NOVARTIS

Clinical Development

INE963, KAE609, KLU156

CADPT13A12201/ NCT05750628

(PLATINUM): A multi-part, multi-center PLATform study to assess the efficacy, safety, tolerability and pharmacokinetics of anti-malarial agents administered as monotherapy and/or combination therapy IN patients with Uncomplicated *Plasmodium falciparum* Malaria

Statistical Analysis Plan (SAP)

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Date	Time point
04-Sep-2025	After DBL for Cohorts A1 & B2

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AE	Adverse event
ACPR	Adequate clinical and parasitological response
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BID	bis in diem/Twice a day
CRF	Case Report Form
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Data base lock
DMS	Document management system
eCRF	Electronic Case Report Form
ETF	Early treatment failure
FAS	Full Analysis Set
IA	Interim Analysis
LCF	Late clinical failure
LPF	Late parasitological failure
MedDRA	Medical Dictionary for Drug Regulatory Affairs
o.d.	Once Daily
PK	Pharmacokinetics
Qd	Qua'que di'e / once a day
RAS	Randomized analysis set
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Single dose
SDF	Single dose formulation
SoC	Standard of care
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study CADPT13A12201 that will be presented in the Clinical Study Report(s) (CSR). This version of the SAP is based on protocol version 03 released 20-Mar-2024.

The output shells accompanying this document can be found in the Tables, Figures and Listings (TFL) shells document.

All changes to the planned analysis described in this document required before or after database lock will be made through an amendment or addendum, respectively.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

The analysis will be performed by Novartis and carried out using SAS, Version 9.4 or higher.

1.1 Study design

This is a Phase 2, multi-part, multi-center, open-label platform study including CCI [redacted] This platform design allows the potential to investigate multiple therapies in the context of a single disease. Each anti-malarial agent entered in the trial at a given time will follow the same design as outlined in Parts A, B, and C. More than one Part A, Part B, and Part C cohort can be conducted at the same time. In addition, Part A, Part B, and Part C cohorts can be conducted at the same time.

CCI [redacted]

Part A is the open-label, randomized, multi-arm monotherapy part of this Phase 2 study evaluating a single oral administration of an anti-malarial agent at 3 parallel dose levels followed by optional adaptive sequential dose level(s).

Part B is the open-label, randomized, two-arm combination therapy part of this Phase 2 study evaluating a single oral dose of up to three anti-malarial agents as a loose combination vs. standard of care (SoC), Coartem in adult and adolescent patients.

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Part C is the open-label, randomized, two-arm combination therapy part of this Phase 2 study evaluating a single oral dose of up to three anti-malarial agents as a loose and/or fixed combination vs. SoC, Coartem, in children aged 2 to < 12 years.

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1.2 Study objectives, endpoints and estimands

The study objectives and endpoints are described in Table 1-1.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
CCI	
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
Part A:	
• CCI	• PCR-corrected and uncorrected adequate clinical and parasitological response (ACPR) at Day 29 (i.e., 28 days post-dose)
Parts B & C:	
• To assess the parasite clearance time (PCT) of oral combinations of anti-malarial agents versus the standard of care (SoC) in patients with uncomplicated *P. falciparum* malaria	• Parasite clearance time (hours) up to Day 7
• CCI	• CCI
Parts A, B, & C:	
• To characterize PK of each anti-malarial agent administered orally as monotherapy [Part A]	• PK parameters such as Cmax, Tmax, and wherever possible AUC0-t, AUClast, AUCinf, T1/2, Cl/F, V/F

Objective(s)	Endpoint(s)
and/or as combination therapy [Parts B and C] in patients with uncomplicated *P. falciparum* malaria	
• To assess the safety and tolerability of each anti-malarial agent administered orally as monotherapy [Part A] and/or as combination therapy versus SoC [Parts B and C] in patients with uncomplicated *P. falciparum* malaria	• Adverse events, vital signs, ECG findings, safety laboratory assessments including chemistry, hematology, and urinalysis results up through EOS
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI	

1.2.1 Primary estimand(s)

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CCI

1.2.2 Secondary estimand(s)

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- The key secondary estimand attributes in Part A are described as identical to the attributes in the primary estimand in Parts B and C, except in Part A:
  - **Population** is adults who receive an anti-malarial agent fully administered
  - CCI
  - **Summary measure** is PCR-corrected ACPR rate by treatment group.

CCI

- The key secondary estimand attributes in Parts B and C are described as identical to the attributes in the primary estimand in Part A, except in Parts B and C:
  - **Population** is adult or adolescent patients (Part B) and pediatric patients (Part C)
  - **Treatment of interest** is anti-malarial agent administered in combination with other antimalarial agents or SoC.

1.2.3 Other secondary estimand

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The other secondary estimand is described by the following attributes:

1. **Population**: Adult (Part A)/Adult or adolescent (Part B)/Pediatric (Part C) patients with acute uncomplicated *P. falciparum* malaria.

2. **Variable**: A binary outcome indicating the patient did not take concomitant medication with anti-malarial activity prior to Day 29 and has achieved uncorrected ACPR at Day 29.
3. **Treatment of interest**: anti-malarial agent administered as monotherapy (Part A)/in combination with other anti-malarial agents or SoC (Parts B and C) regardless of study discontinuation or non-compliance.
4. CCI [redacted]
5. **Summary measure**: Uncorrected ACPR rate by treatment group (Part A)/difference in proportion between the combination therapy and SoC (Parts B and C).

The estimand strategy for this estimand is a mixture of treatment policy (for discontinuation or non-compliance) and composite strategy (for non-study anti-malarial agents).

2 Statistical methods

2.1 Data analysis general information

Unless otherwise noted, by default all outputs will be presented by cohort (e.g. A1, B1, B2, C2) and treatment group within each cohort. Data from common treatment groups and/or doses may be pooled at a later time. ***In the following sections, "by cohort and treatment group" is thus removed as it applies to all outputs***.

2.1.1 General definitions

CCI [redacted]

The following treatment group names will be used in statistical analyses and outputs:

CCI [redacted]

Part B1: INE963+Cipargamin, Coartem

Parts B2 & C2: KLU156+Cipargamin, Coartem

Date of first administration of study treatment

The date of first administration of study treatment is defined as first date when a nonzero dose of study treatment is administered and recorded on the Dosage Administration Record eCRF. The date of first administration of study treatment is also referred to as ***start of study treatment***.

The date of last administration of study treatment is defined as last date when a nonzero dose of study treatment is administered and recorded on the dose administration eCRF.

Study day

Study day 1 for all assessments is taken to be the start of study treatment.

The study day for all assessments will be calculated as follows:

1. If date of assessment occurred on or after the start of study treatment, then
   Study day = Date of assessment - Start of study treatment + 1.
2. If date of assessment occurred before the start of study treatment, then
   Study day = Date of assessment - Start of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Baseline

For safety evaluations, the last available assessment on or before the start date of study treatment is taken as ‘‘baseline” assessment. In case time of assessment and time of treatment start is captured, the last available assessment before the treatment start date/time is used for baseline.

For safety parameters (e.g., ECGs), where the study requires multiple replicates per time point, the average of these measurements will be calculated (if not already available in the database) before determining baseline. The associated time will be the time of the last replicate.

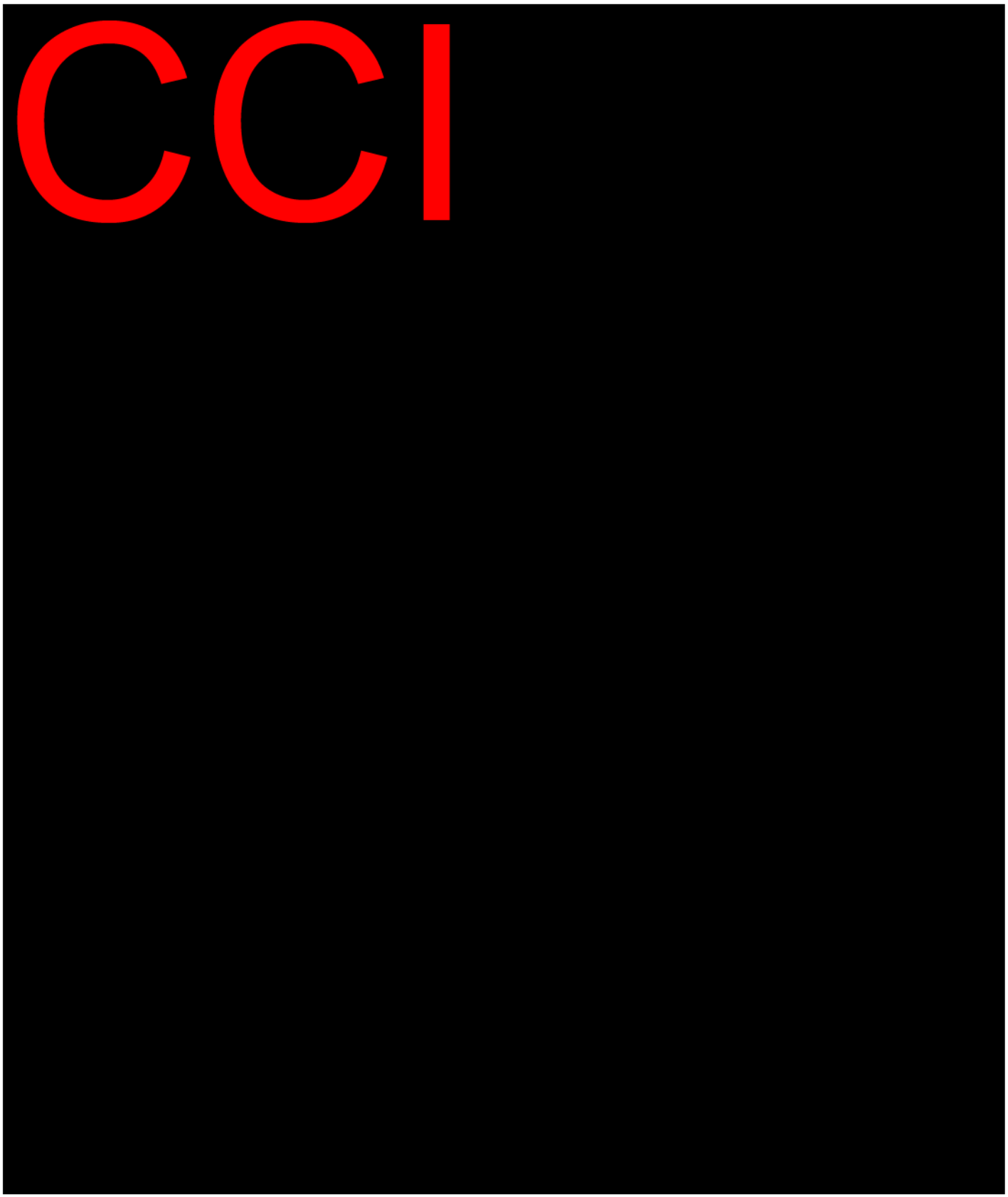
On-treatment assessment/event

The overall observation period will be divided into two mutually exclusive segments:

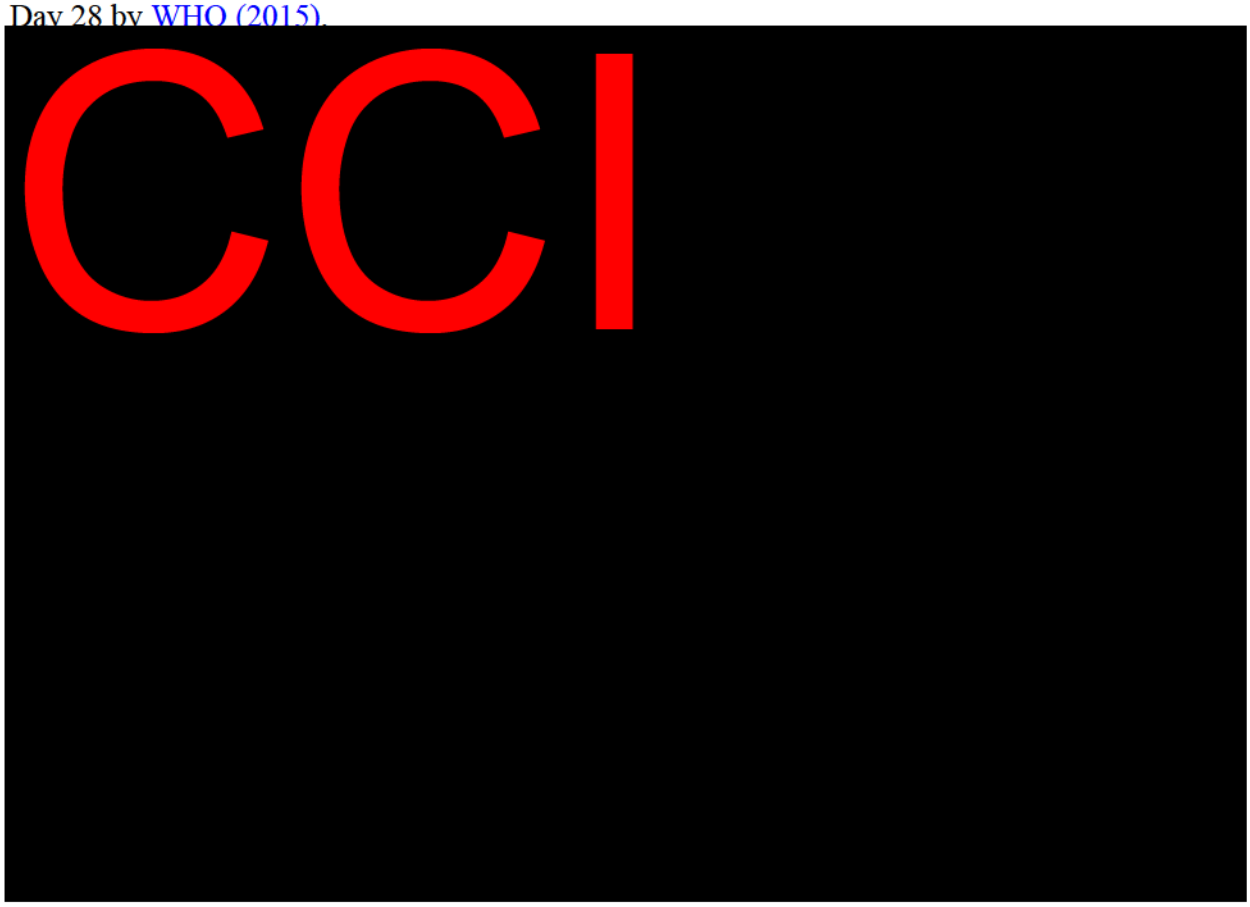
1. ***Pre-treatment period***: from day of patient’s informed consent to before date of first administration of study treatment
2. ***On-treatment period***: from date of first administration of study treatment (study day 1) onwards.

Note: If dates are incomplete in a way that clear assignment to pre- or on-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g., change from baseline summaries). In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).


CCI

Note: The first day of treatment is defined as Day 1 while the day prior to the first day of treatment is defined as Day -1. Compared to WHO (2015) which defined Day 0 as the first day of study treatment, days after treatment are 1 day greater. For example, Day 29 corresponds to Day 28 by WHO (2015).



2.1.2.1 Definition of responder/non-responder by ACPR

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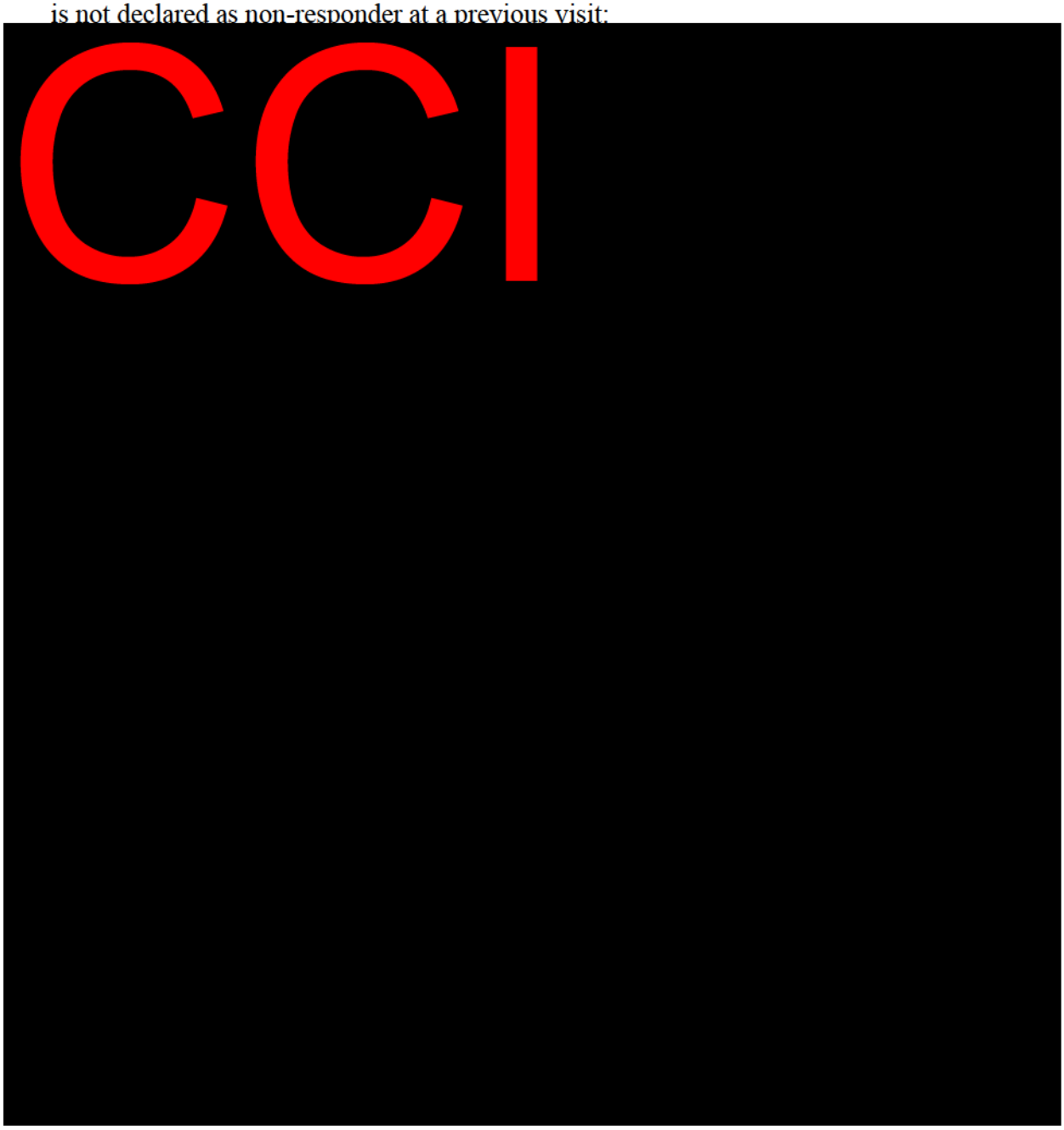
PCR-corrected ACPR at Day X where X=29 (All Parts) or 43 (Parts B & C exploratory analysis)

- Note: once a patient is declared as non-responder at a particular visit, s/he will remain a non-responder for the subsequent visit.
- Response status at Day X will be derived using following rules for patients whose response is not declared as non-responder at a previous visit:



CCI [redacted]

See Section 5.4 for the various scenarios for derivation of the treatment outcomes.

2.1.3 Parasite clearance time (PCT)

PCT is defined as the time (in hours) from the first dose until the first total and continued disappearance of asexual parasite forms which remained at least a further 48 hours. PCT will be calculated based on *P. falciparum* asexual parasite counts.

2.1.5 Tail of Kaplan-Meier (KM) plots

As patients may come to visit earlier or later than the targeted day, the tail of KM plots after the last planned assessment day is not reliable due to small numbers of patients at risk. To account for this, time to event/censoring will be reset CCI [redacted] This principle will be used for relevant outputs using KM method.

2.2 Analysis sets

The following analysis sets are considered for the study:

CCI [redacted] FAS for efficacy analyses and PK analysis set for all PK analyses, unless otherwise indicated.

The number (%) of patients in each analysis set will be summarized. Patients excluded from any analysis set will be listed.

Analysis set exclusions based on protocol deviations

Patients may be excluded from the analysis sets defined above based on protocol deviations entered in the database defined in Table 2-1Protocol deviations leading to analysis set exclusion .

Table 2-1 Protocol deviations leading to analysis set exclusion

Withdrawal of Informed Consent

Any data collected in the clinical database after a patient withdraws informed consent from all further participation in the trial will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

2.2.1 Subgroup of interest

Key efficacy and safety endpoints may be summarized for subgroups of patients by age group (Part B only: <18 and ≥18 years; Part C only: <6 and ≥6 years), sex, region, and relevant resistance mutations.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

A summary of all screened patients will be presented. Screened patients include those who completed screening and were randomized (or enrolled for Part A optional arms), who completed screening and were not randomized, and who did not complete screening (with reasons for not completing screening).

The following summaries will be provided (with % based on total number of RAS patients):

- Number (%) of patients who were randomized but not treated along with the primary reason for not being treated (based on Treatment disposition page)
- Number (%) of patients who were treated, number (%) of patients who completed treatment phase, and those who discontinued treatment phase along with the primary reason for treatment discontinuation (based on Treatment disposition page)

Patient disposition data and screened patients not randomized will be listed.

2.3.2 Demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized for the RAS.

The following demographic variables will be summarized:

- Age and age categories (Part A: 18 to <65, ≥ 65; Part B: 12 to <18, 18 to <65, ≥ 65; Part C: 2 to <6, 6 to <12)
- Sex
- Race
- Ethnicity
- Weight and weight categories (Part A: 40 to <75, ≥75 kg; Part B: 35 to <75, ≥75 kg; Part C: 10 to <15, 15 to <25, 25 to <35, 35 to <55, 55 to <75, ≥75 kg)
- Height
- BMI and BMI categories (<16, 16 to ≤25, >25 kg/m^2); BMI (kg/m^2) = weight [kg] / (height [m])^2 using height and weight at screening visit

The following disease characteristics at baseline will be summarized:

- Body temperature and categories equivalent to axillary method (<37.5, 37.5 to <38.5, ≥38.5 °C) where axillary temperature = oral/tympanic/rectal - 0.5°C
- *Plasmodium* species: *P. falciparum* asexual forms, *P. falciparum* gametocytes, *P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi*
- CCI [redacted]
- Gametocytes counts /µL

Categorical data will be presented as frequencies and percentages. In addition to the categories above for continuous data, the mean, standard deviation (SD), median, minimum, and maximum will be presented along with 25th and 75th percentiles for selected parameters.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class (SOC) and preferred term (PT).

2.3.3 Protocol deviations

Protocol deviations will be summarized.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

CCI

[redacted]

2.4.2 Prior, concomitant and post therapies

Prior medications are defined as drugs taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of study treatment and the last day of study will be a concomitant medication, including those which were started pre-baseline and continued into the treatment period.

Prior and concomitant medications will be coded according to the latest version of WHO Drug Reference List dictionary which employs ATC.

The following will be summarized separately by ATC grade and preferred drug name: (1) prior medications, (2) concomitant medications, and (3) non-study anti-malarial drugs (Table 5-6). The Safety set will be used.

2.5 Analysis supporting primary objective(s)

Refer to Section 2.1 regarding data presentation.

2.5.1 Primary endpoints

The primary efficacy endpoint in Part A is PCT as defined in Section 2.1.3. FAS will be used for the analysis.

The primary efficacy endpoint in Parts B & C is PCR-corrected ACPR at Day 29 as defined in Section 2.1.2; principal stratum strategy will be used for the analysis with principal stratum defined as adult or adolescent patients (Part B)/children (Part C) with acute uncomplicated *P. falciparum* malaria who are fully dosed (for new combination treatment) or received at least 80% of treatment (for Coartem) and take concomitant medication with anti-malarial activity prior to Day 29 only in case of rescue therapy for recrudescence.

PCT and PCR-corrected ACPR will be used for the primary estimand analyses in Part A and Parts B & C, respectively.

2.5.1.1 Assumptions regarding principal stratum strategy

Note first that compliant means fully dosed (for new combination treatment) or received at least 80% of treatment (for Coartem). While the principal stratum includes patients who are compliant with the assigned treatment, some patients may not have been compliant had they been assigned to the other treatment. Thus the 'true' principal stratum (i.e. patients compliant regardless of treatment assigned) may be a proper subset of the observed principal stratum. Given the limited sample size, no sensitivity analyses about deviation from the 'true' principal stratum will be conducted, thus the following assumptions have been made:

- The response rate for new combination (e.g., INE963+Cipargamin, KLU156+Cipargamin) is the same for patients who are compliant to both new combination and Coartem as for patients who are compliant to new combination only
- The response rate for Coartem is the same for patients who are compliant to both new combination and Coartem as for patients who are compliant to Coartem only

2.5.2 Statistical hypothesis, model, and method of analysis

For Part A, PCT descriptive statistics (mean, standard deviation, median, quartiles) will be provided and Kaplan-Meier curves will be presented. The median PCT and corresponding 2-sided 90% CI will be reported.

For Parts B & C, the primary endpoint will be calculated at Day 29 by computing the percent of patients with PCR-corrected ACPR at Day 29 where presence of *P. falciparum* asexual forms on Day 8 or later is considered as failure (not ACPR) only if the parasite strain observed was already present at baseline based on PCR genotyping. Refer to Section 2.1.2 and Section 2.1.2.1 for details. Note: the primary endpoint is binary with 2 outcomes (ACPR or not ACPR). Beside recrudescence, a patient's outcome can be classified as not ACPR due to reasons such as missing PCR genotyping at baseline (i.e. PCR result is undetermined), etc. (Section 2.5.3).

The primary analysis will test for non-inferiority of the CCI [redacted] based on the dual efficacy criteria as specified below, using a Bayesian approach. CCI [redacted]

Part B

CCI [redacted]

$$0.68 \times beta\,(148.1, 3.4) + 0.12 \times beta\,(31.1, 1.5) + 0.20 \times beta\,(0.33, 0.33)$$

where Beta (a,b) represents a Beta distribution of which the density function is $x^{(a-1)}(1-x)^{(b-1)}*\Gamma(a+b)/(\Gamma(a)+\Gamma(b))$.

CCI

$$0.25 \times beta\,(17.9,\ 1.1) + 0.14 \times beta\,(25.0,\ 4.8) + 0.06 \times beta\,(15.6,\ 7.8) + 0.05 \times beta\,(2.1,\ 1.3) + 0.50 \times beta\,(0.33,\ 0.33)$$

CCI

$$0.41 \times beta(93.5, 1.0) + 0.28 \times beta\,(32.2, 2.0) + 0.06 \times beta(19.6, 5.2) + 0.05 \times beta(2.6, 1.5) + 0.2 \times beta(0.33, 0.33)$$

CCI

2.5.3 Handling of intercurrent events

The primary analysis in Part A will account for the below mentioned intercurrent events using a hypothetical strategy. If a patient receives any rescue anti-malarial medication or receives other concomitant medication with anti-malarial activity for any reasons within the first 7 days and before the parasites are cleared, time-to-event PCT will be set to Day 7 (144 hours).

The primary analysis in Parts B & C will account for the below mentioned intercurrent events using a principal stratum strategy. Data will be handled as follows:

The number and percent of patients with intercurrent events will be provided for each intercurrent event using FAS.

2.5.4 Handling of missing values not related to intercurrent event

For handling missing values in the primary analysis in Part A, the following strategies apply:

In Parts B & C, missing values will be handled as per Table 5-9 (#'s 10a-13).

2.5.5 Sensitivity analyses

In Parts B & C, the observed difference between SoC and new combination and 2-sided 80% confidence intervals (CI) of PCR-corrected ACPR will be constructed using the Wilson uncorrected method along with the 2-sided 95% CI for each treatment group using the Clopper-Pearson method.

2.5.6 Supplementary analyses

Supplementary analyses are not planned for Parts A, B, or C.

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoints

The secondary efficacy variable in Part A is PCR-corrected and uncorrected ACPR at Day 29 as defined previously in Section 2.1.2. The secondary efficacy variable in Parts B & C is (1) PCT and (2) PCR uncorrected ACPR at Day 29 as defined previously. The key secondary estimands will be used to analyze PCR-corrected ACPR in Part A and PCT in Parts B & C. The other secondary estimand will be used to analyze uncorrected ACPR in Parts A, B, & C. In addition, pharmacokinetics, safety, and tolerability will also be assessed.

2.6.2 Statistical hypothesis, model, and method of analysis

The secondary analysis for Part A will be the computation of percent of patients with PCR-corrected (using principal stratum) and uncorrected ACPR (using FAS) and 2-sided 95% CI for each treatment group using the Clopper-Pearson method at Day 29. No hypothesis testing will be performed.

CCI

CCI [redacted]

PCR uncorrected failure will be classified into: ETF before Day 4, LCF before Day 8, recrudescence, reinfection, negative PCR, missing PCR, or missing assessment. The classification will be done using FAS.

CCI [redacted]

2.6.3 Handling of intercurrent events

CCI [redacted]

2.6.4 Handling of missing values not related to intercurrent events

The same strategy applicable to the primary endpoint in Part A as described in Section 2.5.4 will be used in Parts B & C for PCT. The same strategy applicable to the primary endpoint in Parts B & C as described in Section 2.5.4 will be used in Part A for PCR-corrected ACPR.

Missing values for uncorrected ACPR in Parts A, B, & C will be handled as per Table 5-9 (#'s 10a-13).

For all other endpoints in Section 2.6.2 (i.e. treatment failure endpoints, PCR uncorrected failure classification at each visit, and incidence rates/time to event of recrudescence and reinfection), missing values will be handled directly as missing.

2.6.5 Sensitivity analyses

CCI [redacted]

2.6.6 Supplementary analyses

No supplementary analysis will be performed for secondary endpoints.

2.7 Safety analyses

For all safety analyses, the Safety set will be used. Safety summaries include data from the on-treatment period with the exception of baseline data which will be summarized where appropriate (e.g., change from baseline summaries). In particular, summary tables for AEs will summarize treatment-emergent AEs (i.e. with a start date on or after the first treatment).

2.7.1 Adverse events (AEs)

The number and percent of patients with treatment emergent AEs (events started after the start of study treatment or events present prior to start of study treatment but increased in severity based on PT) will be summarized in the following ways:

- by primary SOC and PT
- by primary SOC, PT, and maximum severity

Separate summaries will be provided for study treatment related AEs, SAEs, AEs leading to discontinuation, and AEs leading to dose interruption for Coartem in Parts B & C.

A patient with multiple AEs within a primary SOC is only counted once towards the total of the primary SOC.

2.7.1.1 EudraCT and clinicaltrials.gov requirements

For legal requirements of clinicaltrials.gov and EudraCT, two on-treatment tables are required:

- On-treatment deaths resulting from SAEs suspected to be study drug related and SAEs regardless of study drug relationship by SOC and PT
- Non-serious AEs regardless of study drug relationship, with an incidence rate greater than 5% by SOC and PT

These summaries will include any events starting or worsening in the on-treatment period.

If for the same patient, if several consecutive AEs (irrespectively of study treatment causality, seriousness, and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is $\leq$ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

The presence of at least one SAE / SAE suspected to be study drug related / non SAE has to be checked in a block e.g., among AEs in a $\leq$ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

2.7.1.2 AEs of special interest / grouping of AEs

The number and percent of patients with treatment emergent signs and symptoms of severe malaria (i.e., those categorized as Severe Malaria on the AE eCRF) will be summarized by SOC and PT.

AEs of special interest are defined in the Case Retrieval Sheet (CRS) which is updated for each MEDDRA dictionary. The CRS data are stored in TMS.ECRS SAS dataset corresponding to a subset of eCRS SAS view for which the following filtering criteria are applied:

-Drug code = KAE609 (Cohorts B1, B2, & C2), KAF156 (Cohorts B2 & C2)

-Latest version of MedDRA at the time of final database lock

-End date is null (this means this is the latest CRS version)

The number and percent of patients with these special AEs will be summarized. In addition, listings of related AEs will be provided.

Liver related events and QTcF abnormalities will be summarized (see Sections 2.7.3 and Section 2.7.4.1)

2.7.2 Deaths

All deaths will be listed.

2.7.3 Laboratory data

Descriptive statistics will be generated for all clinical laboratory tests performed (actual values and changes from baseline) for three groups of laboratory tests (hematology, clinical chemistry and urinalysis).

Shift tables using the low/normal/high classification will be used to compare baseline to the worst post-baseline value.

Summary with frequency and percent of patients with liver related events (based on AST, ALT, and Total Bilirubin) using the Novartis standard table will be provided.

Boxplots for hematology and biochemistry parameters will be provided.

Listing for patients with lab values outside the normal range (per normal ranges in the source dataset) will be provided. If there is any abnormal lab value for a patient, all measurements of this lab value for the patient will be presented with the abnormal values flagged.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs. ECG data will be read and interpreted (local and centrally). Local readings will be used only for site decision making purposes and not for any analyses; only central readings will be used for the summaries and listings described below.

When ECG triplicates are collected at any assessment, the average of the ECG parameters at that assessment will be used in the analyses.

Categorical analysis of QT/QTc interval data based on the number of patients meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented.

The number and percent of patients with notable ECG values will be presented.

- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from baseline of > 30 ms to ≤ 60 ms
  - Increase from baseline of > 60 ms
- HR (= 60/RR (sec)) for age ≥ 18 years
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- HR (= 60/RR (sec)) for age < 18 years
  - > 90th percentile defined in Table 2-2
  - < 10th percentile defined in Table 2-2
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

ECG data will be summarized by presenting summary statistics of observed data and change from baseline by time point.

A listing will be provided for patients with any notable values defined above. If there is any notable value of an ECG for a patient, all measurements of this ECG value for the patient will be presented in this listing with the notable values flagged. A summary and listing will also be provided of ECG findings for which there is a clinically significant ECG abnormality.

Table 2-2 Heart rate cut-offs (bpm) for 2 to <18 years based on centile charts

Age Range	10th percentile	90th percentile
2 - <3	92	128
3 - <4	86	123
4 - <6	81	117
6 - <8	74	111
8 - <12	67	103
12 – <15	62	96

Age Range	10th percentile	90th percentile
15 – <18	58	92

Reference: Lancet. 2011 March 19; 377(9770): 1011–1018. doi:10.1016/S0140-6736(10)62226-X.

2.7.4.2 Vital signs

Summary statistics will be provided by visit/time.

The number and percent of patients with newly occurring notable vital signs will be presented; for Part B they will be separated by <18 years (Table 2-3) and ≥18 years (Table 2-4).

Table 2-3 Criteria for notably abnormal vital signs for 2 to <18 years (Parts B & C)

Vital sign		Criteria	
Systolic blood pressure [mmHg]	High	≥ 95th percentile of the age and height group[1]	
	Low	≤ 5th percentile of the age and height group[1]	
Diastolic blood pressure [mmHg]	High	≥ 95th percentile of the age and height group[1]	
	Low	≤ 5th percentile of the age and height group[1]	
Body temperature [°C]	High	≥ 37.5°C (*axillary equivalent*)	
Pulse rate [bpm][2]	High	2-<3 years	> 128
		3-<4 years	> 123
		4-<6 years	> 117
		6-<8 years	> 111
		8-<12 years	> 103
		12-<15 years	> 96
		≥ 15 years	> 92
	Low	2-<3 years	< 92
		3-<4 years	< 86
		4-<6 years	< 81
		6-<8 years	< 74
		8-<12 years	< 67
		12-<15 years	< 62
		≥ 15 years	< 58

[1] Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004; 114; 555 (see Section 5.4 for detailed computation)

[2] Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; published online March 15. DOI:10.1016/S0140-6736(10)62226-X.

[Body mass index-for-age (BMI-for-age) (who.int)]

Table 2-4 Criteria for notable vital sign abnormalities for ≥18 years (Parts A & B)

Vital sign	Notable abnormalities
Systolic blood pressure	≥180 mmHg and increase ≥20 mmHg
	≤ 90 mmHg and decrease ≥20 mmHg
Diastolic blood pressure	≥105 mmHg and increase ≥15 mmHg
	≤ 50 mmHg and decrease ≥15 mmHg
Pulse rate	≥100 bpm with increase >25%
	≤50 bpm with decrease >25%

Vital sign	Notable abnormalities
Temperature	>=37.5 (axillary) or >=38.0 (other routes) °C

Listing of patients with notable vital signs will be provided. If there is any notable value for a patient, all measurements of this vital sign for the patient will be presented with the notable values flagged.

2.8 Pharmacokinetic endpoints

The PK analysis set will be used for the pharmacokinetics analyses.

PK parameters in Table 2-5 will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher). If Rsq_adj<0.75 or AUC%Extrap>20%, then Lambda_z, T1/2, AUCinf, Vz/F, CL/F will be flagged for exclusion.

Drug concentrations below the lower limit of quantitation (LLOQ) will be set to zero by the Bioanalyst and will be displayed in the listings as zero and flagged. Below LLOQ values will be treated as missing for the calculation of the geometric means and geometric CV%, and as zero for all other calculations including calculation of PK parameters.

Table 2-5 Non-compartmental pharmacokinetic parameters

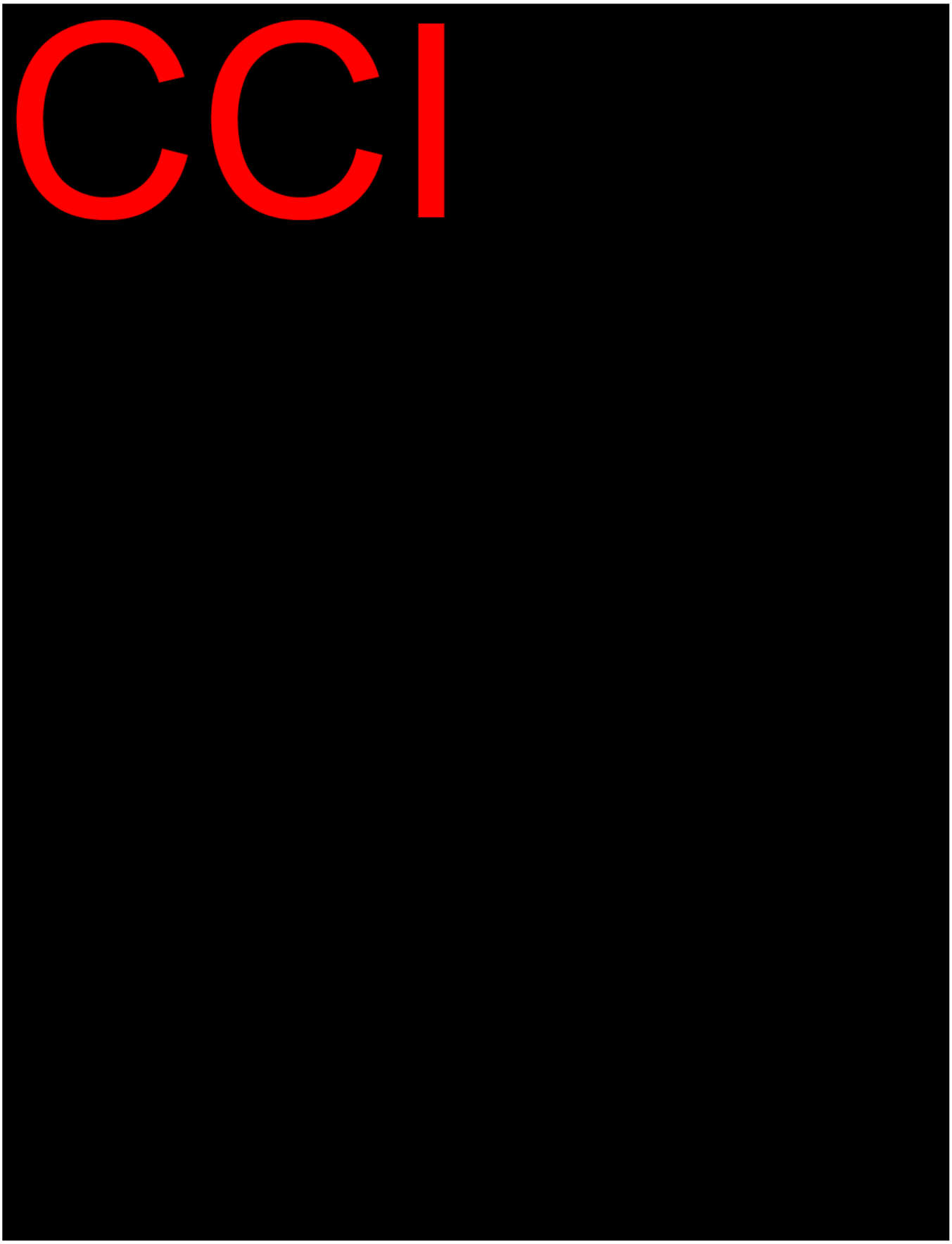
AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume^{-1})
AUCinf	The AUC from time zero to infinity (mass x time x volume^{-1})
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume^{-1})
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (time^{-1}) may also be used for terminal elimination rate constant (time^{-1})
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL/F	The total body clearance of drug from the plasma (volume x time^{-1})
Vz/F	The apparent volume of distribution during terminal phase (associated with λz) (volume)

2.9 PD and PK/PD analyses

CCI [redacted]

2.10 Exploratory endpoint(s)/estimand(s) analysis

CCI [redacted]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- **PK parameters with efficacy outcomes CCI related to parasite dynamics, cure, and protein levels CCI wherever applicable**

See Section 2.9.

- **Presence of gametocytes at baseline (pre-dose) and post-treatment, respectively**

Number and percent of patients with gametocytemia and descriptive summaries at each post-baseline time (2, 4, 6, 8, 12 hours during visit 1, etc.) and during the 28 days post-baseline period will be provided by baseline status of gametocytemia (present, absent, missing). Summaries will be presented using local labs. Any data collected from bioanalytical lab (based on PCR, i.e. baseline, 168h, 360h, EOS) may be summarized in an addendum.

NOTE: The following endpoints, if analyzed, will be done outside the CSR:

- IC50 of parasites isolates before and after treatment (recrudescent infections) by *in vitro* growth inhibition assays
- CCI
- Genetic data (e.g., polymorphisms)

2.11 Interim analysis

CCI

3 Sample size calculation

3.1 Part A

CCI

CCI

3.2.1 B1 – INE963 and KAE609 (cipargamin) combination

CCI

CCI

CCI

The probability to meet the dual non-inferiority criteria for Part B is greater than 89% if SoC cure rate is more than 90%, when the true difference (δ = SoC cure rate - combination cure rate) is zero. Assuming the true SoC cure rate is 98% and the true difference is 0.05, the probability is 95% to meet the dual non-inferiority criteria as shown in Table 3-5.

Table 3-5 Power to declare non-inferiority to SoC for different scenarios

True SoC cure rate	SoC : (KLU + cipargamin) = 30 : 30			
	δ=0	δ=0.05	δ=0.1	δ=0.2
0.85	0.78	0.55	0.34	0.09
0.90	0.89	0.67	0.40	0.09
0.95	0.99	0.84	0.56	0.12
0.98	1.00	0.95	0.71	0.18

KAF156 and lumefantrine-SDF co-administered in a loose combination were assessed in fasted condition in patients down to 2 years of age in a Phase 2b dose finding study (CKAF156A2202). The positive benefit-risk balance supports the evaluation of the identified effective and safe dose (400mg of KAF156 and 480 mg of lumefantrine SDF) of the fixed-dose combination of KAF156 and LUM-SDF, i.e., KLU156 in combination with 75 mg KAE609 to explore possibility of a single dose cure in uncomplicated *P. falciparum* malaria.

Data available for KLU156 as a combination from completed clinical study are summarized in Table 3-6. The dose selected for this combination is KAF156 400 mg and 480 mg of lumefantrine SD using fed conditions, therefore only data from KAF156 of 400 and

lumefantrine 960 mg SD (fasting conditions) was used to derive the MAP prior for patients ≥12 years of age. The expected food effect is approximately two-fold.

3.2.3 C2 – KLU156 and cipargamin in combination

In Cohort C2, approximately 120 evaluable patients infected with *P. falciparum* will be randomized to KLU156+cipargamin vs SoC (Coartem) at a 2:1 ratio (80 evaluable patients treated with KLU156+cipargamin combination vs 40 evaluable patients treated with SoC). The sample size derivation is based on Bayesian analysis using informative priors for the SoC based on data from patients < 12 years.

The probability to meet the dual non-inferiority criteria for Part C is greater than 91% if SoC cure rate is more than 95%, when the true difference (δ = SoC cure rate - combination cure rate) is zero. Assuming the true SoC cure rate is 98% and the true difference is 0.03, the probability is 85% to meet the dual non-inferiority criteria as shown in Table 3-5.

Table 3-7 Power to declare non-inferiority to SoC for different scenarios

True SoC cure rate	SoC : (KLU + cipargamin) = 40 : 80					
	δ=0	δ=0.01	δ=0.03	δ=0.05	δ=0.1	δ=0.15
0.85	0.60	0.54	0.43	0.33	0.14	0.05
0.90	0.65	0.58	0.43	0.31	0.11	0.03
0.95	0.91	0.82	0.60	0.38	0.08	0.01
0.98	1.00	0.98	0.85	0.61	0.12	0.01

Secondary endpoints(s)

CCI [redacted]

For Parts B & C, no formal comparison is planned between the combination therapy and SoC based on PCT.

CCI [redacted]

4 Change to protocol specified analyses

CCI [redacted]

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

A missing AE start date will be imputed using the logic matrix described in Table 5-1.

Table 5-1 Imputation rules for a partially missing AE start date

	AEM missing	AEM<TRTM	AEM=TRTM	AEM>TRTM
AEY missing	Not imputation	Not imputation	Not imputation	Not imputation
AEY<TRTY	(D)	(C)	(C)	(C)
AEY=TRTY	(B)	(C)	(B)	(A)
AEY>TRTY	(E)	(A)	(A)	(A)

AEM=Month AE started, AEY=Year AE started
TRTM=Month treatment started, TRTY=Year treatment started

Table 5-2 is the legend to the logic matrix shown in Table 5-1 and details the relationship of AE start date to study treatment start date.

Table 5-2 Imputation legend and AE/treatment start date relationship

AE start date relationship	Imputation
(A) After treatment start or uncertain	MAX(01MMMYYYY, TRTSDT+1)
(B) Uncertain	TRTSDT+1
(C) Before treatment start	15MMMYYYY
(D) Before treatment start	01JULYYYY
(E) After treatment start	01JANYYYY

Before treatment start: Partial date indicates AE start date is prior to treatment start date.
After treatment start: Partial date indicates AE start date is after treatment start date.
Uncertain: Partial date insufficient to determine relationship of AE start date to treatment start date.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to AEs starting before or on the cut-off date and not having documented end date.

No imputation will be performed for missing/incomplete AE end dates.

5.1.2 Concomitant medication date imputation

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 5.1.2). For concomitant medication reports with no documented end date, medication will be reported as 'ongoing' if captured as such in the eCRF, otherwise it will be reported missing.

No imputation will be performed for concomitant medication end dates.

5.1.2.1 Prior therapies date imputation

Start date

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that scenario (B) will be replaced to be 'start date of study treatment - 1' (see Section 5.1.2).

End date

Imputed date = min (start date of study treatment, last day of the month), if day is missing;

Imputed date = min (start date of study treatment, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

5.1.2.2 Post therapies date imputation

Start date

Imputed date = max (End of Treatment date + 1, first day of the month), if day is missing.

Imputed date = max (End of Treatment date + 1, 01JAN), if day and month are missing.

Imputed date = End of treatment date +1, if the date is completely missing.

End date

No imputation.

5.1.2.3 Other imputations

When a date is recorded as a partial date, the missing day is imputed to the 1st of the month (e.g., DEC2021 imputed to 01DEC2021) and if the day and month are both missing then to 1st of January of that year (e.g., 2021 imputed to 01JAN2021).

5.1.3 Visit windows

When visit windows are used all visits will be re-aligned, i.e.,. they will be mapped to one of the visit windows. E.g. if Day 4 visit for a patient is delayed and occurs on Day 7, it will be re-aligned to visit window Day 8. In case of major deviations from the visit schedule or due to unscheduled visits, several assessments for a patient may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

- The following rules are used to determine the window for visits post baseline:
  - Lower limit = upper limit of prior applicable visit + 1
  - Upper limit = target day of current visit + integer part of (target day of next applicable visit – target day of current visit)/2, except for Days 22, 29, and 43
  - No upper limit for CCI [redacted] to include all assessments

For assessments scheduled only once a day, Table 5-3 describes the analysis visit window mapping (not just scheduled visits) based on study days alone. For assessments performed on multiple timepoints per day, Table 5-4 describes the analysis visit window mapping based on study day and time. Repeat and/or unscheduled visits (which will be numbered in the database accordingly) will be mapped for analysis purposes in the same way. If there are multiple measurements within an analysis window, the conventions defined in Table 5-5 will be used to

determine the appropriate measurement to be selected for analysis. As ECG is based on the average of triplicate ECG, the date of triplicate ECG will be used for determination. If there are repeated ECGs on the same date, the average of scheduled and unscheduled assessments will be calculated separately.

The mapped visits will be used in the by visit analyses. Only planned visits will be presented in summaries, however the listings will show all collected data regardless of used in the by visit analyses. E.g. ECG is not planned at Day 12 but if collected at Day 12, it will not be presented in the summary but shown in the listing.

For gene resistance markers, no visit window will be applied since the assessments are done at baseline and post-baseline in case of parasite reappearance.

5.2 Statistical models

5.2.1 Analysis supporting primary objective(s)

CCI [redacted]

APCR

The primary analysis of ACPR at Day 29 is detailed in Section 2.

SAS procedure FREQ with the EXACT statement will be used to estimate the proportion of responders (binary outcome =1 or "Yes") and SAS or R will be used to compute the associated 2-sided 80% credible intervals based on the posterior probabilities. The posterior probability for the dual criterion will also be calculated. For sensitivity analyses, the Wilson uncorrected method the CI=WILSON | SCORE option in the FREQ procedure will be utilized and the 2-sided 80% CI will be calculated.

5.3 Non-study anti-malarial drugs

Table 5-6 Non-study anti-malarial drugs (from concomitant medication dataset) with respective ATC codes

Non-study drug anti-malarial*	ATC code
Aminoquinolines	P01BA
Biguanides	P01BB
Methanolquinoline	P01BC
Diaminopyridimidines	P01BD
Artemisinin and derivatives, plain	P01BE
Artemisinin and derivatives, combinations	P01BF
Other Anti-malarial	P01BX

* Part A: Applies only to patients who took Coartem prior to Day 29 visit.

Additional non-study anti-malarial drugs will be identified by the PD code COMD02 (Concomitant antimicrobial with antimalarial activity).

5.4 Computation of Blood Pressure Percentiles for Arbitrary Sex, Age, and Height

The below algorithm is described in Appendix B of the following reference: The Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004; 114; 555.

- To compute the systolic blood pressure (SBP) percentile of a boy whose age is y years and height = h inches with SBP = x mmHg:
  - Convert the height of h inches to a height Z-score relative to boys of the same age (as per data tables provided in Table 5-8); this is denoted by Z_{ht}.
  - Compute the expected SBP (μ) for boys of age y years and height h inches given by

$$\mu = \alpha + \sum_{j=1}^{4} \beta_j (y - 10)^j + \sum_{k=1}^{4} \gamma_k (Z_{ht})^k$$

where, regression coefficients are given in the 3rd column of Table 5-7.

- Then convert the boy's observed SBP (x) to a Z-score (Z_{BP}) given by

$$Z_{BP} = \frac{(x - \mu)}{\sigma}$$

where, σ is given in the 3rd column for standard deviation row of Table 5-7.

- To convert the bp Z-score to a percentile (P), compute P = $\phi(Z_{BP})$ x 100%
where $\phi(Z)$ = area under a standard normal distribution to the left of Z.

- Likewise, to compute percentiles for SBP for girls, diastolic blood pressure (DBP) (K5) for boys, and DBP (K5) for girls, use the regression coefficients from the 4th, 5th, and 6th columns of Table 5-8.

For example, a 12-year-old boy with height at the 90th percentile for his age-sex group has a height Z-score = 1.28, and his expected SBP (μ) is

μ = 102.19768 + 1.82416 (2) + 0.12776 (2^2) + 0.00249 (2^3) –0.00135 (2^4) + 2.73157 (1.28) –0.19618 (1.28^2) –0.04659 (1.28^3) + 0.00947(1.28^4) = 109.46 mmHg.

Table 5-7 Regression coefficients from Blood Pressure Regression Models

Regression Coefficients From Blood Pressure Regression Models*

Variable Name	Symbol	Systolic BP		Diastolic BP5	
		Male	Female	Male	Female
Intercept	α	102.19768	102.01027	61.01217	60.50510
Age					
Age–10	β_1	1.82416	1.94397	0.68314	1.01301
(Age–10)^2	β_2	0.12776	0.00598	-0.09835	0.01157
(Age–10)^3	β_3	0.00249	-0.00789	0.01711	0.00424
(Age–10)^4	β_4	-0.00135	-0.00059	0.00045	-0.00137
Normalized height					
Zht	γ^1	2.73157	2.03526	1.46993	1.16641
Zht^2	γ^2	-0.19618	0.02534	-0.07849	0.12795
Zht^3	γ^3	-0.04659	-0.01884	-0.03144	-0.03869
Zht^4	γ^4	0.00947	0.00121	0.00967	-0.00079
Standard deviation	σ	10.7128	10.4855	11.6032	10.9573
ρ†		0.4100	0.3824	0.2436	0.2598
n (persons)		32,161	31,066	24,057	23,443
n (*visits*)		*42,074*	*41,017*	*29,182*	*28,794*

BP, blood pressure; Diastolic BP5, diastolic measurement at Korotkoff 5.

* The coefficients were obtained from mixed-effects linear regression models.

† The value of ρ represents the correlation between BP measurements at different ages for the same child after correcting for age and Zht. This computation was necessary because some studies contributing to the childhood BP database provided BP at more than one age.

Computation of Z-score for height:

As per the recommendation from Centers for Disease Control and Prevention (CDC) use CDC growth charts for age ≥ 2 years. Accordingly, convert the given height into corresponding Z-score as per Table 5-8 given for the growth standards using the following formula:

$$Z_{ht} = \frac{(\frac{height}{median})^L - 1)}{L * S}$$

where median, L, S (i.e. CV) are provided in Table 5-8 for age 2-20 years; height in centimeters.

Table 5-8 CDC growth standard height-for-age growth charts for age 2 -20 years

	Boy			Girl		
Age(year)	L	Median (cm)	S (CV)	L	Median (cm)	S (CV)
2	0.941524	86.4522	0.040322	1.072449	84.97556	0.040791
3	-0.39092	95.27359	0.040534	0.541981	94.21336	0.042018
4	0.827637	102.5105	0.041344	0.225706	101.0339	0.04326
5	1.266367	109.1751	0.042593	-0.05773	107.9566	0.044277
6	1.137443	115.6609	0.043673	-0.21907	115.0055	0.044964

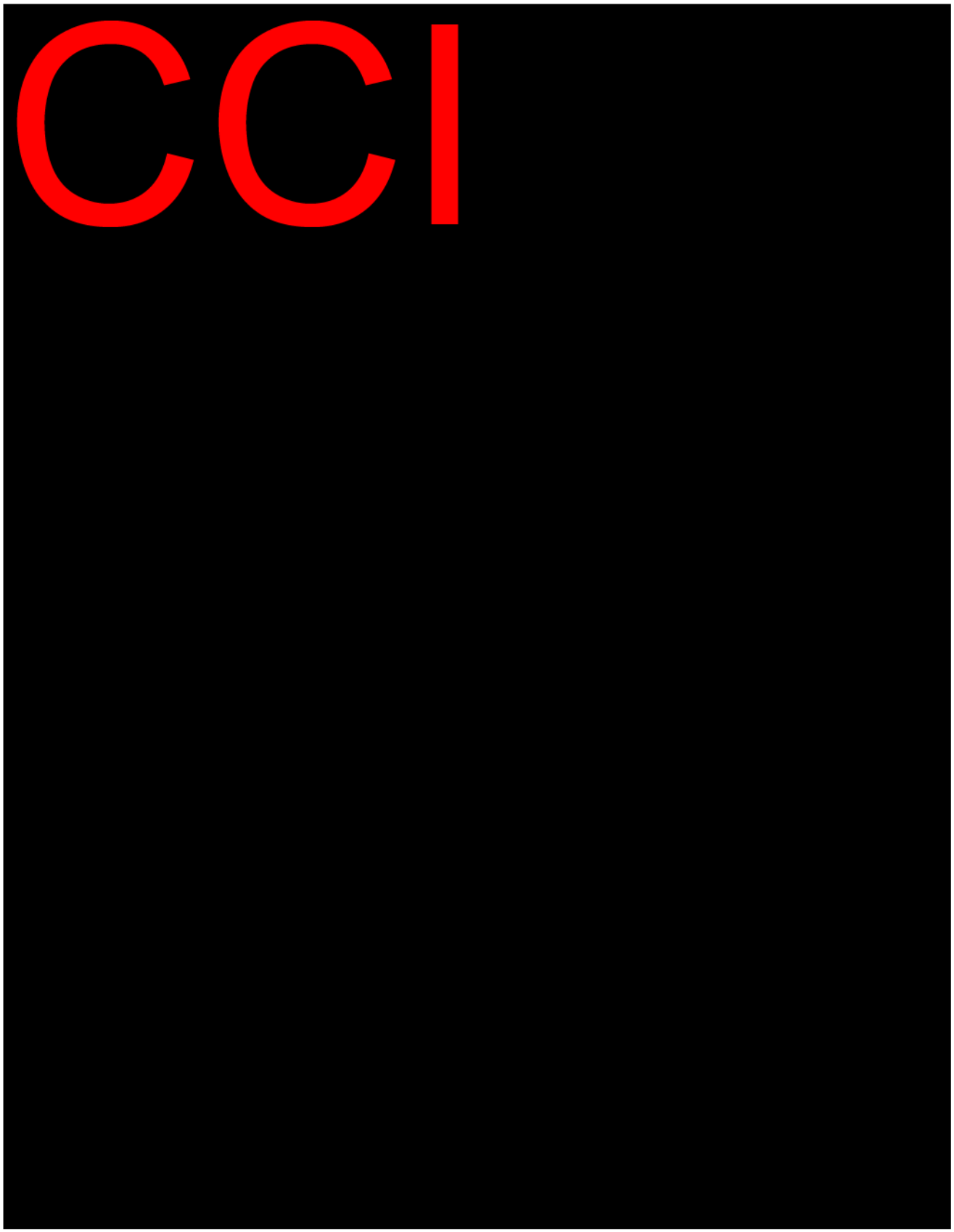
	Boy			Girl		
Age(year)	L	Median (cm)	S (CV)	L	Median (cm)	S (CV)
7	0.753244	122.0305	0.044403	-0.21021	121.7617	0.045461
8	0.455268	128.1237	0.045127	-0.07928	127.8263	0.045968
9	0.415687	133.7345	0.046217	0.084148	133.1304	0.046884
10	0.505564	138.8234	0.04761	0.284749	138.2112	0.048705
11	0.487939	143.7304	0.048938	0.74429	144.2609	0.050524
12	0.420919	149.3088	0.049948	1.303045	151.4866	0.048599
13	0.81624	156.4099	0.050333	1.242968	157.3437	0.043859
14	1.670433	164.1418	0.048945	0.956572	160.4777	0.041022
15	2.20518	170.1393	0.04589	0.89557	161.898	0.040084
16	2.113023	173.6101	0.043086	0.941146	162.569	0.039821
17	1.724738	175.341	0.041408	0.999506	162.9238	0.039732
18	1.399999	176.185	0.040644	1.047571	163.1308	0.039687
19	1.229163	176.6179	0.040391	1.083315	163.259	0.039657
20	1.167279	176.8492	0.04037	1.108046	163.3383	0.039636

Reference: ://.cdc.gov/growthcharts/data/zscore/statage.csv

Note: Table 5-8 can be accessed from the GPSII growth_data (where TEST='HEIGHT' and YEAR_CHG=CDC2000)

5.5 Summary of treatment outcome assignment

The below table provides treatment outcome assignments for uncorrected and PCR-corrected ACPR at Day X = 29 or 43 (Parts B & C only). Note Day X is visit Day X per the visit window mapping.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