered their first dose of the medication. Other study days are defined relative to Day 1 with Day -1 being the day prior to Day 1. Study day prior to the first dose of treatment will be calculated as: date of assessment/event-date of treatment; study day on or after the date of first dose will be calculated as: date of assessment/event-date of treatment +1.

7.2 Analysis Sets

Safety Set:

The Safety Set will consist of all subjects who are enrolled and received 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristics and safety summaries.

PK Set:

The PK Set will consist of all subjects who receive study drug and have at least 1 measurable serum concentration.

7.3 Disposition of Subjects

Disposition of subjects (number of subjects dosed, completed the study, discontinued from the study, and reason(s) for discontinuation) will be summarized for each treatment and overall. Study completion status, including reason for discontinuation, will also be listed by subject. A separate listing will be generated for screen failures.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and overall. Summary statistics (number of subjects [N], mean, SD, minimum, median, and maximum) will be generated for continuous variables (age [calculated from the date of signed Informed Consent Form [ICF], weight, height and body mass index [BMI]) and the number and percentage of subjects within each category will be presented for categorical variables (sex, race, and ethnicity). For height the screening measurement will be reported but for weight and BMI the check-in value will be reported. The demographics listing will also include the date each signed the ICF. A separate listing will be generated for screen failures.

7.5 Medical History and Concurrent Medical Conditions

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before signing of informed consent. Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing the ICF. Each subject's medical history and concurrent medical conditions will be listed. Any medical condition started after taking the study drug will

be classified as an adverse event. The medical history listing will include whether the event was medical or surgical, the body system or organ class involved, start date (if known) and end date or whether the condition was ongoing, and a description of the condition or event. There will be no statistical analysis of medical history.

7.6 Medication History and Concomitant Medications

Medication history to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 14 days prior to signing of informed consent. Concomitant medications are recorded on the CRF and include any medication other than study drug taken at any time between time of signing the informed consent through the end of the study (including follow-up visit). All medication history and concomitant medications recorded during the study will be coded with the World Health Organization (WHO) Dictionary Version 01-Sep-2017 and listed. The listing will include the medication name, dosage, route of administration, start date and time (if known), end date and time, or whether it continued after study completion, and indication for use.

7.7 Study Drug Exposure and Compliance

Not applicable.

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Blood samples (one 5 mL sample per scheduled time) for PK analysis of vedolizumab will be collected as specified in [Table 7.a](#) even if the vedolizumab SC is discontinued before the complete dose is administered to the subject.

Table 7.a Collection of Blood Samples for Pharmacokinetic Analysis

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
Vedolizumab	Serum	1	Within 0.5 hours before the SC injection (predose), 2, 8, 24, 72, 120, and 168 hours after Day 1 dosing, and on Days 10 (Hour 216), 15 (Hour 336), 29 (Hour 672), 43 (Hour 1008), 64 (Hour 1512), 85 (Hour 2016), 106 (Hour 2520), and Final Visit Day 127 (Hour 3024)/Early Termination (a)

(a) If a subject experiences a serious adverse event (SAE), a blood sample for PK analysis should also be obtained at the unscheduled visit. PK samples will be collected at Early Termination at the discretion of the investigator.

The actual date and time of sample collection will be recorded on the source document and electronic case report form (eCRF).

Samples collected outside 10% of the nominal time will not be considered a protocol deviation as long as the exact date and time of PK sampling is recorded in the eCRF.

The PK parameters of vedolizumab listed in the CPAP for this study will be determined from the concentration-time profiles for all evaluable subjects using a noncompartmental analysis method. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If actual sample times are missing, nominal times may be used.

Concentrations will be listed and summarized descriptively by PK sampling time. Summary will be done by treatment using the summary statistics listed in the CPAP. Excluded concentrations will be presented and footnoted as such in the concentration table listings, and those values will be excluded from the descriptive summary. Individual subject and arithmetic mean profiles of the concentration-time data will be plotted by treatment on linear and semi-log scales. For summary statistics and arithmetic 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.

PK parameters will be summarized descriptively by treatment and by site of administration within each treatment using the summary statistics listed in the CPAP. Excluded parameters will be presented and footnoted as such in the PK parameter table listings, and those values will be excluded from the descriptive summary. Scatter plots of the individual AUC_{last} , AUC_{∞} , and C_{max} values, including the median values, will be plotted by treatment and by site of administration within treatment.

Natural log (ln)-transformed AUC_{last} , AUC_{∞} (if data permits), and C_{max} will be analyzed using an ANCOVA model. The model will include treatment and site of administration as fixed-effects and weight as a continuous covariate. The following CCI will be used for the analysis:

CCI

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. Single doses of 108 mg of vedolizumab SC administered as PFS+NSD (test treatment) will be compared vs PFS (reference treatment).

In addition to the analysis described above using all subjects, a sensitivity analysis will be performed excluding subjects that are AVA-positive.

The information collected in this study up to Week 2 will be used to calculate the sample size in study VedolizumabSC-1018 (CCI Study Number CA23615).

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, changes from baseline in the subjects' clinical laboratory results, vital signs, and ECG's using the safety set. Reasons for discontinuation will be tabulated. Exposure to study drug will be presented in by-subject listings. All clinical safety data will be listed by subject and assessment time points, including rechecks, unscheduled assessments, and early termination, chronologically.

Continuous variables will be summarized using n, mean, SD, minimum, median, and maximum. Frequency counts and percentages will be reported for categorical data when appropriate. Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

7.11.1 Adverse Events

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, severity (mild, moderate or severe), relationship to vedolizumab SC and to study procedures (related or unrelated) and action relative to the study drug and procedures. All AEs occurring during this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA[®]), Version 20.1. However, only TEAEs occurring after administration of the first dose of study drug and through the end of the study (127 days after the last dose of study drug) will be summarized.

A TEAE is defined as an AE that is starting or worsening at the time of or after study drug administration. If an AE increases in severity, that AE will be given a resolution date and time, and a new AE will be entered with the new severity. If the severity of an AE remains the same or decreases, the AE will be kept open through to resolution.

For each treatment, TEAEs will be coded using MedDRA[®] Version 20.1 and tabulated by System Organ Class (SOC) and Preferred Term. Summary tables will include number of subjects reporting the AE and as percent of safety set by treatment. The most commonly reported TEAEs (i.e., those events reported by >5% of all subjects) will also be summarized.

In addition, they will be summarized as number of AEs and percentage of AEs for each treatment. Additional summary tables will be presented by severity and relationship to vedolizumab SC and relationship to study procedure. If a subject has multiple AEs with different severity levels within the same term, the subject will be counted in the most severe category only. If a subject has both related and unrelated AEs with the same term, the subject will be counted as having related TEAEs.

Adverse events of special interest (AESI) will be summarized by treatment and injection site using AESI definitions presented in [Table 7.b](#).

Table 7.b Adverse Events of Special Interest

Adverse Event	MedDRA Terms or definitions
Injection site reaction	Injection Site Reaction (HLT)
Hypersensitivity Reactions	Anaphylactic/anaphylactoid shock conditions SMQ (broad). Angioedema SMQ (broad). Hypersensitivity SMQ (broad).
PML	Human polyomavirus infection PT. JC virus infection PT. JC virus test positive PT. Leukoencephalopathy PT. Polyomavirus test positive PT. Progressive multifocal leukoencephalopathy PT.
Liver injury	Cholestasis and jaundice of hepatic origin SMQ (Broad) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ (Broad) Hepatitis, non-infectious SMQ (Broad) Liver related investigations, signs and symptoms SMQ (Narrow) Liver infections SMQ (Broad)

Should any SAEs occur they will be summarized the same way as TEAE. In addition, all SAEs, AEs leading to discontinuation, and AEs resulting in death occur during this study these will be listed by subject. All AEs will be displayed in the data listings and TEAEs will be discussed in the text of the study report.

7.11.2 Clinical Laboratory Evaluations

Hematology, serum chemistry, and urinalysis will be performed at screening, check-in (Day -1) and Days 8, 29, 85 and 127 postdose. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Principal Investigator (PI).

For all laboratory values that are numeric, summary statistics (n, mean, SD, minimum, median, and maximum) will be presented for each laboratory test by treatment and assessment time points. Change from baseline will be summarized using last assessment including rechecks taken prior to dosing.

For each laboratory test, a shift table will be developed comparing the frequency of the results at treatment baseline (above normal (H), normal (N), or below normal (L)) with those postdose time points for each regimen. For urinalysis tests, the categories are normal (N) and abnormal (A). Out-of-range values and corresponding recheck results will be listed.

Out-of-normal range flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. If a value fails the reference range, it will automatically be compared to a clinically significant (CS) range. If the value falls within the CS range, it will be noted as “N” for not clinical significant. If the value fails the CS range, it will be

flagged with a “Y” which prompts the PI to determine how the out-of-range value should be followed using 4 Investigator flags: "N", not clinically significant, "R", requesting a recheck, "^", checking at the next scheduled visit, or "Y", clinically significant. All clinically significant lab tests and the corresponding values will be listed by subject. All clinical laboratory data will be presented in by-subject data listings.

7.11.3 Vital Signs

Vital signs (oral temperature, respiration, pulse, and blood pressure) will be obtained at screening, check-in (Day -1), Day 1 (predose, postdose), Days 8, 106, and Final Visit Day 127/Early Termination. For Day 1, heart rate and blood pressure will be measured after 5 minutes in the supine position and at 1 and 3 minutes after standing. For Days 8, 106, and 127/Early Termination, heart rate and blood pressure will be measured after 5 minutes supine only.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for vital sign results and change from baseline by treatment and time point. Baseline is defined as the last assessment including rechecks taken prior to dosing. Vital signs will also be displayed in a data listing by subject.

7.11.4 12-Lead ECGs

Standard 12-lead ECGs will be recorded at screening, check-in (Day -1), Day 1 (predose; within 0.5 hours before dosing the SC injection), Day 8, and Final Visit Day 127/Early Termination. Additional unscheduled ECGs may be recorded where clinically necessary for subject safety.

Summary statistics (n, mean, SD, minimum, median, and maximum) will be reported for ECG results and change from baseline by treatment and time point. Baseline is defined as the last assessment including rechecks taken prior to dosing. ECG data will also be displayed in a data listing by subject.

7.11.5 Other Observations Related to Safety

7.11.5.1 Standardize immunogenicity analysis for AVA data

Definitions of AVA negative, positive and positive neutralizing:

- AVA Negative: defined as a sample that was evaluated as negative in the AVA screening assay. Samples that were determined to be positive in the AVA screening assay but the result was not confirmed in the AVA confirmatory assay were considered negative.
- AVA Positive: defined as a sample that was evaluated as positive in both the AVA screening and confirmatory assays.
- Neutralizing AVA Positive: defined as a sample that was evaluated as positive in the neutralizing AVA assay.

Subject AVA status will be grouped into 3 categories as follows:

- Negative: defined as subjects who did not have confirmed AVA results
- Positive: defined as patient who had at least 1 positive AVA result
 - Transiently positive: defined as subjects with confirmed positive AVA in 1 sample.
 - Persistently positive: defined as subjects with confirmed positive AVA in 2 or more consecutive positive AVA samples.

Subject AVA positive at baseline is defined as a positive AVA sample at Week 0 (predose).

The proportion and percentage of subjects that are AVA negative, AVA positive, and neutralizing AVA positive will be presented for each visit by treatment (all injection sites combined = overall), by each injection site separately within each treatment, and in total for both treatments combined. The proportion and percentage of subjects that are AVA positive will be presented for each titer for each visit by treatment (all injection sites combined = overall), by each injection site separately within each treatment, and in total for both treatments combined. The frequency and percentage of subjects that are AVA negative, AVA positive, transiently AVA positive, persistently AVA positive, and neutralizing AVA positive will be presented for each visit by treatment (all injection sites combined = overall), by each injection site separately within each treatment, and in total for both treatments combined.

The PML subjective checklist will be administered at Screening Visit, on Day 1 before dose, Day 127/Early Termination Visit, and at any unscheduled visits. Any subjects reporting signs and/or symptoms of PML will undergo objective testing and may be referred to a neurologist for a full evaluation, as described in the Risk Assessment and Minimization for PML (RAMP) algorithm. PML checklist responses and algorithm results will be displayed in a data listing by subject.

The Visual Numeric Scale (VNS) for self-reported pain assessment at the injection site will be completed by each subject on Day 1 immediately following the SC injection and a second

assessment will be performed between 15 and 30 minutes following the injection. Subjects will be presented with the pain scale and instructed to assess their pain on a scale of 0 to 10, with 0=no pain and 10=severe pain. Pain scale assessment responses will be displayed in a data listing by subject.

Subjects will self-report any pain, pruritus, erythema, swelling, hematoma, discoloration, warmth, or bruising at the injection site to study medication. In addition, the location of the reaction (arm, abdomen, thigh), laterality (right or left) and maximum diameter of the reaction will be recorded. Injection site reactions will be graded on a 1 to 4 scale. If there are any hypersensitivity reactions, a hypersensitivity reaction assessment will be completed. Injection site reaction and hypersensitivity reaction (if any) results will be displayed in a data listing.

7.12 Interim Analysis

Not applicable.

7.13 Analysis of Pharmacokinetic Data up to 2 Weeks Postdose

Ln-transformed AUC_{Week2} and C_{max} will be analyzed using the same ANCOVA model described in Section 7.9.1.

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. Single doses of 108 mg of vedolizumab SC administered as PFS+NSD (test treatment) will be compared vs PFS (reference treatment).

The information collected in this study up to Week 2 will be used to calculate the sample size in study VedolizumabSC-1018 (CCI Study Number CA23615).

7.14 Changes in the Statistical Analysis Plan

The protocol specified median profiles of the concentration-time data will be plotted by treatment; however, arithmetic mean profiles will be generated instead.

The protocol stated that single doses of 108 mg of vedolizumab SC administered as PFS will be compared vs PFS+NSD, however single doses of 108 mg of vedolizumab SC administered as PFS+NSD (test treatment) will be compared vs PFS (reference treatment) instead.

The original protocol included site of administration as a fixed-effect in the statistical model. It was later removed when the protocol was amended. However, site of administration is still in the protocol for VedolizumabSC-1018. To keep the analysis of the data consistent between the two studies, and to ensure that site of administration is included in the sensitivity analysis to be performed excluding AVA-positive subjects, site of administration will be included in the statistical model for VedolizumabSC-1017.

A sensitivity analysis using the same model as described in Section 7.9.1 will also be performed excluding subjects that are AVA-positive.

The protocol states that values of subjects with markedly abnormal values for laboratory tests, vital signs and ECG results will be tabulated and mapped. However, after discussions between CCI [REDACTED] and Takeda, it was decided that these would not be presented.

In addition to the 3 additional PK endpoints described in the protocol (AUC_{Week2} , $t_{1/2}$ and t_{max}), CL/F and V_z/F were also included as additional endpoints.

8.0 REFERENCES

Not applicable.

9.0 SUMMARY TABLES AND FIGURES

Summary tables and figures are numbered following the International Conference on Harmonisation (ICH) structure but may be renumbered as appropriate during the compilation of the tables and figures for the clinical study report (CSR). Please note that PK and safety summary tables and figures will be generated using CCI [REDACTED] or higher.

The following are lists of TFL numbers and titles that will be included within the CSR.

9.1 In-text Summary Tables and Figures

CCI [REDACTED]

CCI



Section 12:

CCI



9.2 Section 15 Summary Tables and Figures

CCI



CCI



15.2.2 Pharmacokinetic Data Summary Figures

CCI



CCI



15.3 Safety Data Summary Tables

15.3.1 Displays of Adverse Events

CCI



CCI



15.3.2 Listings of Deaths, other Serious and Significant Adverse Events

CCI



15.3.3. Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

CCI



15.3.5. Displays of Other Laboratory, Vital Signs, Electrocardiogram, Physical Examination, and Other Safety Data

CCI



CCI [REDACTED]

9.3 Section 16 Data Listings

Note: Hepatitis and human immunodeficiency virus (HIV) results that are provided by the clinical laboratory will not be presented in subject data listings or included in any database transfer.

Data listings are numbered following the ICH structure but may be renumbered as appropriate during the compilation of the TFLs for the CSR. The following is a list of appendix numbers and titles that will be included as data listings:

CCI [REDACTED]

CCI



10.0 TABLE AND FIGURE SHELLS

The following table shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the tables that will be presented and included in the final report. Unless otherwise noted, all tables will be presented in Times New Roman font size 8. CCI [REDACTED]

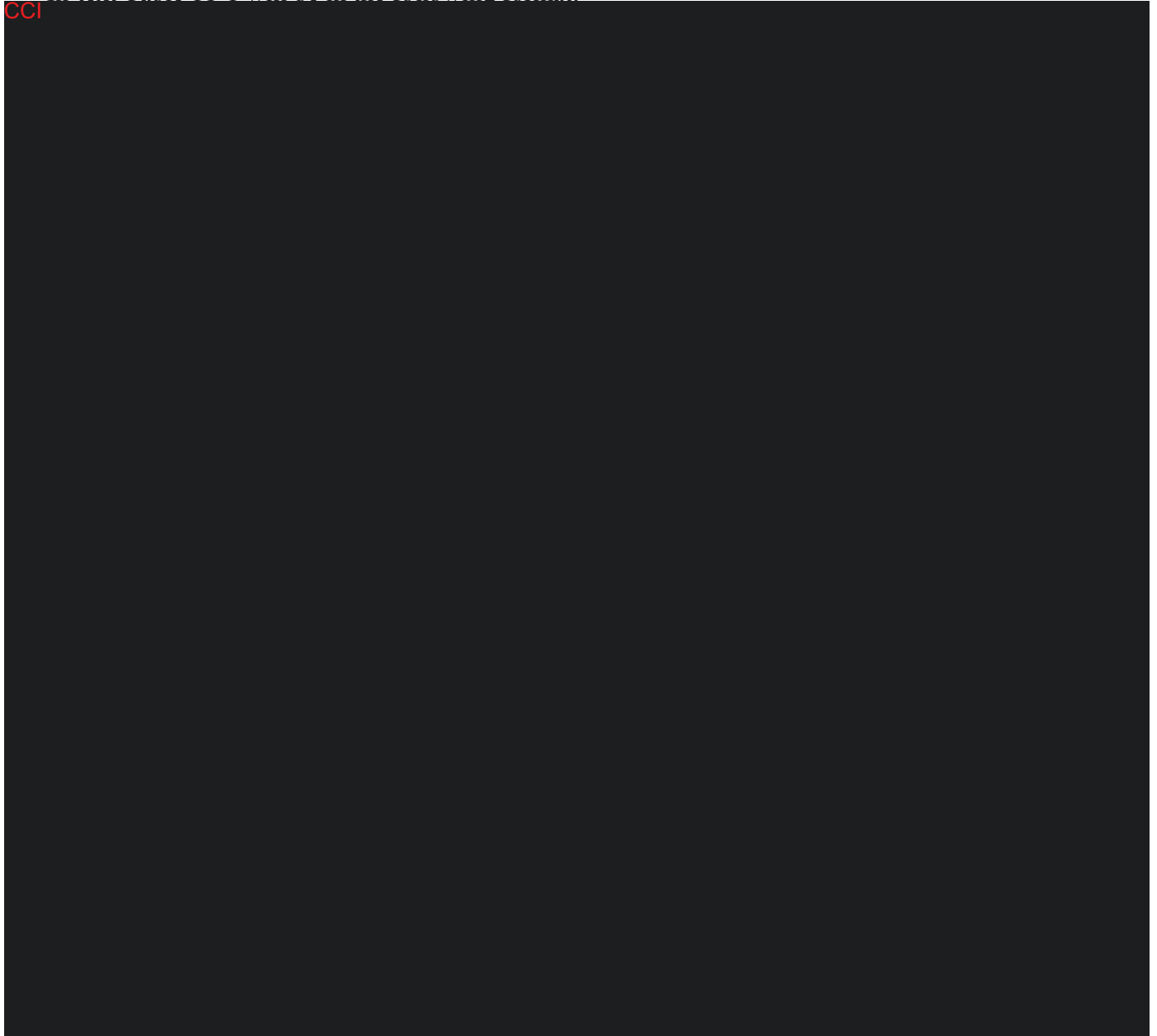
10.1 In-Text Summary Table Shells

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In-text Table 11-1 will be in the following format:

CCI



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Table 11-3

CCI

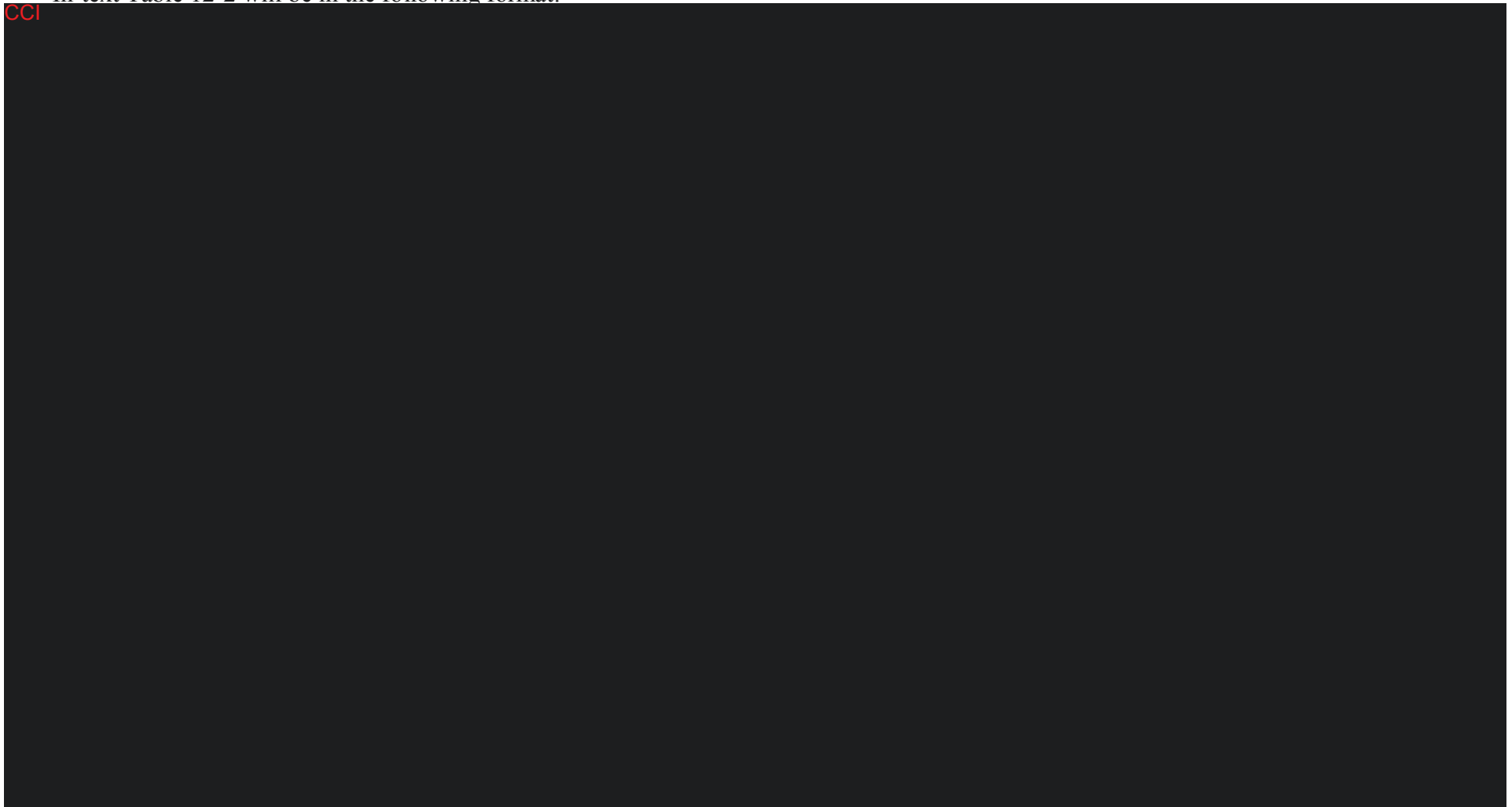


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CCI



In-text Table 12-2 will be in the following format:



10.2 Figure Shells

CCI



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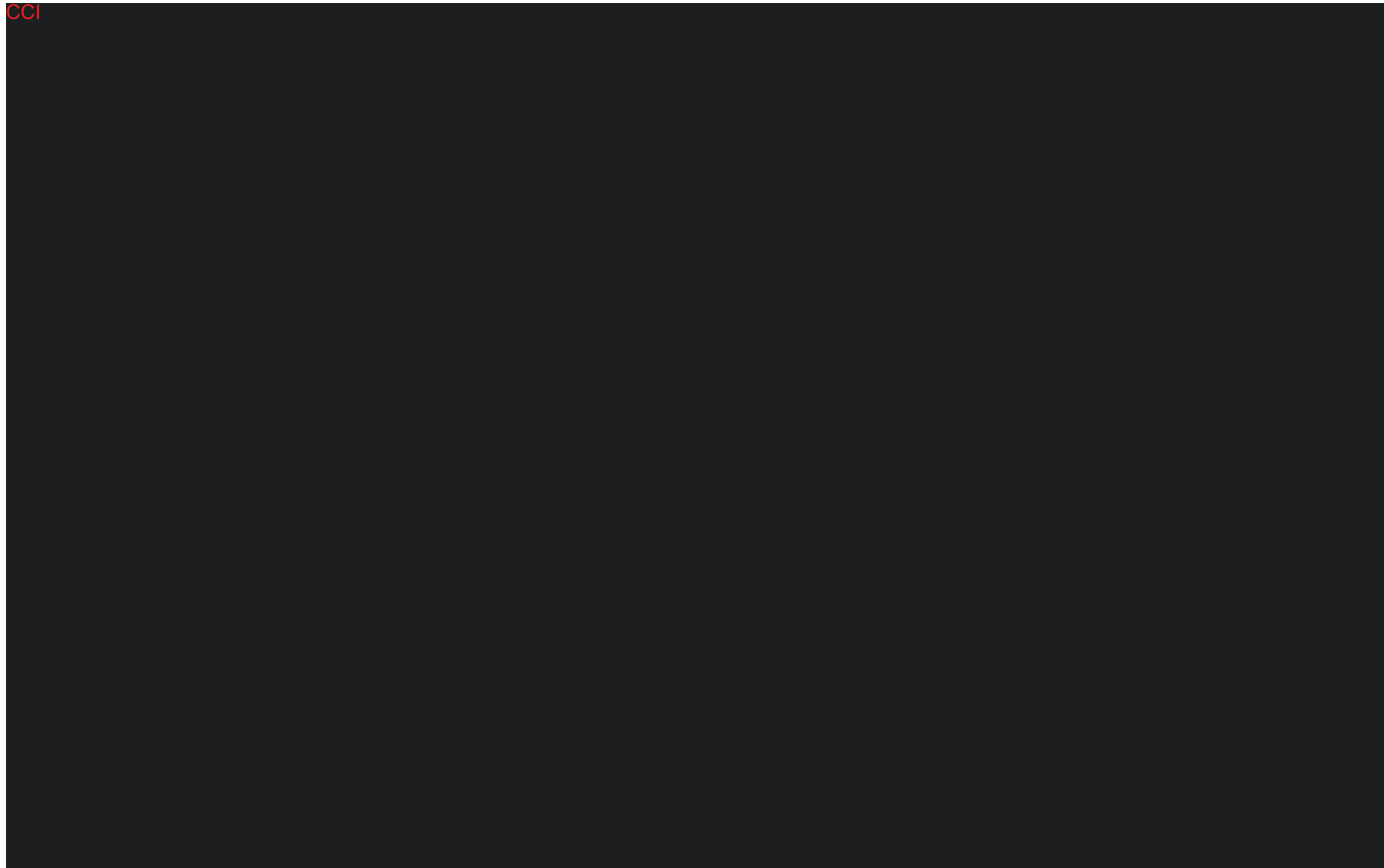
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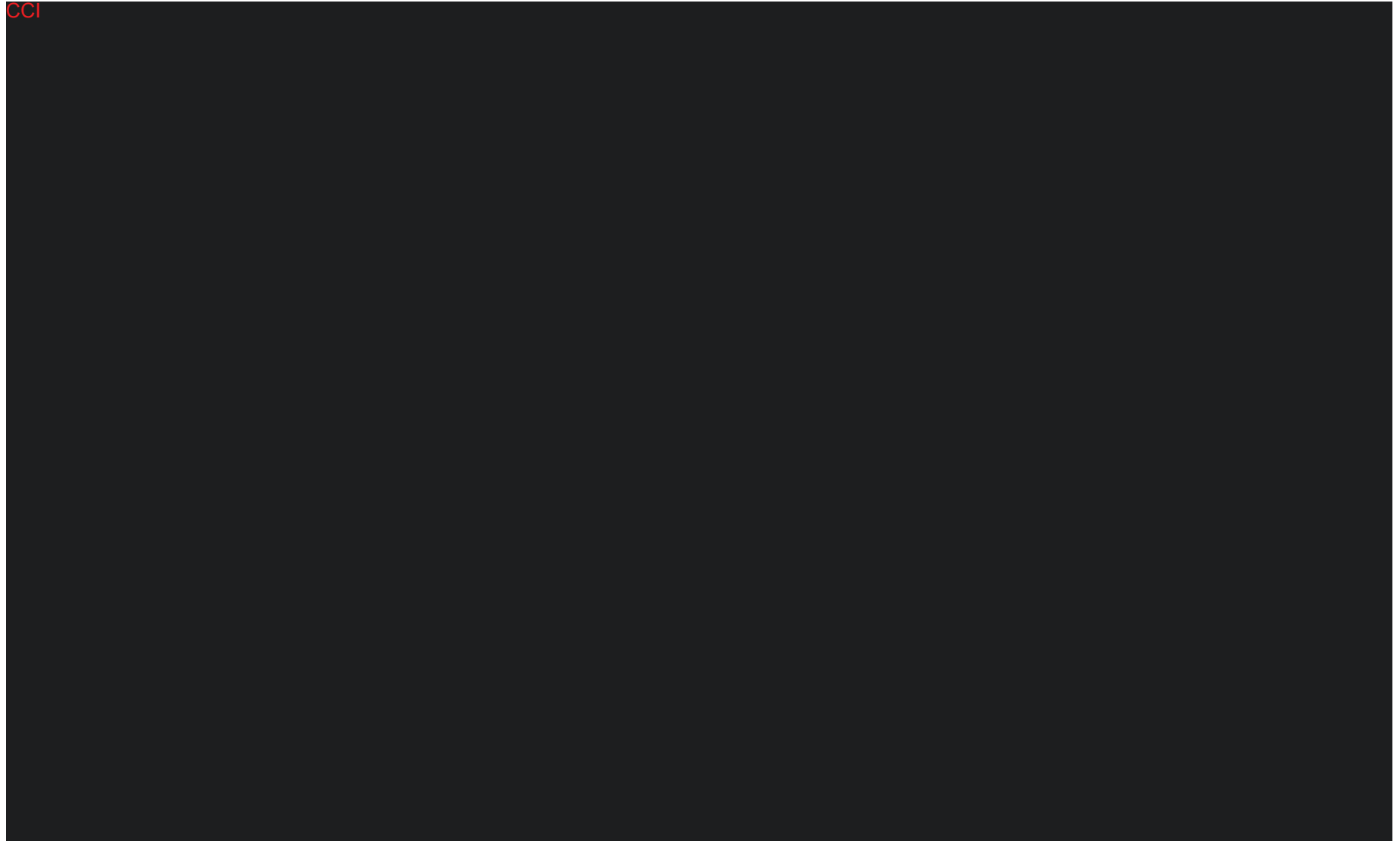


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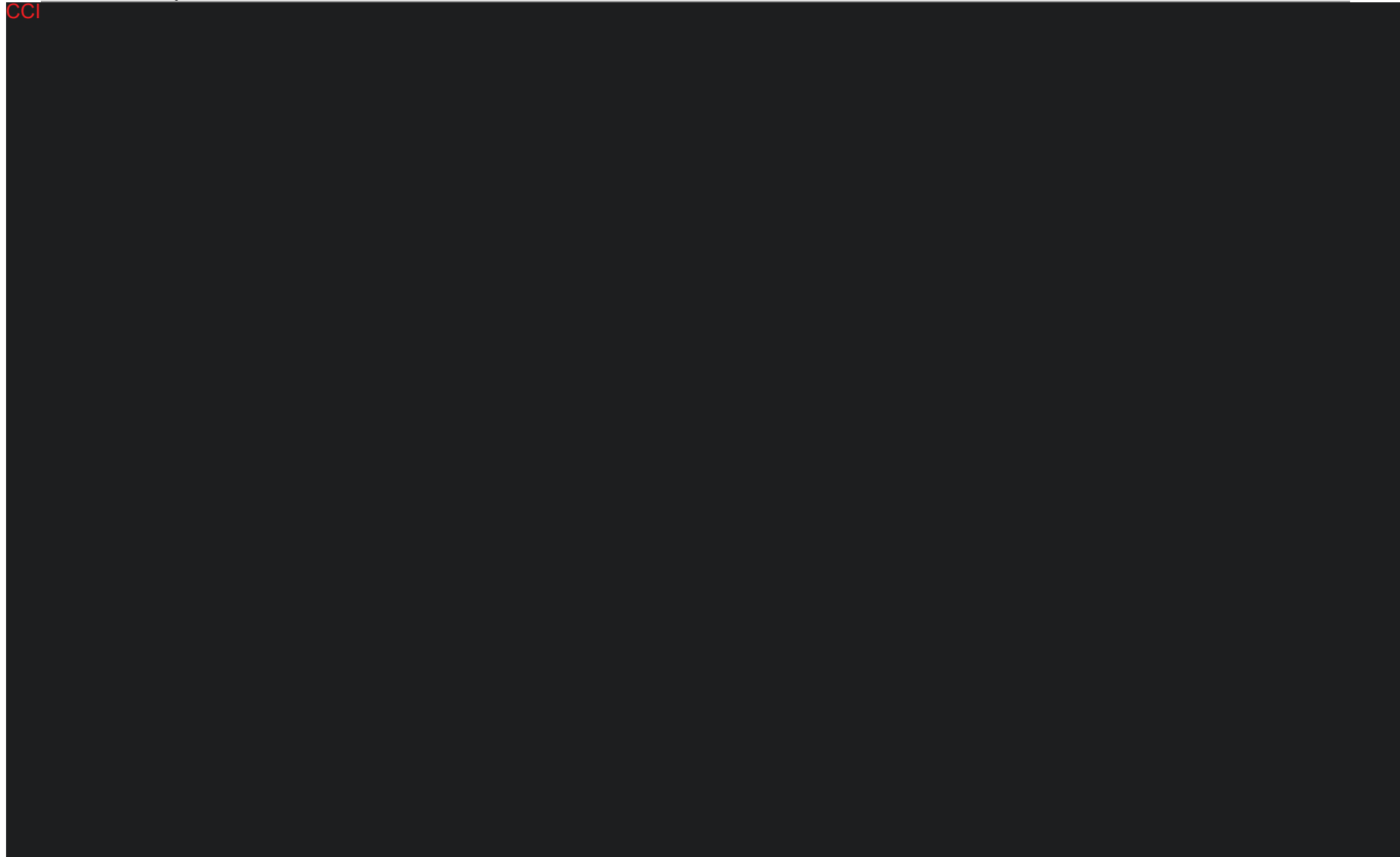
CONFIDENTIAL

11.0 LISTING SHELLS

The following listing shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the listings that will be presented and included in the final report. These listings will be generated off of the CCI SDTM Tabulation Model 1.4 mapped in accordance with SDTM Implementation Guide 3.2. All listings will be presented in Courier New size font 9.

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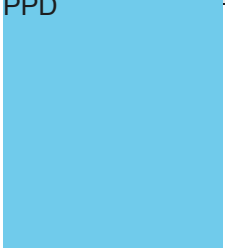
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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD 	Clinical Approval	08-Jun-2018 13:37 UTC
	Biostatistics Approval	08-Jun-2018 13:42 UTC
	Clinical Pharmacology Approval	08-Jun-2018 13:59 UTC
	Biostatistics Approval	08-Jun-2018 15:03 UTC