Statistical Analysis Plan	
Title:	A Phase I/II, randomised, controlled study to assess the safety, effectiveness and immune response of meningococcal combined ABCWY vaccine when administered to healthy adults (Phase I) and to healthy adolescents and adults (Phase II).
eTrack study number and Abbreviated Title	212458 (MENACWY=CCI -001 PRI)
Scope:	All analyses for the primary and secondary objectives of the study and interim analysis. The analysis details for tertiary objectives are described in separate Statistical Analysis Plan (SAP).
Date of Statistical Analysis Plan	Amendment 5 Final: 29 Aug 2023

APP 9000058193 Statistical Analysis Plan Template V5 (Effective date: 1July2020)

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CI	Confidence Interval
CRF	Case Report Form
CTRS	Clinical Trial Registry Summary
EL.U/mL	ELISA unit per millilitre
Eli Type	Internal database code for type of elimination code
ELISA	Enzyme-linked immunosorbent assay
ES	Exposed Set
FAS	Full Analysis Set
F&SF	Formulation and Schedule-finding
GMC	Geometric mean antibody concentration
GMT	Geometric mean antibody titre
GSK	GlaxoSmithKline
HR	Hazard Ratio
IU/mL	International units per millilitre
LL	Lower Limit
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
PDMP	Protocol Deviation Management Plan
PPS	Per-Protocol Set
RR	Relative Risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBIR	GSK Biologicals Internet Randomisation System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SR	Study Report
SUSAR	Suspected Unexpected Serious Adverse Reaction
UL	Upper Limit

1. DOCUMENT HISTORY

Date	Description	Protocol Version
02 June 2021	First Version	Final: 15 January 2021
22 July 2021	Amendment 1 • Tdap has been replaced with placebo in the phase II formulation and schedule finding • Update of the number of participants enrolled in the phase II formulation and schedule finding (change of testing strategy, split of the alpha, cf. to the protocol for more details) • Update of number of participants enrolled in the phase II Sourcing and the age range for inclusion criteria	Amendment 2: 24 June 2021
19 October 2021	Amendment 2 • In the Phase II Formulation and Schedule finding, the participants in the Control group will have no study intervention at Visit V3 (Month 4). This visit (Visit V3) has been replaced by a phone call (TC).	Amendment 3: 28 September 2021
11 May 2022	Amendment 3 • Two dosing schedules have been added in the Phase II Sourcing part, leading to changes in study design and to some objectives and endpoints • Detailed definition populations by phases	Amendment 4: 22 March 2022
06 June 2023	Amendment 4 • Minor corrections throughout the document to improve clarity • Section 4.2: Exclusion criteria for FAS were made explicit • Section 4.2: All the exclusion criteria for PPS were corrected (when needed) and split by phase of the study • Section 5 – Statistical analyses: It was added a subsection 5.1 – Disposition of subjects. Therefore, the following subsections have been renumbered (e.g., 5.1 became 5.2, etc.)	Amendment 4: 22 March 2022

	• Section 5.2 (formerly 5.1): description of analyses for demography were corrected • Section 5.3 (formerly 5.2) – Primary analyses: categorization of each AESI either as a new onset condition or as an exacerbation of a pre-existing chronic condition (as proposed by CBER) is documented in each "Safety" subsection • Section 5.4 (formerly 5.3): removal of the sentence "The 95% CIs for the difference in percentages between ABCWY groups and control group will be constructed using the method of Miettinen and Nurminen", as the respective objective does not involve any difference. • CCI [redacted] • Subsection 10.1.3: - definitions of GMT and GMC were rephrased - new subsection with updated 4-fold rise definition - amendment of rules on how to address possible incoherence in e-diary-recorded solicited administration site adverse events • Subsection 10.1.4: rules for the display of decimals have been corrected / clarified	
29 Aug 2023	Amendment 5 • Section 4.2: All the criteria for eliminating data from analysis sets have been reformulated using categories and subcategories of the PDMP, as per new process • Section 6: Figure 4 has been re-made to add one arrow that goes from the right column to the left column • Subsection 10.1.3.14: Counting rules to address ambiguities in e-diary-recorded solicited administration site adverse events have been better detailed	Amendment 4: 22 March 2022

2. OBJECTIVES/ENDPOINTS

Objectives	Endpoints
Phase I – Safety lead-in, Dose escalation	
Primary	
To evaluate the safety and reactogenicity of the 2 formulations (CCI of the CCI vaccine.	• The frequencies and percentages of participants with solicited administration site and systemic events during the 7 days (including the day of vaccination) following each vaccination at Day 1 and Day 31 in all groups. • The frequencies and percentages of participants with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, and AESIs) during the 30 days (including the day of vaccination) following each vaccination at Day 1 and Day 31 in all groups. • The frequencies and percentages of participants with SAEs, AEs leading to withdrawal and AESIs throughout the study period in all groups (Day 1 through Day 211). • The frequencies and percentages of participants with haematological and biochemical laboratory abnormalities, and changes from the baseline values, after the first vaccination at Day 8, in all groups.
Phase II – Formulation and Schedule-finding	
Primary	
To demonstrate the superiority of the effectiveness of the CCI vaccine (CCI) when administered at 0,2- or 0,6-months schedule, compared to the MenB vaccine administered at 0,6-months schedule*.	The percentages of samples with bactericidal serum activity using enc-hSBA against a panel of 110 randomly selected endemic US *N. meningitidis* serogroup B invasive disease strains at 1 month after the last vaccination (Day 211, Month 7) in all groups.
To demonstrate the immunological non-inferiority of the CCI vaccine (CCI) administered at 0,2- or 0,6-months schedule compared to the MenACWY vaccine (single dose)*;†.	The percentages of participants achieving a 4-fold rise** in hSBA titres against serogroups A, C, W and Y at 1 month after the • last CCI vaccination (Day 211, Month 7) for the ABCWY groups and, • MenACWY vaccination (Day 31, Month 1) in the Control group, relative to Day 1, Month 0 in CCI and Control groups and relative to 3 months pre-first CCI vaccination (Day 31, Month 1) in CCI groups.

Objectives	Endpoints
To evaluate the safety and reactogenicity of the CCI vaccine (CCI), the MenB vaccine and the MenACWY vaccine.	• The frequencies and percentages of participants with solicited administration site and systemic events during the 7 days (including the day of vaccination) following each vaccination at: – Day 1, Day 121 and Day 181 in the CCI groups, and – Day 1 and Day 181 in the Control group • The frequencies and percentages of participants with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, and AESIs) during the 30 days (including the day of vaccination) following each vaccination at: – Day 1, Day 121 and Day 181 in the CCI groups, and – Day 1 and Day 181 in the Control group. • The frequencies and percentages of participants with SAEs, AEs leading to withdrawal and AESIs throughout the study period in all groups (Day 1 through Day 541).
Phase II –Sourcing	
Primary	
To evaluate the safety and reactogenicity of the 2 formulations (CCI) of the CCI vaccine.	• The frequencies and percentages of participants with solicited administration site and systemic events during the 7 days (including the day of vaccination) following each vaccination at: – at Day 1 and Day 31 in CCI *groups,* – *at Day 1 and Day 61 in* CCI *groups, and* – *at Day 1 and Day 181 in* CCI *groups.* • The frequencies and percentages of participants with any unsolicited AEs (including all SAEs, AEs leading to withdrawal, and AESIs) during the 30 days (including the day of vaccination) following each vaccination at: – at Day 1 and Day 31 CCI *groups,* – *at Day 1 and Day 61 in* CCI *groups, and* – *at Day 1 and Day 181 in* CCI *groups.*

Objectives	Endpoints
	• The frequencies and percentages of participants with SAEs, AEs leading to withdrawal and AESIs throughout the study period: – *Day 1 through Day 211 in* CCI *groups,* – *Day 1 through Day 241 in* CCI *groups, and* – *Day 1 through Day 361 in* CCI *groups*
Phase II – Formulation and Schedule-finding	
Secondary	
To describe the distribution of participants by percentages of serogroup B invasive disease strains killed using enc-hSBA at 1 month after the last vaccination of the CCI vaccine (CCI) administered at 0,2 and 0,6-months schedule and of the MenB vaccine administered at 0,6-months schedule.	The percentages of serogroup B invasive disease strains killed using enc-hSBA in each participant sample at 1 month after the last vaccination (Day 211, Month 7) in all groups.
To assess the immune response to the CCI vaccine (CCI) administered at 0,2 and 0,6-months schedule and to the MenB vaccine administered at 0,6-months schedule against serogroup B indicator strains.	• The percentages of participants with hSBA titres ≥LLOQ for each and all serogroup B indicator strains at: – Day 1, Month 0 in CCI and Control groups, – 3 months pre-first CCI vaccination (Day 31, Month 1) in CCI groups and, – 1 month after the last vaccination (Day 211, Month 7) for all study groups. • The percentages of participants with 4-fold rise in hSBA titres** at 1 month after the last vaccination for all study groups (Day 211, Month 7), relative to: – Day 1, Month 0 for CCI and Control groups and, – 3 months pre-first CCI vaccination (Day 31, Month 1) for CCI groups. • hSBA GMTs against serogroup B indicator strains at: – Day 1, Month 0 in CCI and Control groups, – 3 months pre-first CCI vaccination (Day 31, Month 1) in CCI groups and, – 1 month after the last vaccination (Day 211, Month 7) for all study groups. • hSBA GMRs against serogroup B indicator strains at 1 month after the last vaccination (Day 211, Month 7) for all study groups relative to:

Objectives	Endpoints
	– Day 1, Month 0 for CCI and Control groups and – 3 months pre-first CCI vaccination (Day 31, Month 1) for CCI groups.
To assess the immune response to the CCI vaccine (CCI) administered at 0,2 and 0,6-months schedule and to the MenACWY vaccine (single dose) against serogroups A, C, W and Y.	• The percentages of participants with hSBA titres ≥LLOQ for serogroups A, C, W and Y at: – Day 1, Month 0 in CCI and Control groups, – 3 months pre-first CCI vaccination (Day 31, Month 1) in CCI groups, – 1 month after the first CCI vaccination (Day 31, Month 1) in the CCI groups, – 1 month after the last CCI vaccination (Day 211, Month 7) for all ABCWY groups and, – 1 month after the MenACWY vaccination in the Control group (Day 31, Month 1). • The percentages of participants with 4-fold rise in hSBA titres** for serogroups A, C, W and Y at 1 month after the first CCI vaccination (Day 31, Month 1) relative to Day 1, Month 0 for CCI groups. • hSBA GMTs against serogroups A, C, W and Y at: – Day 1, Month 0 in CCI and Control group, – 3 months pre-first CCI vaccination (Day 31, Month 1) in CCI groups, – 1 month after the first CCI vaccination (Day 31, Month 1) in the CCI groups, – 1 month after the last CCI vaccination (Day 211, Month 7) for all ABCWY groups and, – 1 month after the MenACWY vaccination in the Control group (Day 31, Month 1). • hSBA GMRs against serogroups A, C, W and Y at 1 month after: – the first CCI vaccination (Day 31, Month 1) in the CCI groups, – the last CCI vaccination (Day 211, Month 7) for all ABCWY groups and – the MenACWY vaccination in the Control group (Day 31, Month 1),

Objectives	Endpoints
	relative to Day 1, Month 0 for CCI and Control groups and 3 months pre-first CCI vaccination (Day 31, Month 1) for CCI groups. • The total IgG as measured by ELISA GMCs against serogroups A, C, W and Y at: – Day 1, Month 0 in CCI and Control groups, – 3 months pre- first CCI vaccination (Day 31, Month 1) in CCI groups, – 1 month after the first CCI vaccination in the CCI groups and after the MenACWY vaccination in the Control group (Day 31, Month 1) and, – 1 month after the last CCI vaccination (Day 211, Month 7) for all ABCWY groups.
CCI	

CCI

Abbreviations: AE, Adverse event; SAE, Serious adverse event; AESI, Adverse event of special interest; ELISA, enzyme-linked immunosorbent assay; GMC, geometric mean concentrations; enc-hSBA, endogenous complement human serum bactericidal assay; GMT, geometric mean titre; GMR, geometric mean ratio; hSBA, human serum bactericidal assay; LOD, limit of detection; LLOQ, lower limit of quantitation.
Note 1: MenB immune response will be assessed against *N. meningitidis* serogroup B indicator strains CCI

Note 2: Evaluation of the tertiary objectives may or not be performed. If the tertiary objectives are evaluated, it may be assessed in a subset of participants using remaining serum after the primary and secondary analyses have been completed; no additional blood samples will be collected from participants.
*All statistical criterion linked to evaluation of the objectives can be found in Section 9.4 in the protocol.
**For the serogroup A C, W, Y and serogroup B evaluations, the 4-fold rise (for serogroup B - per each indicator strain) is defined in section 10.1.3.10.
† The primary objective of immunological non-inferiority of the CCI vaccine to MenACWY will be evaluated only in participants without a previous MenACWY vaccination (unprimed). All other primary and secondary objectives will be evaluated in participants with and without previous MenACWY vaccination (primed and unprimed).
CCI

3. STUDY DESIGN

3.1. Overall design

This is a seamless Phase I/II multi-country, self-contained study comprising of 2 phases, in order to ensure the safety of participants.

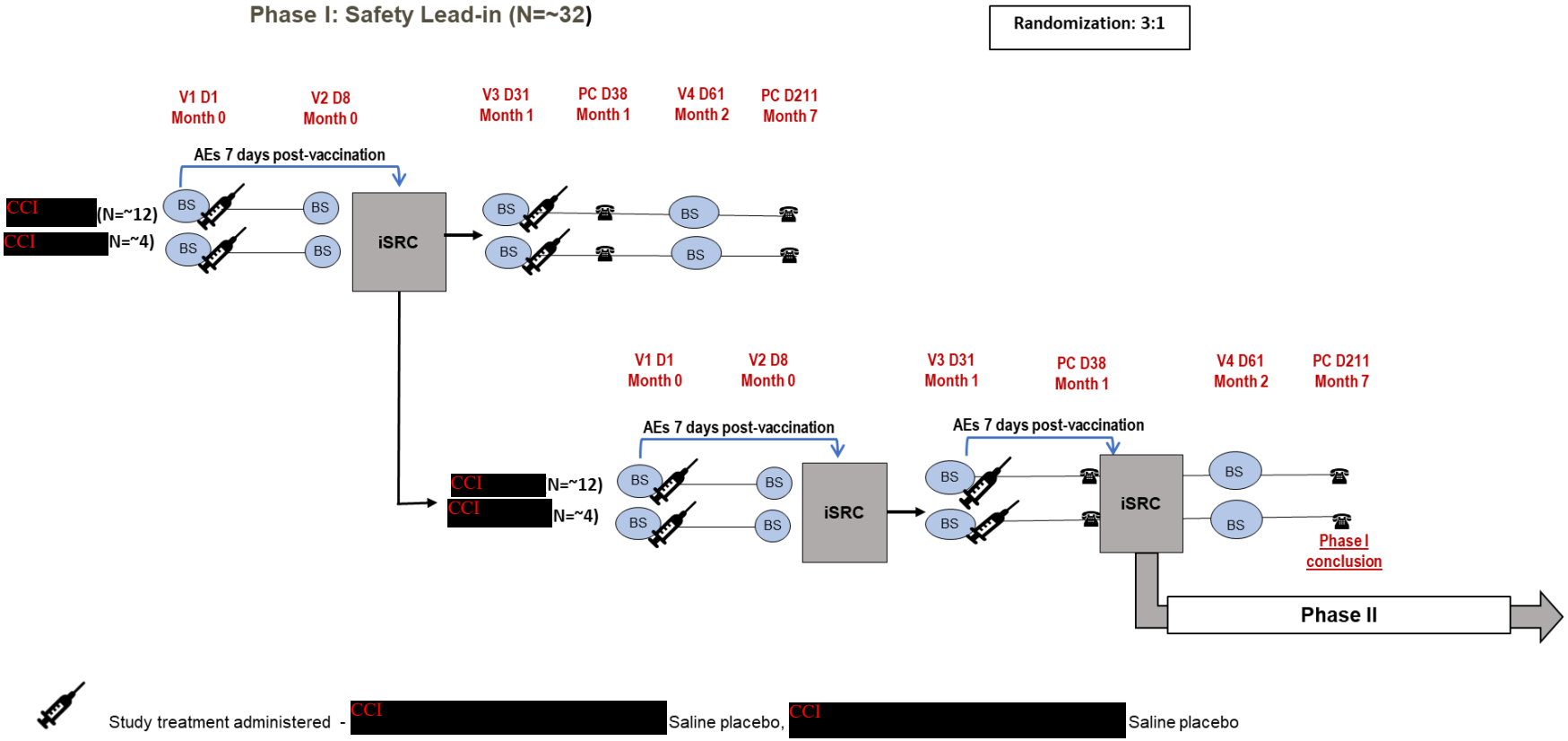
3.1.1. Phase I study design

The Phase I safety lead-in will include 4 study groups (randomised 3:1), with a staggered enrolment (16 participants initially followed by 16 participants later) of a total of 32 participants (Figure 1).

- CCI : Participants will receive the CCI vaccine in a 0,1-month schedule.
- CCI Participants will receive a saline placebo in a 0,1-month schedule, as control group for CCI .
- CCI Participants will receive the CCI vaccine in a 0,1-month schedule.
- CCI Participants will receive a saline placebo in a 0,1-month schedule, as control group for CCI

For more detailed information on study groups and treatments administered, refer to Table 1.

Figure 1 Study design overview – Phase I (Safety Lead-in)



Abbreviation: N, number of participants; V, clinic visit; D, day; iSRC, internal safety review committee; PC, phone contact; BS, blood sample.
Note 1: This figure represents the main aspects of the study design. Refer to protocol Table 1 Schedule of activities, for details on all visits and contacts
Note 2: Refer to protocol Section 8 for information on study procedures during special circumstances.

Table 1 Study groups, intervention and blinding – Phase I

Study groups	Number of participants	Age (Min-Max)	Study intervention(s)	Blinding
CCI	12	18-40 years	CCI	Observer-blinded
	12	18-40 years		
	4	18-40 years	NaCl	
	4	18-40 years	NaCl	

Duration of the Phase I of the study: The intended duration of the Phase I of the study, per participant is approximately 7 months.

Data collection: Standardised Electronic Case Report Form (eCRF). Solicited events will be collected using a participant diary (electronic Diary [eDiary]).

Sampling schedule for Phase I of the study:

- Blood sample: An overall blood volume of ***approximately*** 240 mL per participant will be collected over the course of the Phase I part of the study, 80 mL at Visit 1 (Day 1), Visit 3 (Day 31) and Visit 4 (Day 61). An additional 7 mL of blood will be collected at Visit V1 and Visit V2 from all participants for the safety laboratory evaluation.
- Urine sample: Urine samples for pregnancy testing will be collected from female participants of childbearing potential at Visit 1 (Day 1) and Visit 3 (Day 31) prior to the study intervention.

3.1.2. Phase II study design

Phase II will start only after a positive outcome from the iSRC review of the safety data from participants receiving both vaccinations of the higher-dosage vaccine formulation in Phase I of the study. Phase II will be conducted in 2 parts: Formulation and Schedule-finding and Blood sourcing with enrolment commencing parallelly to both these parts.

3.1.2.1. Phase II: Formulation and Schedule-finding

Phase II (Formulation and Schedule-finding) will include 5 study groups, with a staggered enrolment (45 participants for safety lead-in and 955 participants thereafter) of a total of 1000 participants (Figure 2):

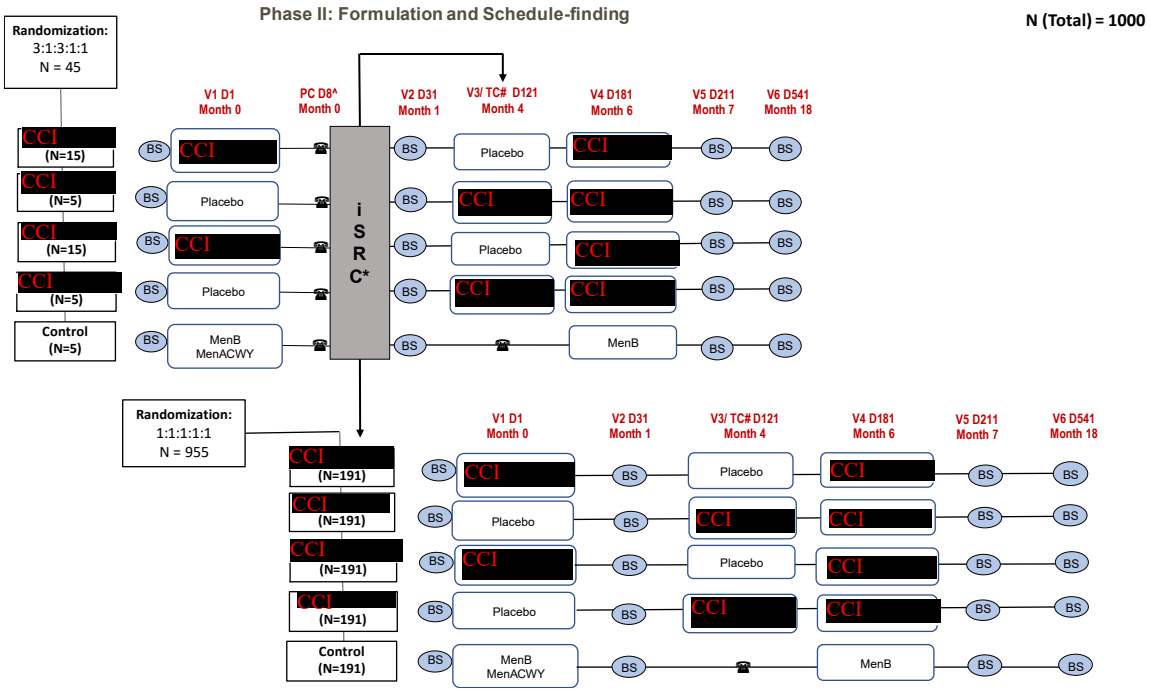
- CCI: Participants will receive 2 vaccinations of the CCI vaccine in a (0,6-months) schedule.
- CCI: Participants will receive 2 vaccinations of the CCI vaccine in a (0,2-months) schedule.
- CCI: Participants will receive 2 vaccinations of the CCI vaccine in a (0,6-months) schedule.
- CCI Participants will receive 2 vaccinations of the CCI vaccine in a (0,2-months) schedule.

The above 4 groups will also receive 1 injection of placebo, according to the schedule described in Figure 2.

- **Control**: Participants will receive 2 vaccinations of MenB vaccine (*Bexsero*) in a (0,6-months) schedule and a single vaccination of MenACWY vaccine (*Menveo*).

For more detailed information on study groups and treatments administered, refer to Table 2.

Figure 2 Study design overview – Phase II (Formulation and Schedule-finding)



Abbreviation: N, number of participants; V, clinic visit; D, day; TC, Telephone contact for Control group only; iSRC, internal safety review committee; PC, phone contact; BS, blood sample.

^ The phone call at Day 8 is only for the first 45 participants (15 participants in CCI, 5 participants in CCI, 15 participants in CCI, 5 participants in CCI and 5 participants in the Control groups).

* The outcome of the iSRC will impact the next study intervention at Month 4. The Month 1 blood sampling will proceed as planned

Note 1: Blood draw at Visit 6 Month 18 will be used only for assessment of tertiary objectives.

Note 2: This figure represents the main aspects of the study design.

Note 3: The Phase II (Formulation and Schedule-finding) is partially blinded. Study conduct and data collection in groups CCI will be observer-blind while in group Control it will be open-label.

 # Day 121 Month 4 is a visit for CCI groups (Visit V3) and is a telephone call for Control group (TC)

Note 4: If local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g., home visits) for the collection of biological samples and/or study intervention administration (except for Visit V1 which will always be a clinic visit). These remote visits must be performed by qualified study staff/ HCPs. Refer to the SoA (protocol Table 3) for the timing of these visits. Details of how these visits will be conducted are outlined in the SPM. Refer to protocol Section 8 (decentralised study procedures) for details

Note 5: Refer to protocol Section 8 for information on study procedures during special circumstances

A total of 45 participants will be randomised with 3:1:3:1:1 ratio to the 5 groups (15 in the CCI, 5 in the CCI, 15 in the CCI, 5 in the CCI and 5 in the Control group). A "go-no go" decision will be taken by the iSRC based on safety and reactogenicity data from these participants (Section 8.2.2.1 in the protocol).

Table 2 Study groups, intervention and blinding – Phase II (Formulation and Schedule-finding)

Study groups	Number of participants	Age (Min-Max)	Study intervention(s)	Blinding
CCI	206	10 – 25 years	CCI NaCl	Observer-blinded
	196	10 – 25 years	CCI NaCl	
	206	10 – 25 years	CCI NaCl	
	196	10 – 25 years	CCI NaCl	
Control	196	10 – 25 years	MenACWY rMenB+OMV NZ	Open label

Duration of the Phase II (Formulation and Schedule-finding) of the study: The intended duration of the Phase II of the study, per participant is approximately 18 months.

Data collection: standardised eCRF. Solicited events will be collected using a participant diary (eDiary).

Sampling schedule for Phase II (Formulation and Schedule-finding) of the study:

- Blood sample: In order to provide the necessary serum volume for the bactericidal assays (enc-hSBA and/ or hSBA), an overall blood volume of ***approximately*** 90mL, per participant, will be collected over the course of the Phase II step of the study. Urine sample: Urine samples for pregnancy testing will be collected from female participants of childbearing potential at Visit 1 (Day 1), Visit 3 (Day 121) and Visit 4 (Day 181) prior to the vaccination in the ABCWY groups and at Visit 1 (Day 1) and Visit 4 (Day 181) prior to the vaccination in the Control group.

3.1.2.2. Phase II: Sourcing

The blood sourcing part of the Phase II study will include 2 groups (randomised 1:1), with a parallel enrolment of a total of 226* participants:

- CCI: Participants will receive 2 vaccinations of the CCI vaccine in a (0,1-month) schedule.
- CCI: Participants will receive 2 vaccinations of the CCI vaccine in a (0,1-month) schedule.

* At the time of the protocol amendment to which this document refers (Protocol amendment 4), enrolment to these 2 groups had been stopped. The total number of participants enrolled have been presented in Figure 3.

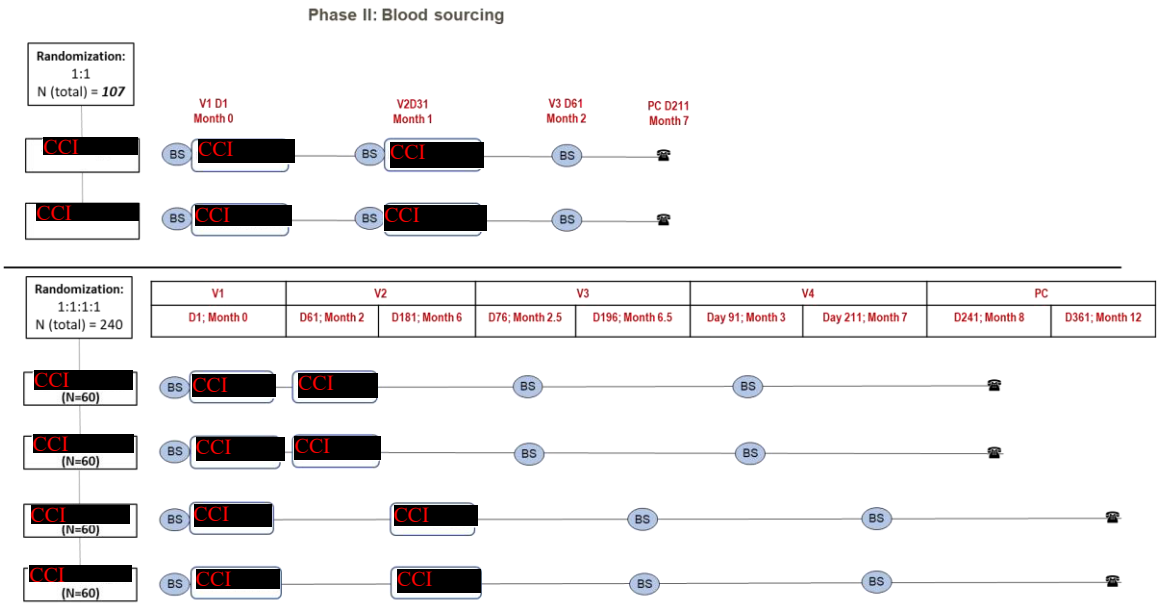
Additionally, the Phase II sourcing part will include 4 more groups (randomised 1:1:1:1), with a parallel enrolment of a total of 240 participants (Figure 3):

- CCI: Participants will receive 2 vaccinations of the CCI vaccine in a (0,2-month) schedule.
- CCI Participants will receive 2 vaccinations of the CCI vaccine in a (0,2-month) schedule.
- CCI Participants will receive 2 vaccinations of the CCI vaccine in a (0,6-month) schedule.
- CCI: Participants will receive 2 vaccinations of the CCI vaccine in a (0,6-month) schedule.

For more detailed information on study groups and treatments administered, refer to Table 3.

The schedule of activities in the Phase II (sourcing) is described in Table 5, Table 6 and Table 7 in the protocol.

Figure 3 Study design overview – Phase II (Sourcing)



Abbreviation: N, number of participants; V, clinic visit; D, day, PC, phone contact; BS, blood sample.
Note 1: This figure represents the main aspects of the study design. Refer to protocol Table 5, Table 6 and Table 7, Schedule of activities, for details on all visits and contacts
Note 2: If local regulations allow and quality of study procedures is maintained, participant(s) can be offered remote visits (e.g., home visits) for the collection of biological samples and/or study intervention administration (except for Visit V1 which will always be a clinic visit). These remote visits must be performed by qualified study staff/ HCPs. Refer to

the SoA (protocol Table 5, Table 6 and Table 7) for the timing of these visits. Details of how these visits will be conducted are outlined in the SPM. Refer to protocol Section 8 (decentralised study procedures) for details
Note 3: Refer to protocol Section 8 for information on study procedures during special circumstances.

Table 3 Study groups, intervention and blinding – Phase II (Sourcing)

Study groups	Number of participants	Age (Min-Max)	Study intervention(s)	Blinding
CCI	107	18-50 years	CCI	Observer-blinded*
	60			
	60			
	60			
	60			

* Due to the different vaccination schedules in Phase II Sourcing, the study will be observer blind only in terms of the vaccine formulations.

Duration of the Phase II (Sourcing) of the study: The intended duration of the Phase II (sourcing) of the study, per participant is:

- approximately 7 months for the CCI groups,
- approximately 8 months for the CCI groups, and,
- approximately 12 months for the CCI groups.

Data collection: Standardised Electronic Case Report Form (eCRF). Solicited events will be collected using a participant diary (electronic Diary [eDiary]).

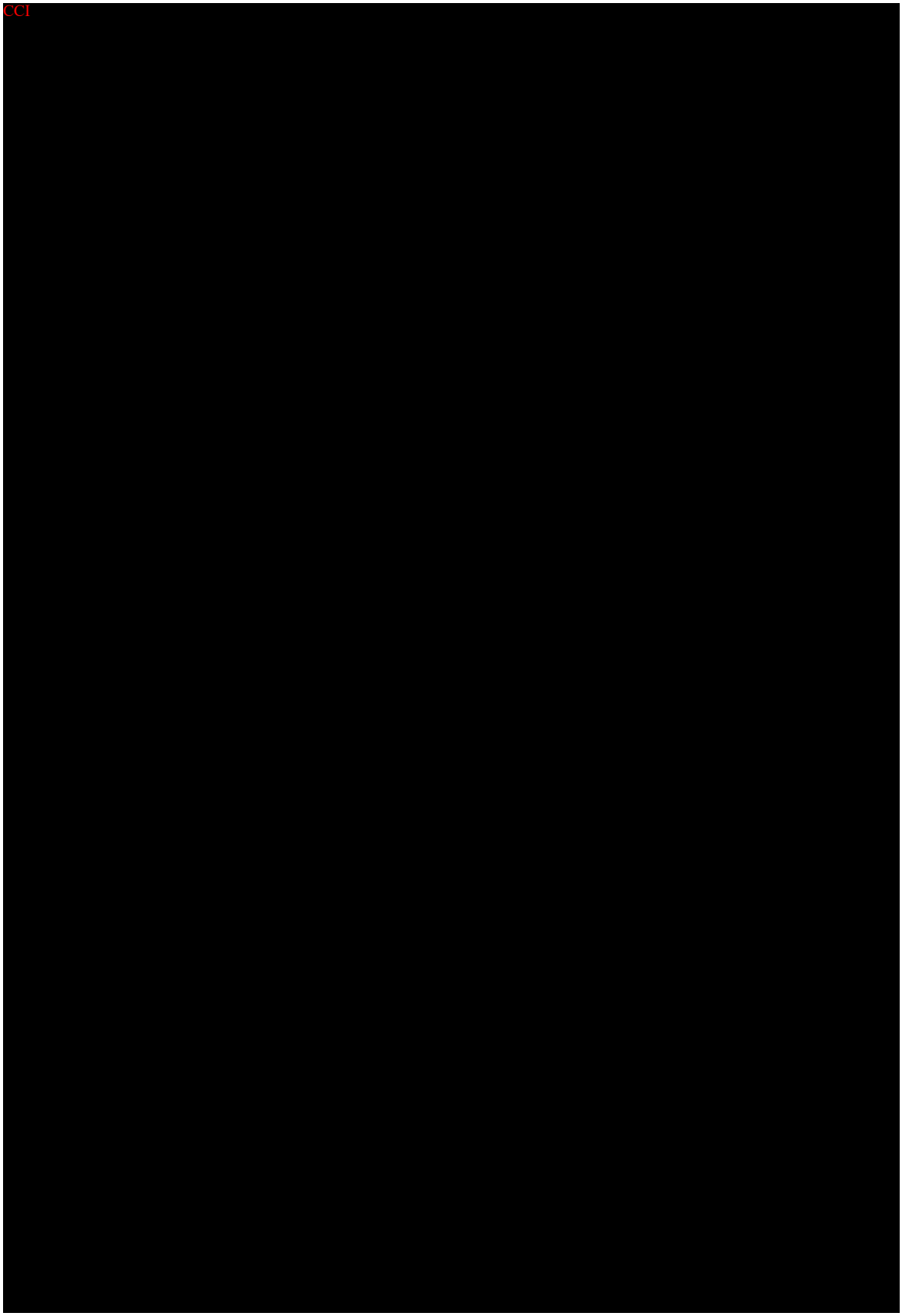
Sampling schedule for Phase II (Sourcing) of the study:

- Blood sample: An overall blood volume of ***approximately*** 285 mL per participant will be collected over the course of the Phase II, Sourcing part of the study. Urine sample: Urine samples for pregnancy testing will be collected from female participants of childbearing potential prior to the study intervention at the following timepoints:
  - at Visit 1 (Day 1) and Visit 2 (Day 31) for the CCI groups,
  - at Visit 1 (Day 1) and Visit 2 (Day 61) for the CCI groups, and,
  - at Visit 1 (Day 1) and Visit 2 (Day 181) for the CCI groups.

The **primary completion date** for the study is the Day 541, Month 18 timepoint in Phase II. Refer to Protocol Section 9.4.6 for the planned interim analysis.

4. ANALYSIS SETS

CCI



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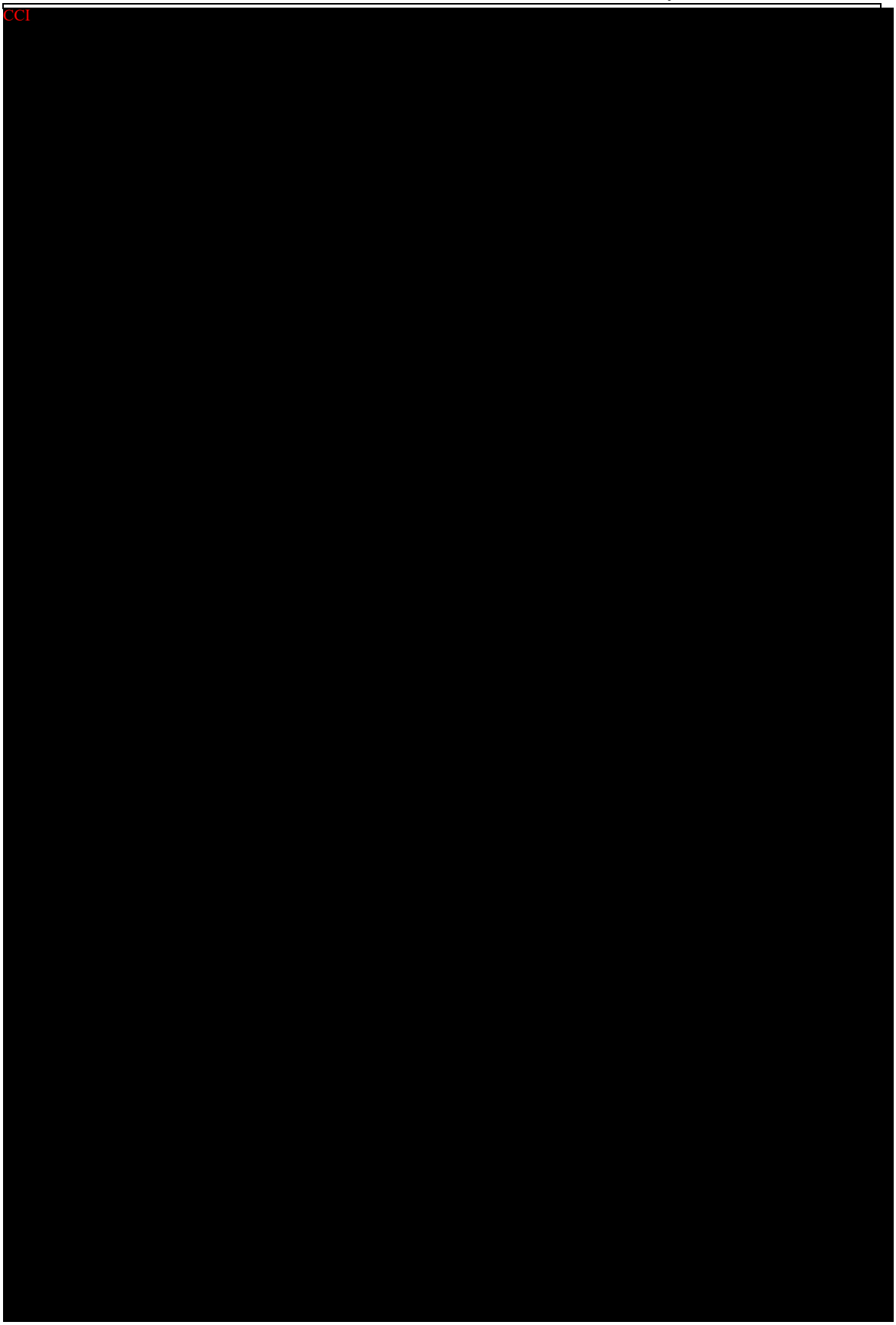

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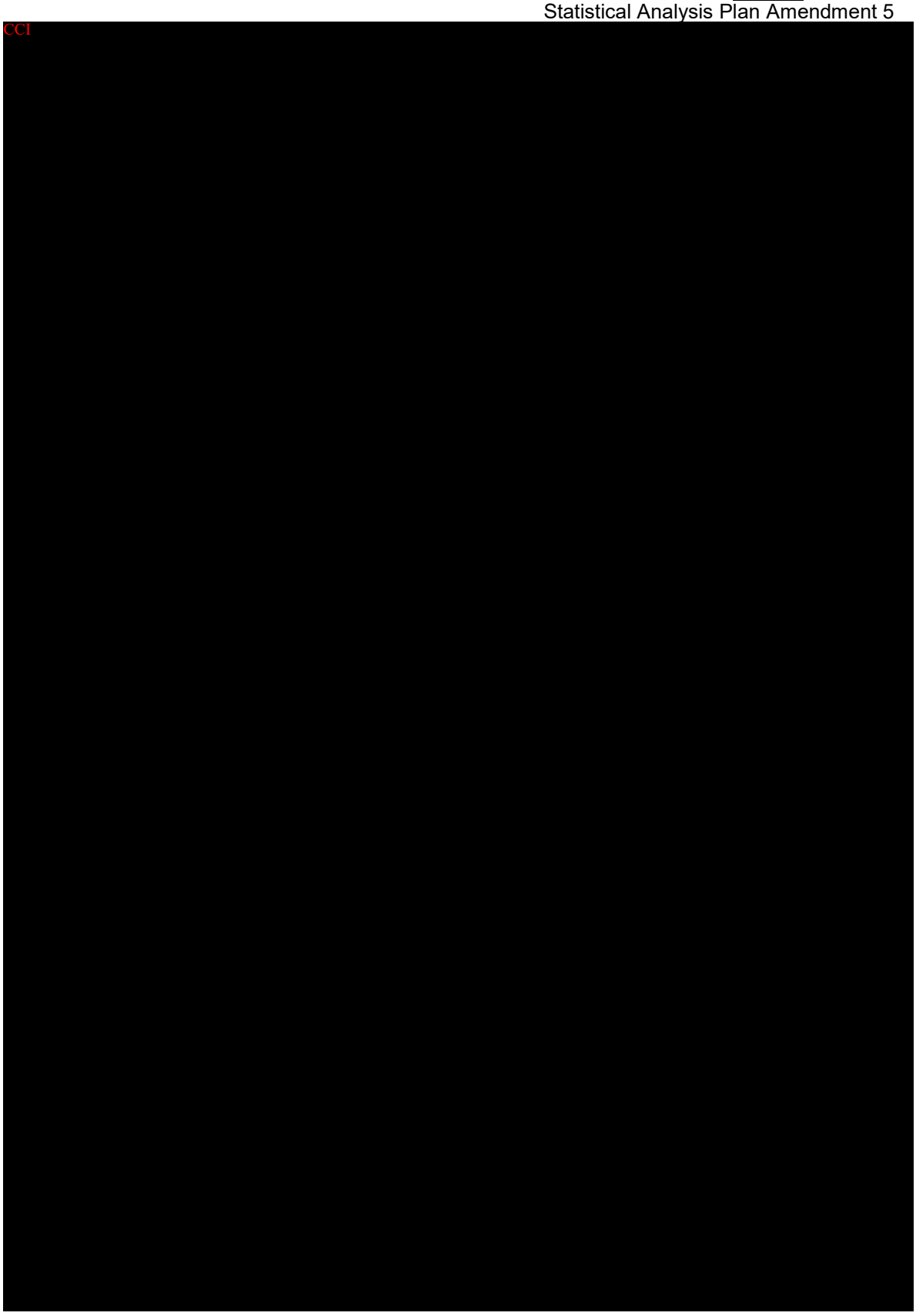
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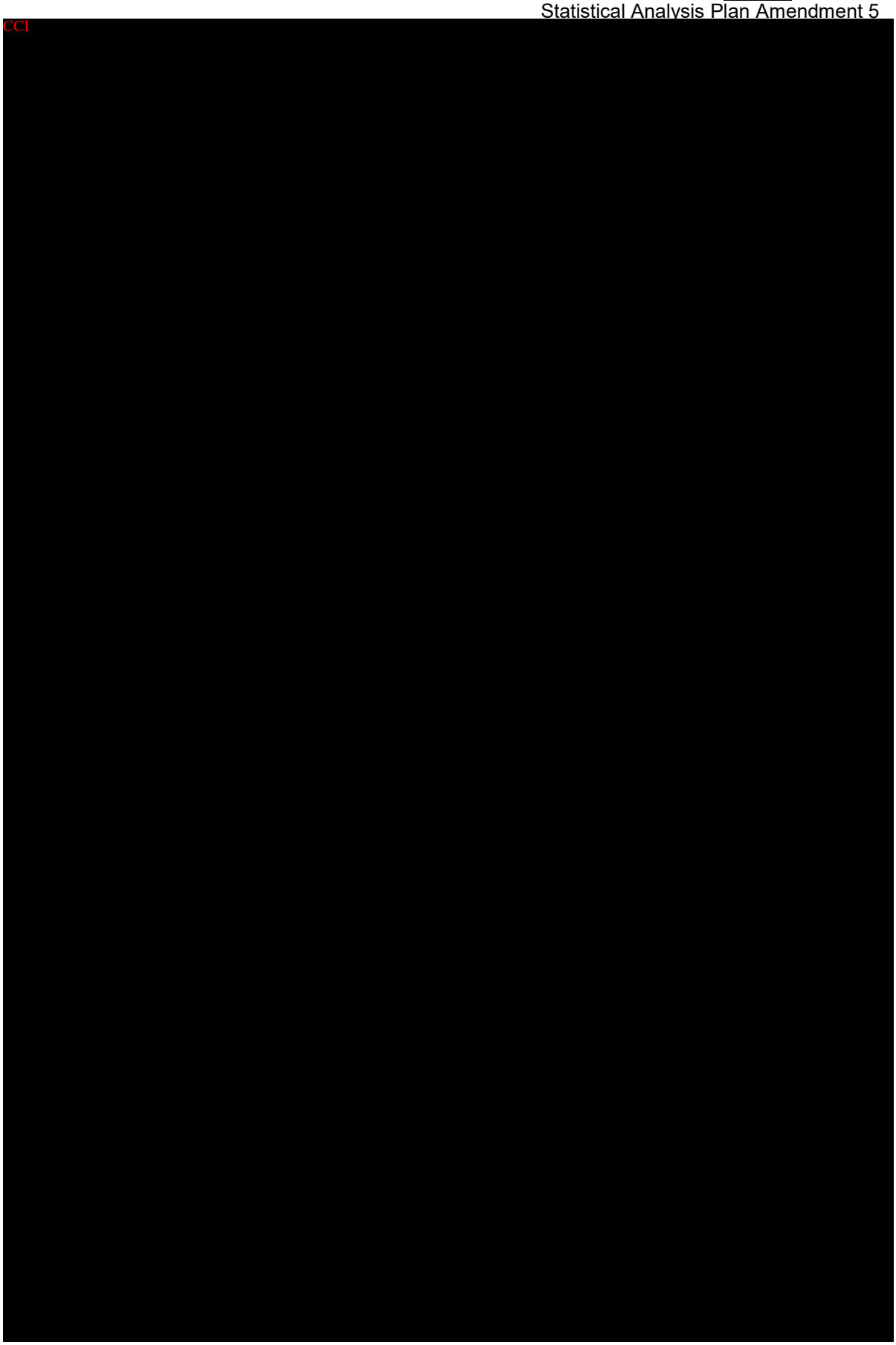

CCI

5. STATISTICAL ANALYSES

Standard data derivation rules and stat methods are described in section 10.1 while the study specific data derivation rules and stat methods are described in section 9.

5.1. Disposition of subjects

5.1.1. Analysis of disposition of subjects

Number of subjects enrolled, vaccinated subjects (at least 1 vaccination, full vaccination course), reason for early withdrawal, FAS, and PPS will be described by vaccine group.

5.2. Analysis of demography and baseline characteristics

5.2.1. Analysis planned in the protocol

Demography and baseline characteristics analysis are not described in the protocol.

5.2.2. Additional considerations

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height, weight, and body mass index (BMI) at enrolment will be calculated overall and by vaccine group.

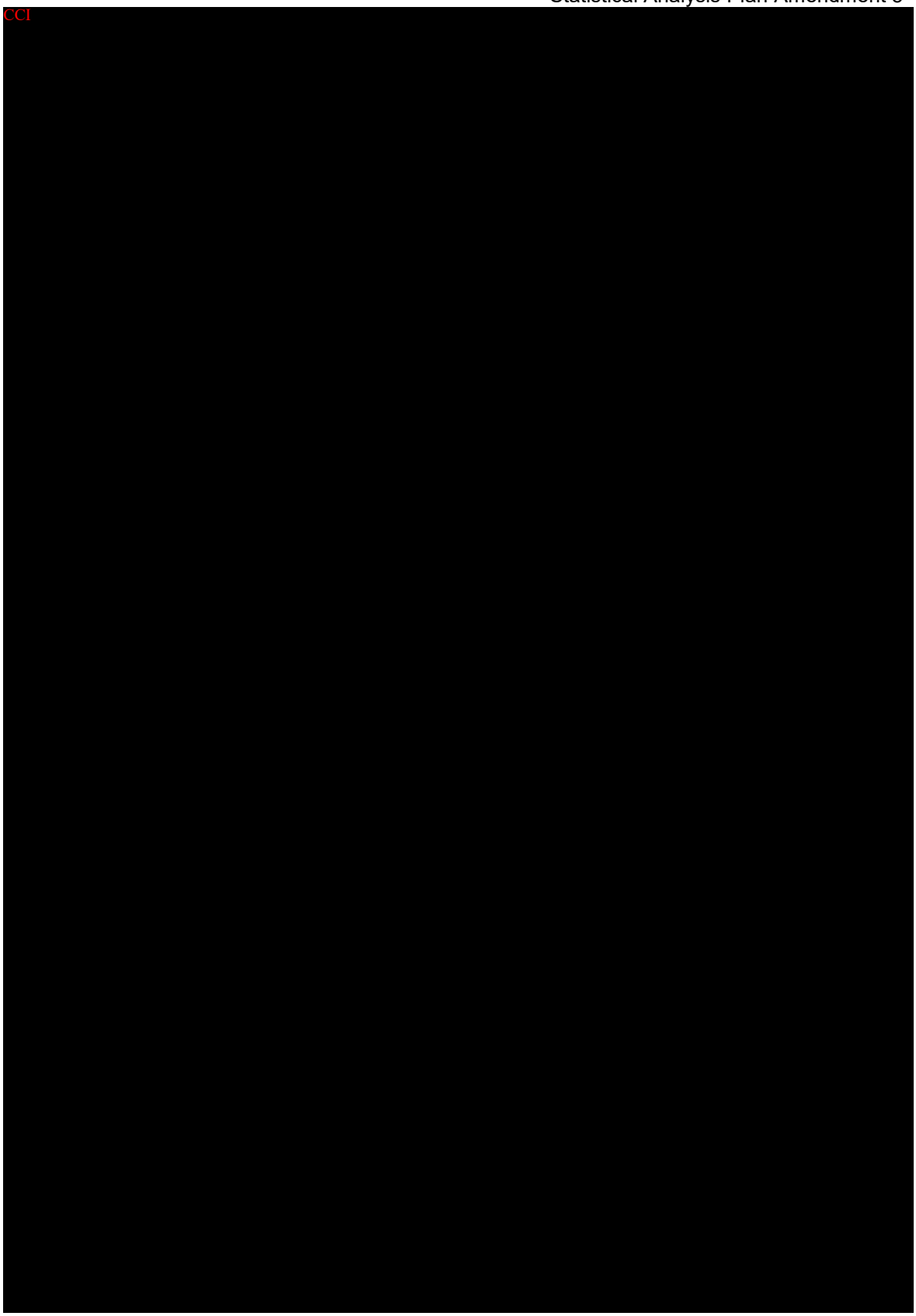
Distributions of subjects by sex, race, ethnic origin will be summarised overall and by vaccine group.

5.3. Primary endpoints

CCI

CCI

[redacted]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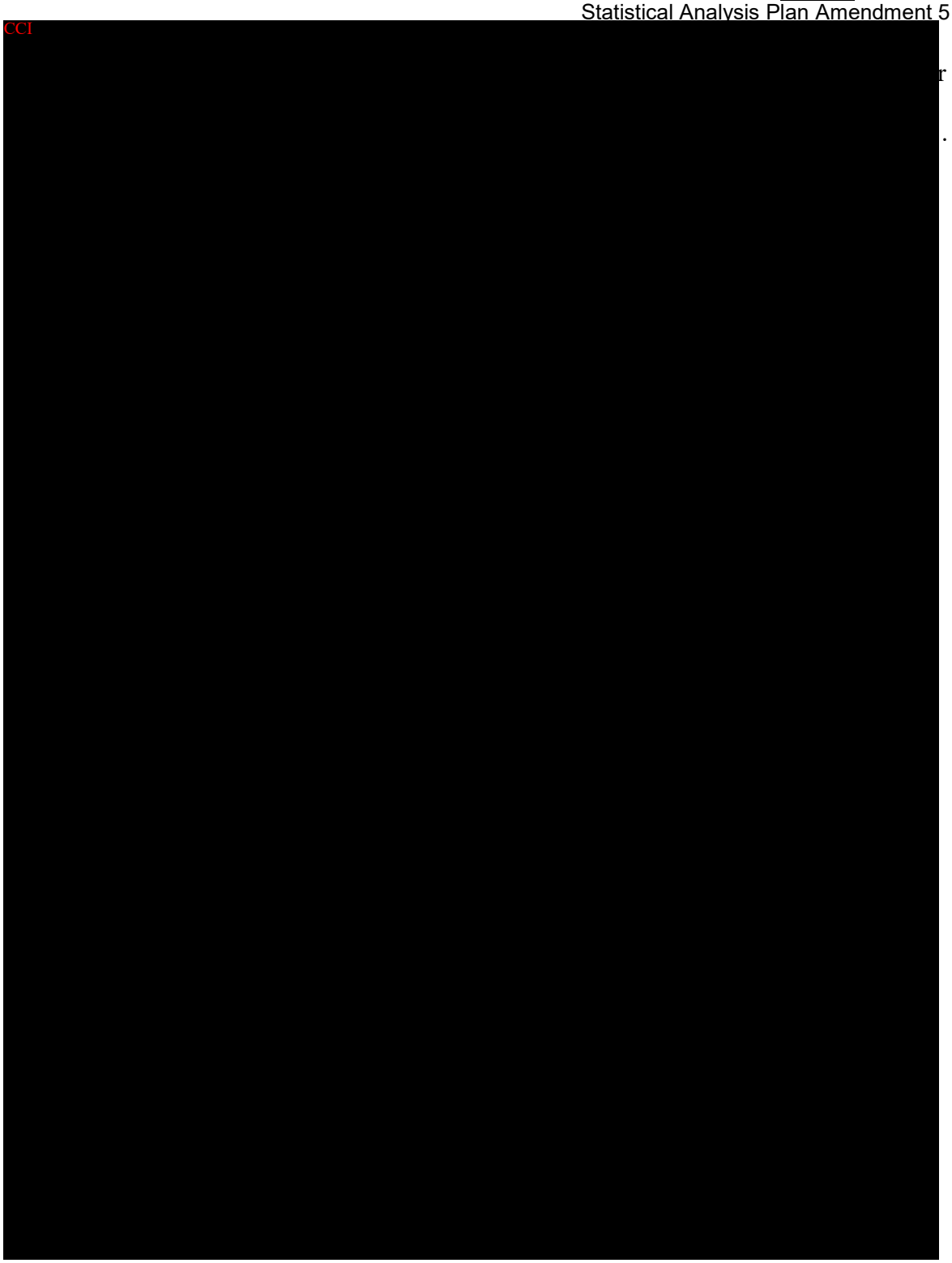


CCI

5.3.2. Additional considerations

NA

CCI

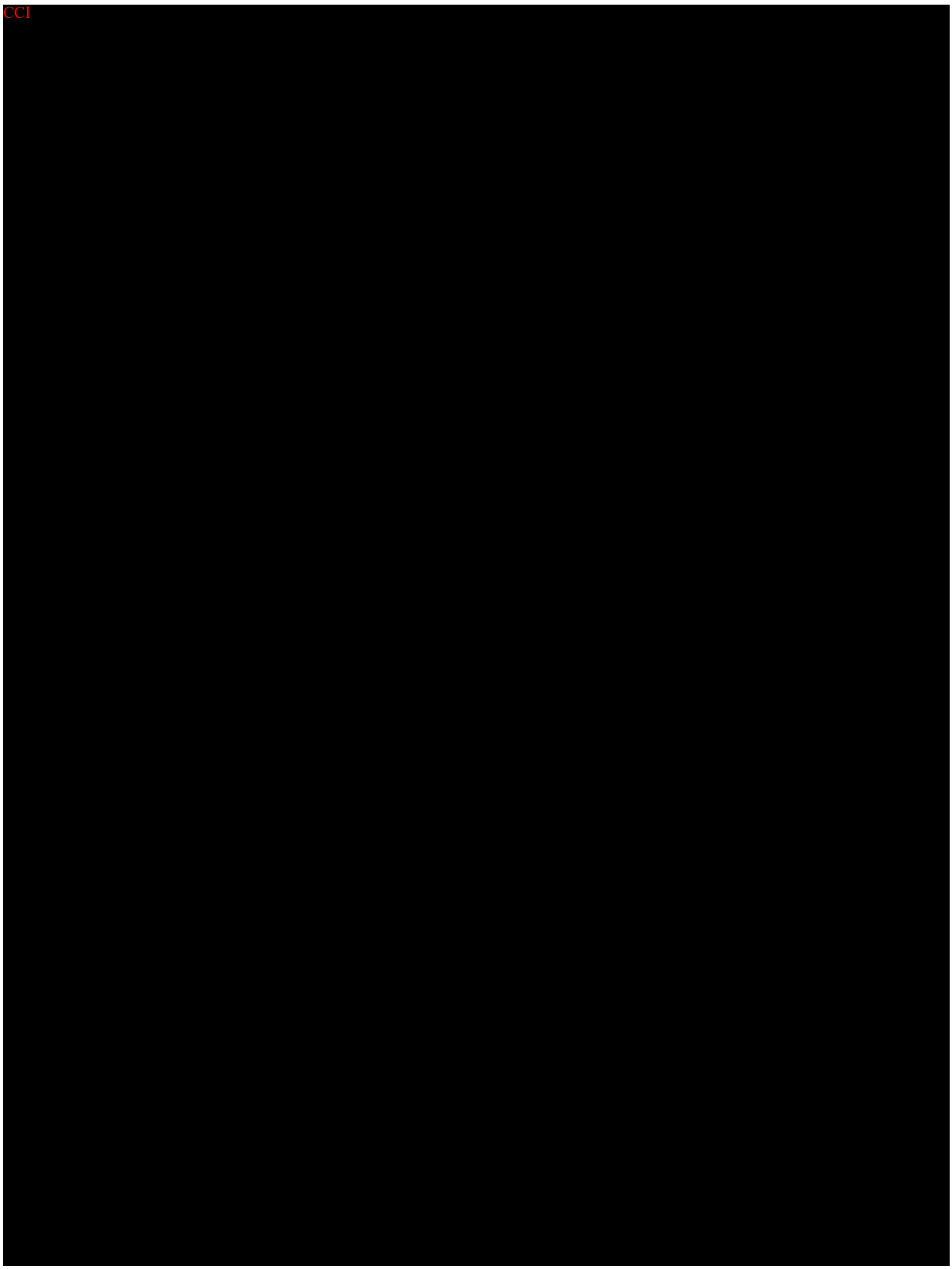
5.4. Secondary endpoints

5.4.1. Analysis planned in the protocol

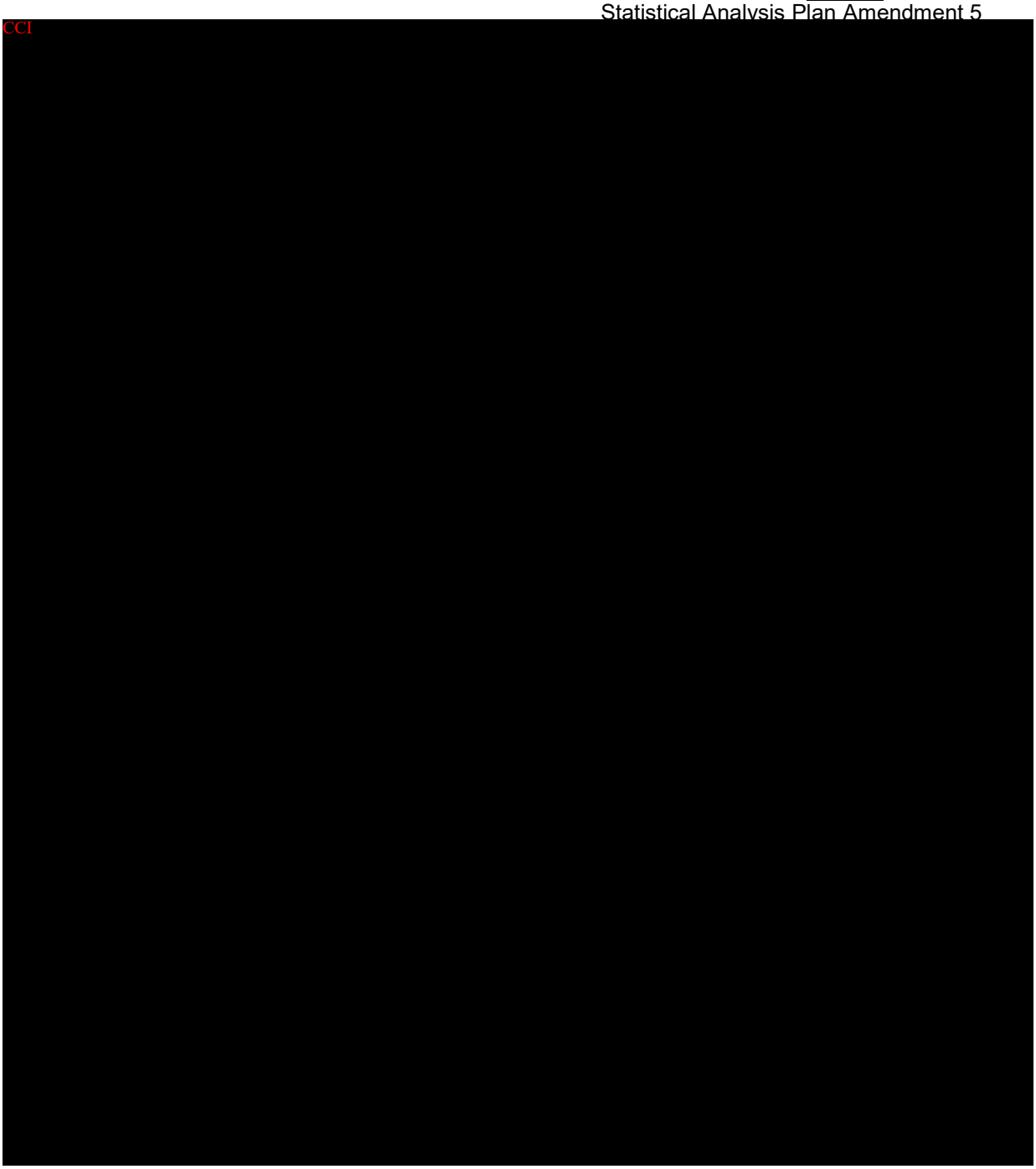
5.4.1.1. Phase I (Safety Lead-in)

NA

CCI



CCI



5.4.1.3. Phase II (Sourcing)

NA

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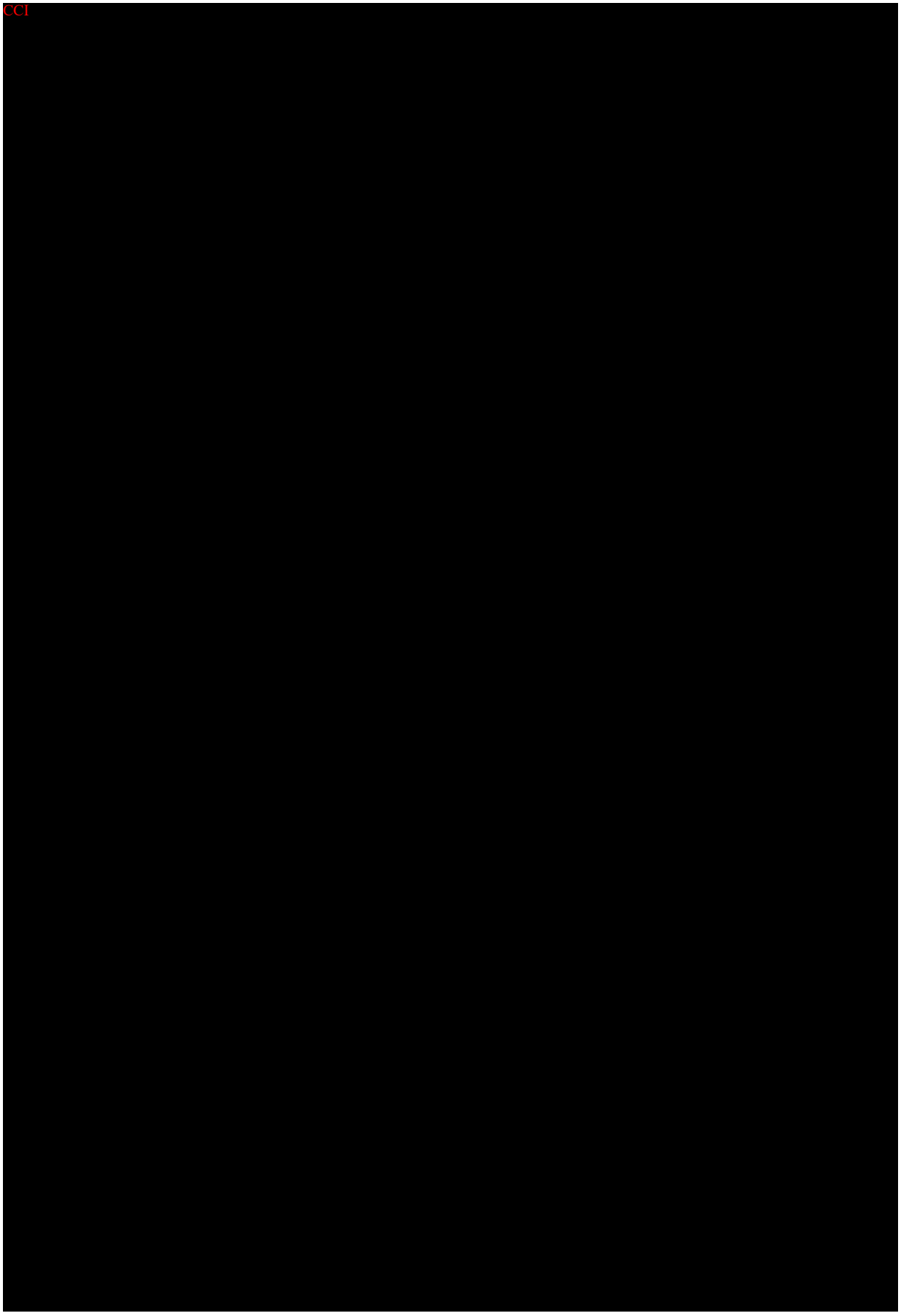

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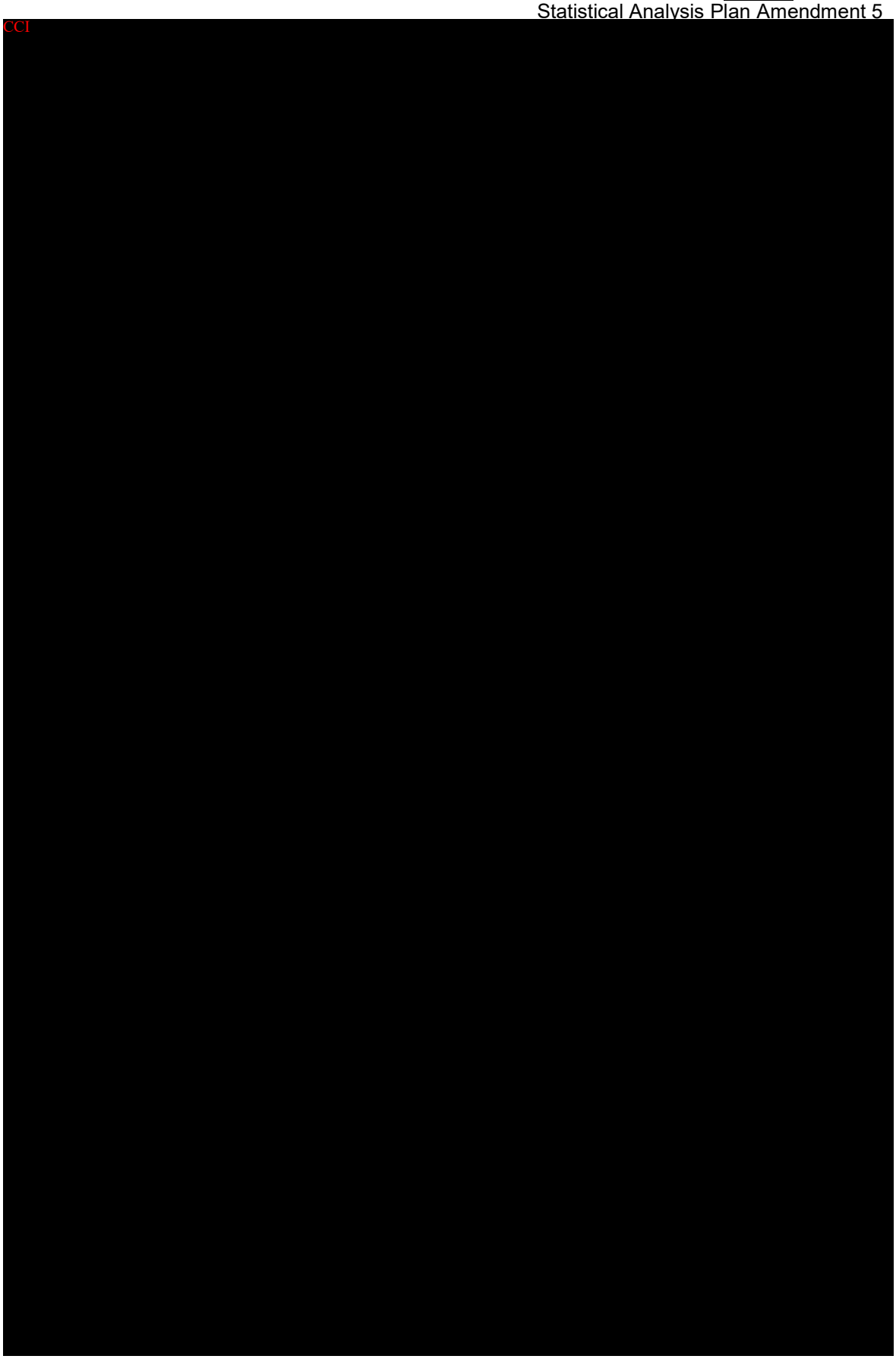

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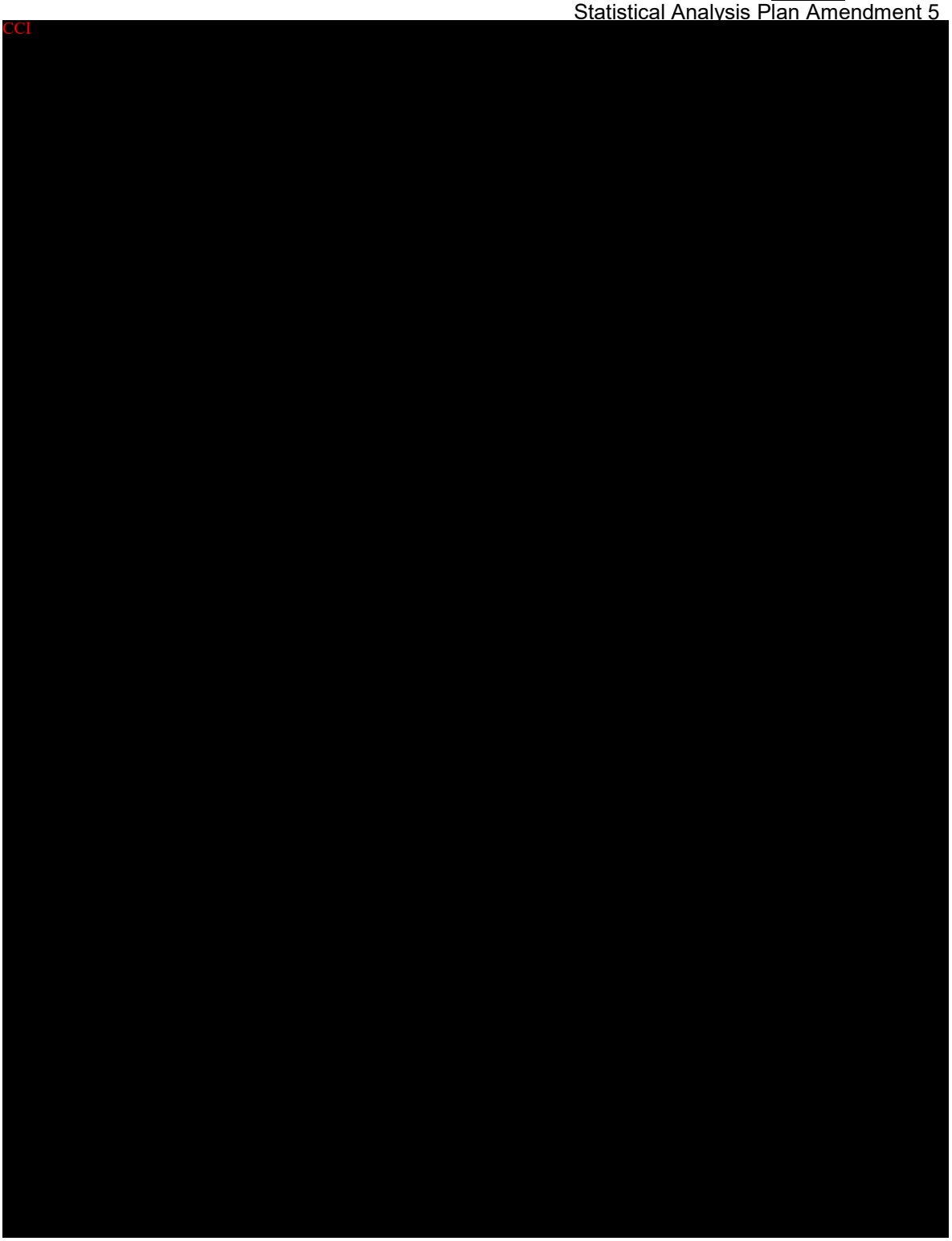

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9.1. Data derivation

NA

9.2. Statistical method

NA

9.2.1. Adjusted GMT ratios

NA

9.2.2. Vaccine efficacy

NA

10. ANNEXES

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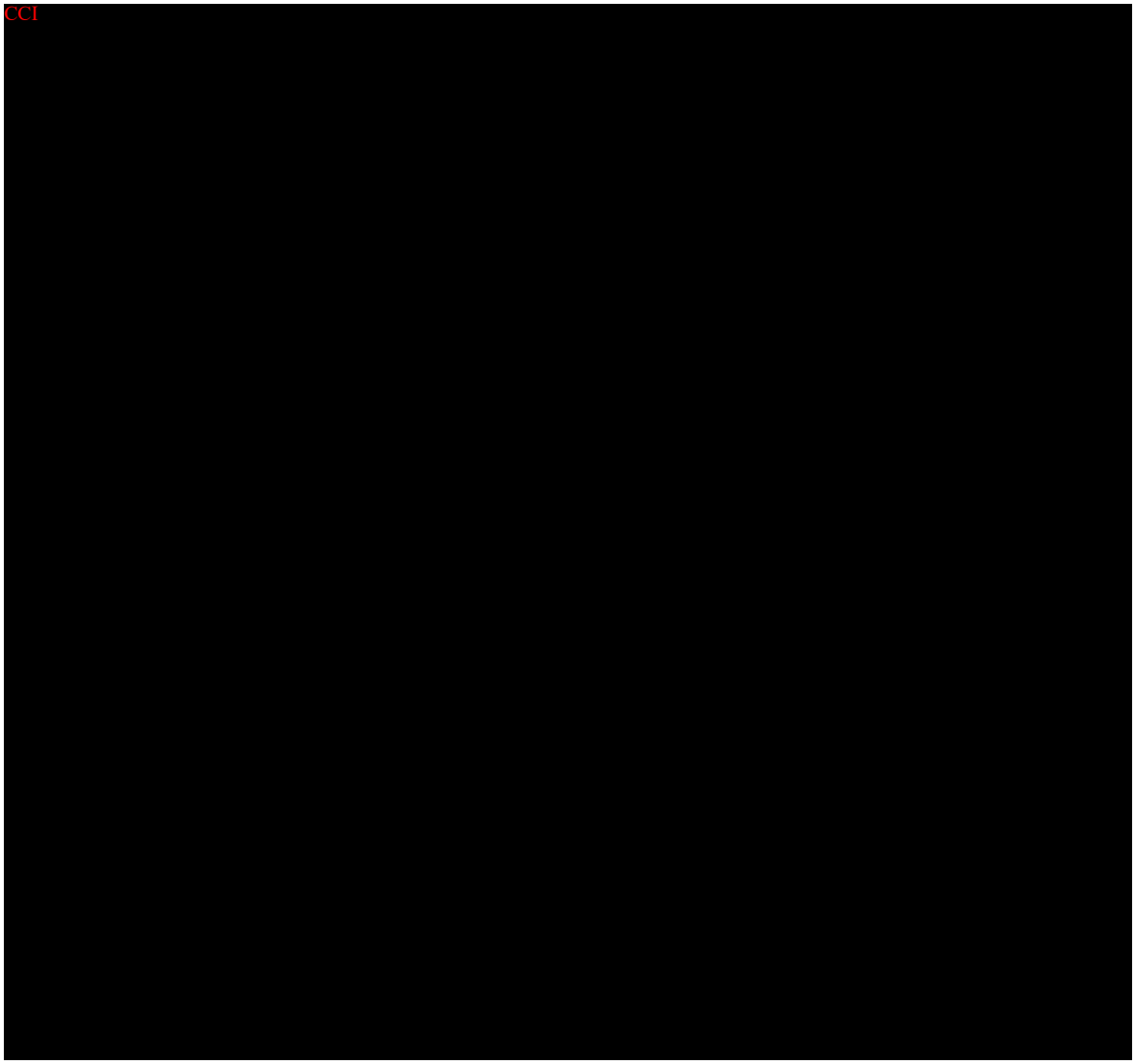

CCI

[redacted]

10.1.2.2. Laboratory data

Missing laboratory results (including immunological data) will not be replaced.

10.1.2.3. Daily recording of solicited events

10.1.2.3.1. Studies with electronic diaries

For studies using electronic diaries for the collection of solicited events, a solicited event will be considered present only when a daily recording of grade 1 or more is present.

10.1.2.4. Unsolicited adverse events

Unsolicited adverse event summaries are including serious adverse events unless specified otherwise.

Missing severity, relationship with study vaccine, and outcome of unsolicited adverse events will not be replaced and will appear as 'UNKNOWN' when displayed in a statistical output.

10.1.3. Data derivation

10.1.3.1. Age at first dose in days

When age at first dose is to be displayed in days, it will be calculated as:

Age = date of first dose minus date of birth

10.1.3.2. Age at first dose in months

When age at first dose is to be displayed in months, it will be calculated as the number of complete calendar months between the date of birth (DOB) and the date of first dose. For example:

DOB = 10JUN2017, Date of first dose = 09JUL2018 -> Age = 12 months

DOB = 10JUN2017, Date of first dose = 10JUL2018 -> Age = 13 months

10.1.3.3. Age at first dose in years

When age at first dose is to be displayed in years, it will be calculated as the number of complete calendar years between the date of birth and the date of first dose. For example:

DOB = 10SEP1983, Date of first dose = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of first dose = 10SEP2018 -> Age = 35 years

10.1.3.4. Weight

Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:

Weight in kilograms = Weight in pounds / 2.2

10.1.3.5. Height

Height will be presented in centimetres. Heights reported in feet and inches will be converted as follows:

Height in centimetres = Height in inches x 2.54

10.1.3.6. Body mass index (BMI)

BMI will be calculated as follows:

BMI = (Weight in kilograms) / (Height in meters)^2

10.1.3.7. Temperature

Temperatures will be presented in degrees Celsius (°C). Temperatures reported in degrees Fahrenheit (°F) will be converted as follows:

Temperature (Celsius) = ((Temperature (Fahrenheit) - 32) x 5)/9

10.1.3.8. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off, the following derivation rules apply:

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off	value
All other cases	missing

10.1.3.9. Geometric mean titres (GMTs) and concentrations (GMCs)

Geometric Mean Titre (GMT) or Concentration (GMC) calculations are performed by taking the inverse logarithm of the mean of the log titre or concentration transformations. Antibody titres or concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off of the assay for the purpose of GMT/GMC calculation. Cut-off values are defined by the laboratory before the analysis.

10.1.3.10. Calculation of the 4-fold rise

The 4-fold rise for serogroups A, C, W, Y and for serogroup B indicator strains is defined as:

- a post-vaccination hSBA titre ≥4 times the LOD or ≥LLOQ, whichever is greater, for subjects with a pre-vaccination hSBA titre <LOD,
- a post-vaccination hSBA titre ≥4 times the LLOQ for subjects with a pre-vaccination hSBA titre ≥LOD but <LLOQ, and
- a post-vaccination hSBA titre ≥4 times the pre-vaccination titre for subjects with a pre-vaccination hSBA titre ≥LLOQ.

The LOD and the LLOQ depend on the serogroup and the indicator strain, and are still under evaluation while this document is being amended.

10.1.3.11. Onset day

The onset day for an event (e.g., AE, concomitant medication/vaccination) is the number of days between the last study dose and the start date of the event. This is 1 for an event occurring on the same day as a study dose (and reported as starting after study dose).

10.1.3.12. Duration of events

The duration of an event with a start and end date will be the difference between the start and end date plus one day, i.e., an event that starts on 03MAR2018 and ends on 12MAR2018 has a duration of 10 days.

10.1.3.13. Counting rules for combining solicited and unsolicited adverse events

Unsolicited adverse events with missing administration site flag will be considered systemic.

Multiple events with the same preferred term which start on the same day are counted as only one occurrence.

10.1.3.14. Counting rules for occurrences of solicited events

When the occurrences of solicited events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs. In case of multiple reporting for the same solicited adverse event, the worst reported grade will be considered.

At visit 1 of Control group in Phase II F&SF two vaccines are injected, one in either arm. Therefore, administration site adverse events imputed during the first seven days after visit 1 must be related to a specific arm and vaccine. For subjects where, instead, it is not possible to uniquely associate one or more records of administration site adverse events to one of the two vaccines, then all the administration site events recorded by those subjects during the first seven days after vaccination will be excluded from the analysis. In this way, ambiguous records will not contribute to the denominator – nor to the numerator – when calculating frequencies and percentages of administration site adverse events at visit 1 of Control group. Systemic adverse events will still be reported as usual, as their records are never associated to a specific arm.

10.1.4. Display of decimals

10.1.4.1. Percentages

Percentages and their corresponding confidence limits will be displayed with:

- no decimals when there are fewer than 50 subjects in each tabulated group
- one decimal when there are at least 50 subjects in at least one tabulated group
  - Exceptions will be made for percentages that are not 0% or 100% but appear as 0% or 100% due to rounding. For these specific cases the number of decimals will be increased until the displayed value is no longer 0% or 100%. Examples are given in the following table.

n/N	Displayed percentage
10/45	22%
1/45	2%
10/55	18.2%
1/55	1.8%
1/300	0.3%
1/3000	0.03%
1/30000	0.003%
299/300	99.7%
2999/3000	99.97%
29999/30000	99.997%

- The display of additional decimals for values close to 0% or 100% will be applied only to point estimates and not confidence limits, which can be rounded and displayed as 0% or 100%.
- Values of exactly 0% or 100% will be presented with no decimals regardless of the number of subjects per tabulated group.

10.1.4.2. Differences in percentages

Differences in percentages and their corresponding confidence limits will be displayed with one more decimal than the maximum number used to display the individual percentages, for example the difference between two percentages displayed with one decimal will be displayed with two decimals.

10.1.4.3. Demographic/baseline characteristics statistics

The mean, median, and standard deviation for continuous baseline characteristics (height, weight, body mass index (BMI), pre-dose body temperature) will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

The maxima and minima of transformed height/weight variables will be displayed without decimals, with the exception of infant studies where one decimal will be displayed for the transformed weight.

The maximum and minimum of transformed body temperatures will be displayed with one decimal.

10.1.4.4. Serological summary statistics

The number of decimals used when displaying geometric mean titres (GMT) or concentrations (GMC) and their confidence limits is shown in the following table:

GMT or GMC value	Number of decimals to display
<0.1	3
>=0.1 and <10	2
>=10 and <1000	1
>=1000	0

When multiple categories of GMT or GMC values are present in the same table, the number of decimals displayed should match that of the smallest category (i.e., the one with the higher number of decimals). For example, if GMT or GMC values of <0.1 appear in the same table as values of >=0.1 and <10, 3 decimals should be displayed for both.

GMT or GMC group ratios and their confidence limits will be displayed with 2 decimals regardless of the actual values.

CCI [redacted]

11. REFERENCES

CCI [redacted]