NOVARTIS

Clinical Development

PLATFORM
Iscalimab (CFZ533) + LYS006 + MAS825 + Remibrutinib (LOU064) + Ianalumab (VAY736)

CCFZ533H12201BC

A randomized, subject and investigator blinded, placebo-controlled and multi-center platform study, to assess efficacy and safety of different investigational drugs in patients with moderate to severe hidradenitis suppurativa

Statistical Analysis Plan (SAP)

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List of abbreviations

ADA	Anti-drug Antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AN	Abscess and inflammatory nodule counts
aPTT	activated Partial Thromboplastin Time
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
APTT	Activated partial thromboplastin time
ATC	Anatomical Therapeutic Chemical Classification
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
(P/A)CD	(Planned/Actual) Cumulative Dose
CDC	Complement Dependent Cytotoxicity
CREDI	Clinical REsearch Documentation and Information system
CTCAE	Common Terminology Criteria for Adverse Events
(e)CRF	(electronic)Case Report Form
CRO	Contract Research Organization
CCI	
CV	Coefficient of Variation
DAR	Dosage Administration Record
DBL	database lock
(P/R)DI	(Planned/Relative) Dose Intensity
CCI	
DMS	Document Management System
DOE	Duration of Exposure
ECG	Electro-Cardiogram
EOS/T	End of Study/Treatment
FAS	Full Analysis Set
Fc	Fragment crystallizable
FIR	First Interpretable Results
GPS	Global Programming and Statistical Environment
(s)HiSCR	(simplified) Hidradenitis Suppurativa Clinical Response
hsCRP	High sensitivity C-reactive protein
HS	Hidradenitis Suppurativa
CCI	
ICF	Informed Consent Form
ID	Investigational Drug
CCI	
LPLV	last patient last visit
LOCF	Last Observation Carried Forward

LTB4	Leukotriene B4
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MI	Multiple Imputation
CCI	
PdS	Pharmacodynamic Analysis Set
PDS	Programming Datasets Specifications
CCI	
PkS	Pharmacokinetic Analysis Set
PD	Protocol Deviation
PDT	Programming Deliverables Tracker
PPS	Per-Protocol Set
CCI	
PT	Preferred Term
RAP	Reporting & Analysis Process
SAE	Serious Adverse Event
CCI	
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
SS	Safety Analysis Set
SSD	Study Specification Document
TBL	Total Bilirubin
TFLs	Tables, Figures, Listings
ULN	Upper Limit of Normal
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study CCFZ533H12201BC that will be presented in the Clinical Study Report (CSR). The output shells (in-text and post-text) accompanying this document can be found in the Tables, Figures and Listings (TFL) shells document. The specifications for derived variable and datasets can be found in the Programming Datasets Specifications (PDS) document. This version of the SAP is based on the Protocol version 10.

All changes to the planned analysis described in this document required before or after final database lock will be made through an amendment or addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in the TFL shells document without the need to amend.

The SAP, TFL shells and PDS documents may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., IB updates, abstracts, posters, presentations, manuscripts and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

1.1 Study design

Figure 1-1 Cohort A, B and C study design

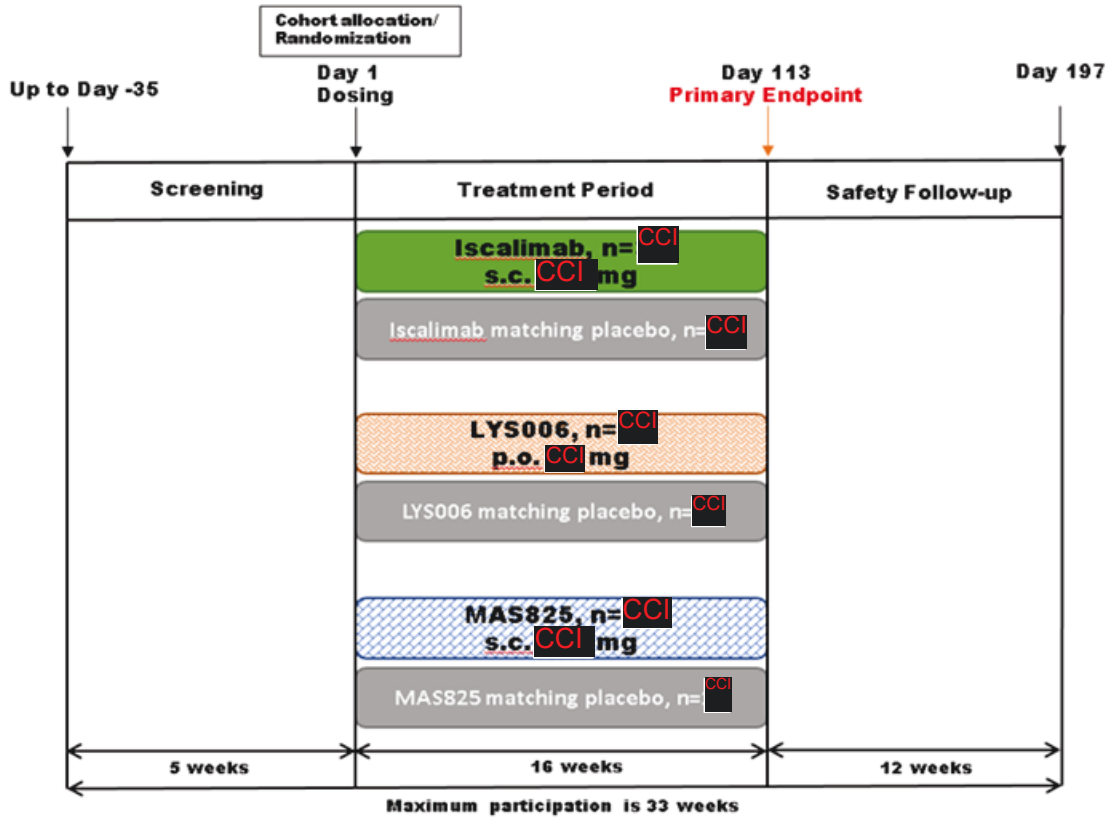


Figure 1-2 Cohort D study design

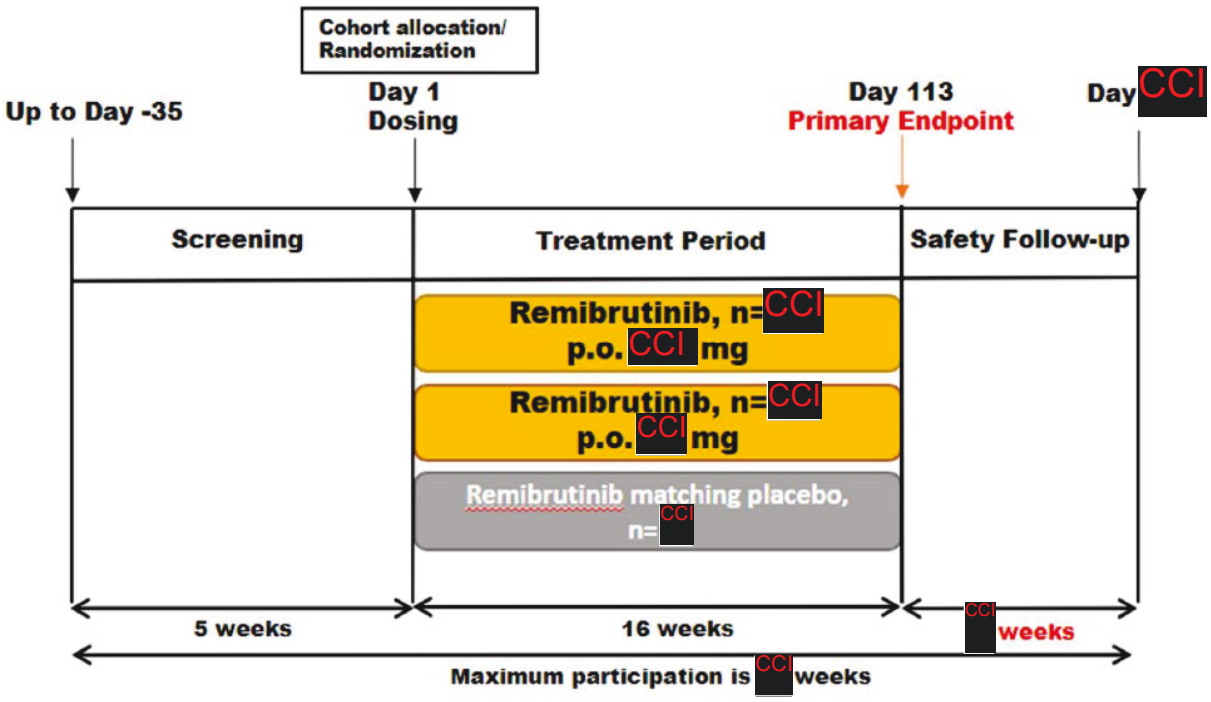
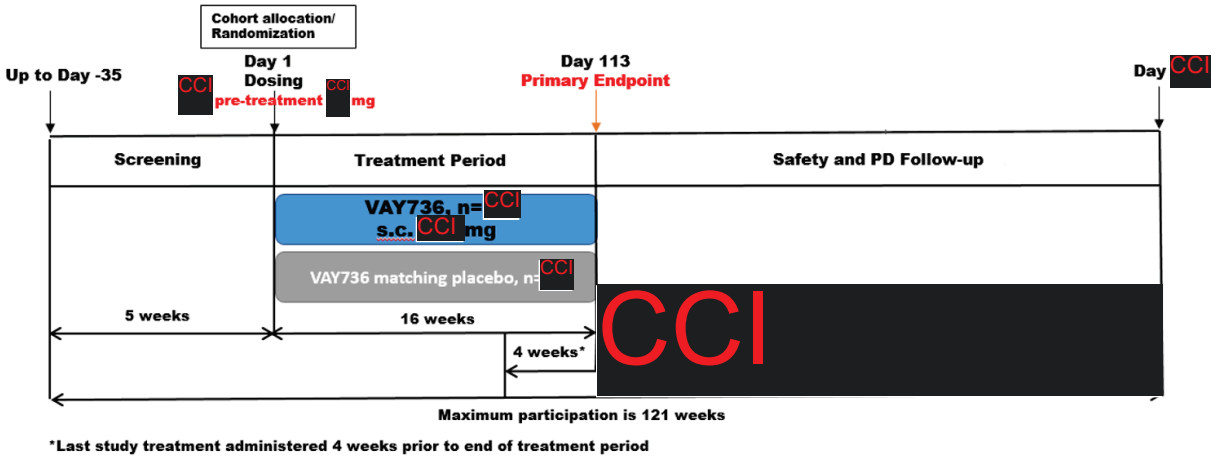


Figure 1-3 Cohort E study design



This is an exploratory, randomized, subject and investigator-blinded, placebo-controlled, multicenter and parallel-group non-confirmatory study to assess the efficacy, safety and tolerability of five investigational drugs including Iscalimab (CFZ533), LYS006, MAS825, Remibrutinib (LOU064) and Ianalumab (VAY736) in subjects with moderate to severe HS.

This platform study is set up to allow early discontinuation of cohorts and inclusion of new cohorts of similar size and population, for other investigational treatments in early clinical phase for subjects with moderate to severe HS. These additional cohorts may include orally administered or injectable compounds. Inclusion of cohorts, to up to 5 in total, will only be proposed via substantial protocol amendment and will depend on the following criteria:
- at least one study cohort still ongoing

- sound scientific rationale
- perceived favorable benefit-risk profile
- pre-requisites that allow for at least 12, ideally 16 weeks of treatment duration

It is expected that additional cohorts will be subject and investigator-blinded and include a placebo.

Adult subjects with confirmed HS and with moderate to severe disease severity will be enrolled. They will be allocated to either Cohort A or Cohort B or Cohort C, D or E based on their HS disease severity determined at Day 1.

- **Cohort A (Iscalimab)**: This cohort will comprise approximately CCI subjects, CCI will receive the investigational treatment (Iscalimab, CCI s.c. CCI) and CCI will receive matching placebo.
- **Cohort B (LYS006)**: This cohort will comprise approximately CCI subjects, CCI subjects will receive the investigational treatment (LYS006, CCI mg CCI p.o) and CCI subjects will receive matching placebo.
- **Cohort C (MAS825)**: This cohort will comprise approximately CCI subjects, CCI will receive the investigational treatment (MAS825, CCI mg s.c. CCI and CCI will receive matching placebo.
- **Cohort D (Remibrutinib)**: This cohort will comprise approximately CCI subjects and consisting of two investigational treatment arms (in each arm CCI subject will receive the investigational treatment remibrutinib) and placebo (CCI subject) CCI p.o.:
  - CCI mg CCI remibrutinib plus placebo to CCI mg remibrutinib CCI.
  - CCI mg CCI remibrutinib plus placebo to CCI mg remibrutinib CCI.
  - Placebo to CCI mg remibrutinib CCI and placebo to CCI mg remibrutinib CCI.
- **Cohort E (Ianalumab):** This cohort will comprise approximately CCI subjects, CCI will receive the investigational treatment (ianalumab, CCI mg s.c. CCI and CCI will receive matching placebo.

Subjects only eligible for one cohort will be assigned directly to the corresponding cohort; when a subject is eligible for more than one cohort, allocation will be done randomly by the Interactive Response Technology (IRT) system. The sponsor can set the allocation ratio to favor one or more cohorts in order to enhance enrolment into a specific cohort depending on the strategic importance of a given compound, or a cohort can be temporarily stopped to assess safety. The allocation to any cohort would not exceed 80%. If a cohort is stopped for safety reasons the relevant Health Authorities and IRBs/IECs would be notified as per local regulations.

Subjects with a minimum of 5 or more lesions at randomization (pre-dose on Day 1) will be eligible for cohorts A, C, and E.

In Cohort B, a stratification factor (baseline lesion count >=5 or 3-4) will be utilized, to cap the number of subjects with 3-4 lesions at randomization (pre-dose on Day 1) to a maximum number of CCI subjects; subjects with a minimum of 5 or more lesions will be eligible for all cohorts. When the number of subjects allocated to one cohort reaches as planned, the enrollment for this cohort will be closed and subjects in screening afterwards will only be evaluated for eligibility into another cohort.

For Cohort D, all subjects must have 3 or more lesions. CCI

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After cohort allocation, subjects will be randomized to the investigational treatment or placebo arm with a ratio of 2:1 in Cohorts A and B, 3:1 for Cohort C and E, and 3:3:1 for Cohort D. For any prematurely terminated cohort, all ongoing subjects in both treatment arms in this cohort will be discontinued and not be replaced. The enrollment into this cohort will also be stopped.

The study will consist of a screening period of up to 35 days, a treatment period of 16 weeks and a safety follow-up of 12 weeks CCI . Safety and selected efficacy assessments will be conducted during these visits CCI . The primary clinical endpoint is the simplified HiSCR (Hidradenitis Suppurativa Clinical Response) after 16 weeks of treatment.

On Day 113(Week 17), all subjects will enter the follow-up period and will not receive any further study drug administrations. If medically justified, and if no potential safety concerns have been identified (after discussion with the sponsor), subjects may receive previously prohibited medication during this follow-up period. CCI

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of the investigational treatments, compared to placebo in moderate to severe inflammatory hidradenitis suppurativa (HS) patients	• Proportion of patients achieving clinical response evaluated by the simplified Hidradenitis Suppurativa Clinical Response (HiSCR) after 16 weeks of treatment
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the safety and tolerability of the investigational treatments in patients with moderate to severe hidradenitis suppurativa (HS)	• Number and severity of AEs • Physical examination, vital signs, safety laboratory measurements, ECGs at baseline and repeatedly until study completion visit
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
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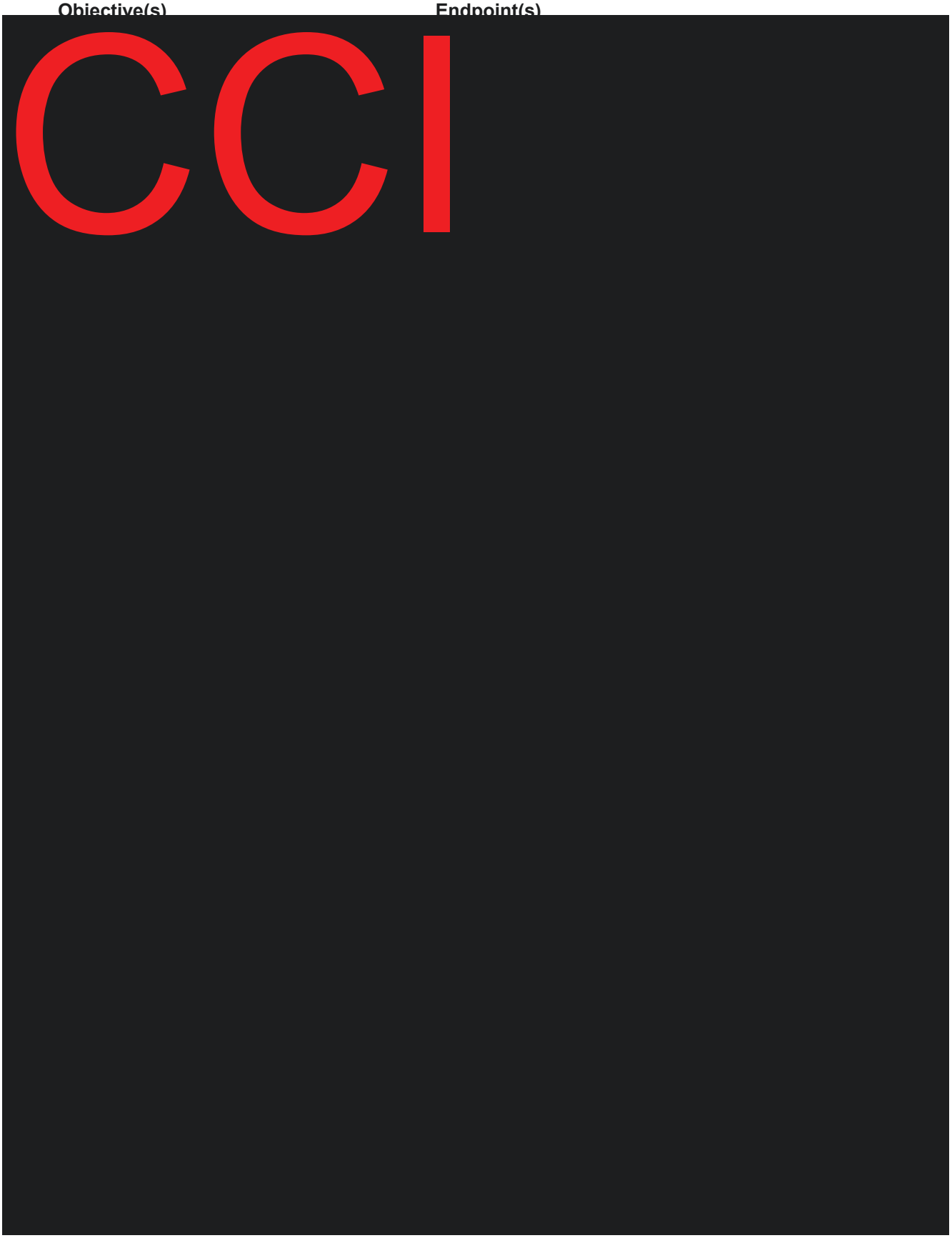
Objective(s)	Endpoint(s)
CCI	

Objective(s)	Endpoint(s)
CCI	

Objective(s) **Endpoint(s)**



2 Statistical methods

2.1 Data analysis general information

Study data will be analyzed by Novartis personnel and/or designated CRO(s) using the most updated SAS® version 9.4 or higher and/or R (version 3.4.3 or higher). PK parameters will be calculated using non-compartmental methods available in Phoenix WinNonlin version 6.4 or higher.

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The primary CSR will include all outputs planned within the TFL shells document. Additional data for subjects continuing to receive study treatment past the data cutoff date of the primary CSR, as allowed by the protocol, will be reported once all subjects have discontinued the study. However, only a selection of key outputs for which additional data was collected will be provided for the final report.

First Interpretable Results (FIR)

FIR will be provided for all the milestones listed above. The study FIR template (mock slides) can be found in CREDI in the study RAP folder. The template shows the analysis results to be presented in the FIR. Study outputs required to be created at the time of the FIR (see TFL shells

document) will be marked as "Key" in the Programming Deliverables Tracker (PDT) output list.

Data from participating centers in this study protocol will be combined, so that an adequate number of subjects will be available for analysis. No center effect will be assessed. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant pharmacokinetic (PK) and pharmacodynamics (PD) measurements using descriptive statistics for quantitative data and contingency tables (frequencies and percentages) for qualitative data.

2.1.1 General definitions

2.1.1.1 Investigational drug and study treatment

Investigational drug (ID) will refer to the active drug being administered to the study enrollees, specifically, Iscalimab (CFZ533), LYS006, MAS825, Remibrutinib (LOU064) and Ianalumab (VAY736). The terms investigational drug and study drug are used interchangeably.

Study treatment will refer to either study drug or placebo.

Study arm will refer to individual grouping of subjects randomized to either active drug or placebo. For example, a study arm for cohort A represents subjects randomized to either Iscalimab or Placebo. The terms 'study arm' or 'treatment arm' or 'treatment group' are used interchangeably. Subjects on active drug are also referred to as active arm and those on placebo as placebo arm.

Cohort is a mutually exclusive grouping of subjects that they were recruited to for studying the effect of an ID by comparing with matching placebo. Each cohort constitutes an active drug arm and a placebo arm.

Pooled placebo will refer to the group of subjects from placebo arms of multiple cohorts.

2.1.1.2 Date of first/last administration of study treatment

In a cohort, the date of first (last) administration of study treatment is derived as the first (last) date when a non-zero dose of study treatment (i.e. study drug to the active arm and placebo to the placebo arm) was administered and recorded on the Dosage Administration Record (DAR) eCRF.

2.1.1.3 Baseline

Baseline is the result of an investigation describing the "true" state of a subject before the start of study treatment administration.

For *safety assessments*, the last available evaluation on or before the date of start of study treatment is taken as "baseline" assessment. In case time of assessment and time of treatment start is captured (e.g. pre-dose ECG), the last available assessment before the treatment start date (day 1)/time is used for baseline.

For safety parameters (e.g. ECGs or vital signs), where study requires multiple replicates per time point, the average of these measurements would be calculated for baseline (if not already available in the database).

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) or collected for ECGs or vital signs, then the last value should be considered as baseline.

If subjects have no value as defined above, the baseline result will be missing.

For *efficacy assessments*, the last available evaluation on or before the date/time of start of study treatment is taken as "baseline" assessment.

2.1.1.4 Study day

The study day for *safety assessments* (e.g. adverse event (AE) onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) will be calculated as the difference between the date of the event (onset date of an event, assessment date etc.) and the start of study treatment plus 1. The first day of study treatment is therefore study day 1. Example: if start of study treatment is on 05-Jan-2014 and start date of an adverse event is on 09-Jan-2014 then the study day of the adverse event onset is 5. For safety assessments before start of study treatment, the study day is negative and derived by (date of event – start date of study treatment). For example: if start of study treatment is on 05-Jan-2014 and date of lab measurement is on 02-Jan-2014 then the study day of the laboratory abnormality is -3. Note, the day of start of study treatment is day 1, and the day before the date of first study treatment is day – 1, not day 0.

The study day for *other assessments* (e.g. efficacy, biomarker etc.) will be calculated the same way as safety assessments.

For the purposes of reporting summary of assessments, **study week** will be used to include assessments that were collected from past 6 days up-to the scheduled dose administration day. Based on the planned assessment schedule, a study week will comprise study days given by the following formula: Week k = (k*7-6, k*7+1] for k≥1 and 'Baseline' for k=0 to represent day 1. Note that the interval does not include the left limit, but includes the right. Thus, a *study week* can take the following values: 'Baseline' (study day 1), 'Week 1' (study days 2 through 8),..., 'Week 16' (study days 107 through 113) etc. with 'Baseline' strictly adhering to the definition given above, Section 2.1.1.3.

2.1.1.5 On-treatment assessment / event and observation periods

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

pre-treatment period starts from day of subject's first informed consent to the day before first administration of study treatment

on-treatment period lasts from the date of first administration of study treatment to [redacted] days after the date of the last actual administration of LYS006 and remibrutinib or [redacted] months after the last actual treatment of iscalimab, MAS825 and ianalumab.

post-treatment period starts at day [redacted] after last administration of study treatment until the end of study (EOS) visit for LYS006 and remibrutinib or from [redacted] days after the last actual treatment for iscalimab, MAS825 and ianalumab (including start and stop date) until the end of study (EOS) visit

For Cohort E, the post-treatment period is further split into :

The mandatory post treatment follow-up spans CCI weeks, starts at day CCI after the last actual treatment for ianalumab with the subperiods defined as below

- subperiod 1: spans CCI weeks starting day CCI after the last actual treatment for ianalumab
- subperiod 2: spans CCI weeks, starting day after the end of subperiod 1,

and the conditional post treatment follow-up, starting day after the end of mandatory post treatment follow-up defined above until EOS.

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

Safety summaries (adverse events, laboratory test results, vital signs, and ECGs) are generated for the on-treatment period. For Cohort E, additional safety summaries will be generated, details provided in section 2.7.1. In addition, a separate summary for death during both on treatment and post treatment periods will be provided. When appropriate, on treatment safety variables from laboratory tests, vital signs and ECGs are compared to their respective baseline values. It is recognized that the difference in the length of on-treatment periods between cohorts A,B, C, D and E may introduce some confounding in reporting of the safety events comparing the active arm vs. the pooled placebo; however, this is expected to be minimal considering the dissipated effect of LYS006 and remibrutinib beyond 30 post-treatment days due to its relatively short half-life. A direct comparison between within-cohort placebo and pooled placebo will provide an opportunity to assess the degree of confounding if it exists.

2.1.1.6 Lost to follow-up

A subject whose status is unclear because he/she fails to appear for study visits without stating an intention to discontinue or withdraw cannot be formally considered lost to follow-up until his/her scheduled EOS visit would have occurred.

2.2 Analysis sets/ Subject Classification/ Withdrawal of ICF/ Subgroups

2.2.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The **Safety analysis set (SS)** will include all subjects that received any study drug.

The **Pharmacokinetic (PK) analysis set (PkS)** will include all subjects who received any study drug and had at least one available valid (i.e. not flagged for exclusion) PK concentration measurement with no protocol deviations (PDs) that impact PK data.

The **Pharmacodynamic (PD) analysis set (PdS)** will include all subjects who received any study drug and had no protocol deviations with relevant impact on PD data.

For the purpose of summary tables on demography, safety and efficacy, data will be reported according to the following treatment arms present at the time of analyses:

1. Iscalimab
2. LYS006

3. MAS825
4. Remibrutinib p.o. CCI mg CCI
5. Remibrutinib p.o. CCI mg CCI
6. Ianalumab
7. Placebo cohort A
8. Placebo cohort B
9. Placebo cohort C
10. Placebo cohort D
11. Placebo cohort E
12. Pooled placebo

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2.2.2 Subject classification

Subjects may be excluded from the analysis populations defined above based on the PDs entered in the database and/or on specific classification rules as defined in Table 2-1 below. Any updates to this table will require an amendment to the SAP implemented prior to final DBL.

Table 2-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set
INCL##	*Xxxxxxx*	
EXCL##	*Xxxxxxx*	
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
INCL##	*Xxxxxxx*	
EXCL##	*Xxxxxxx*	
Subjects are excluded from safety analysis in case of these PDs:		Exclude subject safety analysis sets
INCL##	*Xxxxxxx*	
EXCL##	*Xxxxxxx*	

2.2.3 Withdrawal of Informed Consent

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

For US and Japan, all biological samples not yet analyzed at the time of withdrawal may be used for further testing/analysis in accordance with the terms of the protocol and of the informed consent form. However, for EU and RoW, they will not be used unless permissible by applicable law.

2.2.4 Subgroup of interest

Not Applicable.

2.3 Patient disposition, demographics and other baseline characteristics

Unless noted otherwise, summaries and listings described in this section will be based on the SS and will be provided for each cohort within the scope of analysis at a given milestone (see Section 2.1) stratified by treatment arms (as defined in Section 2.1.1.1) and overall.

2.3.1 Patient disposition

The following will be tabulated for all reports:

- Number (%) of subjects randomized;
- Number (%) of subjects treated;
- Number (%) of subjects who completed study at the time of data cut-off;
- Number (%) of subjects who discontinued treatment and primary reasons for discontinuation;
- Number (%) of subjects who discontinued from study and reasons for discontinuation;

In addition, the following will be reported for IA-cohort-specific CSR as well as final primary CSR:

- Number (%) of subjects followed up during the post-treatment follow up period;
- Number (%) of subjects lost to follow-up

2.3.2 Demographics

Demographic and other baseline disease characteristics data including age, sex, race, ethnicity, height, weight, BMI, smoking status, CCI [redacted], hurley score, hsCRP, CCI [redacted] and time since HS diagnosis will be listed and summarized.

BMI will be calculated as: BMI [kg/m^2] = weight[kg] / (height[m]**2)

Time since diagnosis of hidradenitis suppurativa will be calculated using the following formula:

Time since HS diagnosis = (date of first treatment –first diagnosis date + 1)/365.25

In case of partial or missing first diagnosis date of HS, the date will be imputed according to the imputation rules in Section 5.1.1.3.

2.3.3 Medical History

A listing of medical history and ongoing medical conditions will be provided, using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting.

2.4 Protocol Deviations (PDs)

The SS will be used for the protocol deviation listing. Subjects with any CSR-reportable protocol deviation will be listed by the deviation category, including those specified in Section 2.2.2.

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

2.5.1 Study treatment and Compliance

The safety set will be used for all summaries of study treatment. The number (%) of subjects who have dose changes or interruptions, and the reasons, will be summarized by treatment, separately for each cohort. Duration of exposure (DOE) to study treatment, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by means of descriptive statistics for each treatment arm within the scope of analysis at a specific study milestone. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for subjects in each interval.

Subject level listings of all doses administered on treatment along with dose change/interruption reasons will be produced. Such dose adjustments and/or interruptions are not permitted as per the protocol and are captured as protocol deviations.

Duration of exposure (DOE) to study treatment is defined as the total number of days elapsed on the last day of dose administration since day 1 of the study treatment.

DOE (days) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1.

DOE (weeks) = DOE (days) /7

The date of first administration of study treatment is as defined in Section 2.1.1.2. However, for cohorts A, C and E the last date of exposure to a study treatment is defined as the planned date based on assessment schedule for which the last dose was administered plus the number of days added as an upper bound for the planned date. For example, if the last dose of Iscalimab was administered on Day 70 in lieu of the planned assessment on day 71, then the last date of exposure will be the date corresponding to day 71 + 3 (the upper bound for the planned visit). For cohorts B and D, since the dose is administered on daily basis at home and only calibrated on scheduled visits at the site, the data suffers from recall bias. Hence, DOE for cohorts B and D is defined to be the last day of reported drug exposure converted to whole week, which is equivalent to the DOE (weeks). For example, if a subject took his last dose on day 63 which corresponds to week 9 [Week k = (k*7-6, k*7+1] for k≥1], then DOE is 9 weeks.

Cumulative Dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each treatment arm.

The *planned cumulative dose* (PCD) for a study drug refers to the total planned dose as per the protocol up to the last date of subject's investigational drug administration. The planned cumulative dose is not summarized/listed. It is used for relative dose intensity calculations.

The *actual cumulative dose* (ACD) refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the Dose Administration eCRF.

Dose intensity (DI) for subjects with non-zero duration of exposure is defined as

DI (mg/week) = ACD(mg) / DOE(week); and,

planned dose intensity (PDI) is defined as:

PDI (mg/week) = PCD(mg) / DOE(week).

Compliance to study treatment will be summarized in terms of the *Relative Dose Intensity* (RDI), defined as RDI = DI (mg/week) / PDI (mg/week). DI and RDI will be summarized separately for each of the treatment arms, using the DOE of each of the components.
Compliance is also expressed as the percentage of subjects who took a predefined proportion of the weekly cumulative dose prescribed. The predefined RDI categories are ≤ 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of subjects falling in each category will be presented.

2.5.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies (Protocol Section 6.2.1) prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by treatment group.

The conventions for imputing a missing concomitant medication start or end date are described in Appendix Section 5.1.3.

For cohort E, corticosteroid premedication prior to the first administration of the study treatment will be listed and summarized by treatment group.

2.6 Analysis of the primary objective

The primary objective (Protocol Section 12.4) of this study is to assess the efficacy of investigational drugs against placebo among subjects with moderate to severe inflammatory hidradenitis suppurativa (HS). PdS will be used for the analyses.

2.6.1 Primary endpoint

The primary endpoint (Protocol Section 12.4.1) of this study is the proportion of subjects who have achieved a clinical response, as defined by simplified HiSCR (sHiSCR), after 16 weeks of treatment. The sHiSCR is defined as

- a reduction of at least 50% in abscess and inflammatory nodule counts and
- no increase in draining fistula count related to baseline.

2.6.2 Statistical hypothesis, model, and method of analysis

The primary variable will be modeled with the binomial distribution. A neutral non-informative Beta (1/3, 1/3) distribution will be used as the prior for the response rate for all treatment groups. Based on the priors and the observed primary outcome, posterior distributions for the response rate for the investigational treatment and pooled placebo groups will be computed respectively. The posterior distribution of the difference of response rates, investigational treatment (iscalimab/LYS006/MAS825/each remibrutinib regimen/ianalumab) minus placebo, will be obtained by simulations, i.e. sampling from the posterior distributions of the corresponding treatment groups. The posterior probabilities for the difference of response rates will be assessed according to the following dual criteria as a guide to decision making. Each investigational treatment will be assessed separately in comparison to the pooled placebo group.

The efficacy criteria are predefined as:

1. Better than placebo with high confidence (at least 90% probability that the simplified HiSCR rate at week 16 for an investigational treatment is better than placebo, i.e., Prob (delta >= 0) > 90%), AND
2. sHiSCR rate 15% above placebo (at least 50% probability that the sHiSCR rate at week 16 for an investigational treatment is 15 percentage points above that of placebo, i.e., Prob (delta >= 0.15) > 50%.),

where delta is the difference in percentage points for investigational treatment versus placebo for sHiSCR rate.

2.6.3 CCI

CCI

2.6.4 CCI

CCI

2.7 Analysis of the secondary objective

The secondary objective of the study is to characterize the safety and tolerability of investigational treatments that were administered to subjects with mild and moderate HS. All safety analyses for remibrutinib cohort iCSR will be reported with on-treatment period cut-off with 30 days after the last study treatment administration for the pooled placebo group. All safety analyses for LYS006, iscalimab and MAS825 cohorts iCSR will be reported with on-treatment period cut-off as defined in Section 2.1.1.5.

2.7.1 Key safety endpoints

The key safety endpoints include:

- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs);
- Changes in laboratory parameters, vital signs and ECGs from baseline.
- Deaths

The SS within the scope of analysis for the study milestones (Section 2.1) will be used for cohort-specific summaries and listings of safety data. All listings and tables will be presented for each cohort by the treatment arms (cohort-specific investigational treatment, cohort-specific placebo and pooled placebo) and overall, except for lab parameters, vitals and ECG that are not summarized for overall. Safety summaries (tables, figures) will include data only 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 addition, a separate summary for on-/post-treatment deaths will be provided, along with a listing with post-treatment deaths flagged. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (*treatment-emergent* AEs).

2.7.1.1 Adverse events

2.7.1.1.1 Data handling

Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) and assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 or higher, respectively.

CTCAE is a standard classification and severity grading scale for adverse events in clinical trials and oncology settings. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening adverse events and death.

AE Summaries

AE summaries will include all AEs occurring during on-treatment period. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, outcome etc. AEs starting during the post-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT), having AEs of maximum severity for each PT within SOC using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category.

A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. If CTCAE grading does not exist for an AE, investigator determined grades 1, 2, 3, or 4 corresponding to mild, moderate, severe, and life-threatening, respectively, will be used. CTCAE grade 5 (death) will not be used in this study. AEs with missing CTCAE grades will be included in the 'All grades' column of the summary tables.

When AE summaries are presented by either SOC or PT, the sort order for the SOC or PT will be based on their frequency in 'All subjects' column. When presented by both in a single summary, the primary SOC will be presented in alphabetically ascending order and the PTs will be sorted within primary SOC in descending frequency. The sort order for the PT will be based on their frequency in 'All grades' of 'All subjects' column.

For Cohort E, in addition to the AE summaries generated over the on-treatment period, the AEs falling under the mandatory and the conditional post-treatment periods as defined in section 2.1.1.5, will be summarized in 3 different tables as below :

1) One table will summarize AEs falling under the subperiod 1 of the mandatory follow-up for VAY736, pooled placebo and cohort E placebo
2) One table will summarize AEs occurring in subperiod 2 of the mandatory follow-up for VAY736 and cohort E placebo
3) One table will summarize AE occurring during the conditional follow-up

The following AE summaries will be produced by treatment arm for each cohort and will selectively constitute FIR/iCSR/primary CSR (see TFL Shells document, section 1.8.1):

- Overview of AEs (number and % of subjects with any AE and by grade, any SAE, any AE leading to dose reduction/interruption/treatment withdrawal (each on a different row), any AE leading to study discontinuation, any AE leading to death. Also include similar counterparts for study-drug related AEs except for by grade)
- AEs by SOC and by PT
- AEs by SOC, PT and maximum severity grade (Grade 3/4) for each PT within SOC, summarized by relationship (all AEs and AEs related to study treatment)
- Adverse event of special interest. For remibrutinib the AESIs are infections, bleeding and cytopenia) by SOC and PT. The number (and proportion) of participants with AEs of crystalluria, renal toxicity, lipase and amylase elevation will be summarized by treatment for LYS006. For CFZ533, the number (and proportion) of participants with events of

infection (all PTs) and thrombosis will be summarized. For VAY736, the number (and proportion) of participants with adverse events of special interest/related to identified potential risks (infections, opportunistic infections, injection-related reactions (both systemic and local), allergic hypersensitivity reactions, CCI malignancies, leukopenia (low neutrophils (CTC Grade 3/4) or AEs neutropenia (severe), AEs lymphopenia (severe))) will be summarized for each treatment group. These AEs will be based on the excerpts from Electronic Case Retrieval Strategy (eCRS) for VAY736.

For Cohort E, exposure adjusted incidence rates output by SOC and PT will be produced only for the on-treatment period.

If the number of events warrants further detail, separate summaries by SOC and/or by PT will be provided for:

- Serious Adverse Events (SAEs)
- study drug-related AEs
- study drug-related SAEs
- AEs/study drug-related AEs leading to treatment discontinuation
- AEs/study drug-related AEs leading to dose interruption/adjustment
- AEs/study drug-related AEs leading to study discontinuation
- AEs/study drug-related AEs leading to death

The following listings will be produced:

- All adverse events (safety set)
- Serious adverse events (safety set)
- AEs leading to treatment discontinuation (safety set)
- AEs leading to dose interruption/adjustment (safety set)
- Adverse events among subjects who were not treated (all screened subjects)
- Adverse event of special interest (AESIs) (safety set)

For cohort E, injection-related reaction (systemic and local) will be listed and summarized by treatment.

Listing of AEs of cohort E will include the information on the relationship of AE to the premedication.

2.7.1.2 Deaths

The number of deaths (both on-/post-treatment) resulting from SAEs irrespective of study treatment relationship will be provided by SOC and PT.

All deaths will be listed for the safety set and post treatment deaths will be flagged.

EudraCT and clinicaltrials.gov requirements for AEs and Deaths summaries

For the legal requirements for submission of the study results after completion of the clinical trial (***defined as last subject last visit***) at clinicaltrials.gov and EudraCT, two required tables on treatment-emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment-emergent SAEs and SAEs suspected to be related to study

treatment will be provided by SOC and PT on the safety set population. These tables will be produced by Novartis.

If for a same subject, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single 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
- 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

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.7.1.3 Laboratory data

All laboratory may be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing may be provided presenting all parameters in a subject with any abnormal values. Graphical displays of lab parameters over time may be provided including that for hsCRP.

The summaries will include all on-treatment assessments available at the time of analysis for the lab parameters listed in Appendix Section 5.3 (Table 5-4). Shift tables using the low/normal/high classification (see Appendix Section 5.3 (Table 5-5)) will be used to compare pretreatment to the worst on-treatment value. For Cohort E, shift tables using the CTCAE grade will also be produced to compare pretreatment to the worst on-treatment value for the parameters specified here - hemoglobin, platelet, WBC, neutrophils, lymphocytes, serum creatinine, total bilirubin, ALT, AST, ALP.

Summary of the change from baseline to maximum/minimum post-baseline value for the lab parameters will be provided. Summary for newly occurring or worsening lab abnormalities based on CTCAE grade will be provided.

Liver function parameters

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, the following liver function parameters are collected: ALT, AST, TBL(total bilirubin), PT/INR, ALP and G-GT. A listing of liver events by each threshold category as defined in Appendix Section 5.3 (Table 5-6) will be provided.

Summary of newly occurring liver enzyme abnormalities will be provided. Newly occurring means subjects not meeting criterion at baseline and meeting criterion post-baseline. The notable criteria for liver parameters that needs to be reported in the summary table are:

- ALT > 3x ULN
- ALT > 5x ULN
- ALT > 10x ULN

- ALT > 20x ULN
- ALT or AST > 3x ULN
- ALT or AST > 5x ULN
- ALT or AST > 8x ULN
- ALT or AST > 10x ULN
- ALT or AST > 20x ULN
- ALT or AST > 3x ULN and TBL > 1.5x ULN
- ALT or AST > 3x ULN and TBL > 2x ULN
- ALP > 1.5x ULN
- ALP > 2x ULN
- ALP > 5x ULN
- TBL > 1x ULN
- TBL > 1.5x ULN
- TBL > 2x ULN
- ALP > 3x ULN and TBL > 2x ULN
- ALP > 5x ULN and TBL > 2x ULN
- ALT or AST > 3x ULN and INR > 1.5
- ALT or AST > 3x ULN and TBL > 2x ULN and ALP < 2x ULN (Potential Hy's law)

Additionally, for Cohort E:

- GGT ≥ 5x ULN

Renal events

CCI

2.7.1.4 Other safety data

2.7.1.4.1 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters are collected: systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), body temperature (°C), and weight (kg).

Vital signs collected during on-treatment will be summarized by treatment and visit/time. Listings will be provided by treatment arm, subject, and visit/time. If ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Graphical displays of data over time will be provided if relevant.

In the listing, the assessments collected during the post-treatment period will be flagged.

Summary of newly occurring clinically notable changes in vital signs parameters will be provided. The clinically notable criteria are:

- Pulse rate (low: < 50 beats/min, high: > 100 beats/min)
- Systolic blood pressure (low: < 90 mmHg, high: >=140 mmHg)
- Diastolic blood pressure (low: < 60 mmHg, high: >=90 mmHg)

2.7.1.4.2 12-lead ECG

All single 12-lead ECG data (included but not limited to PR, QRS, QT, QTcF and RR intervals) will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. All ECG data will be displayed graphically showing data over time, if relevant.

The number and percentage of subjects with notable ECG values will be presented by treatment group. A listing of these subjects by treatment arm will then be presented.

In the listings, the assessments collected during the post-treatment period will be flagged.

Criteria for notable ECG parameters:

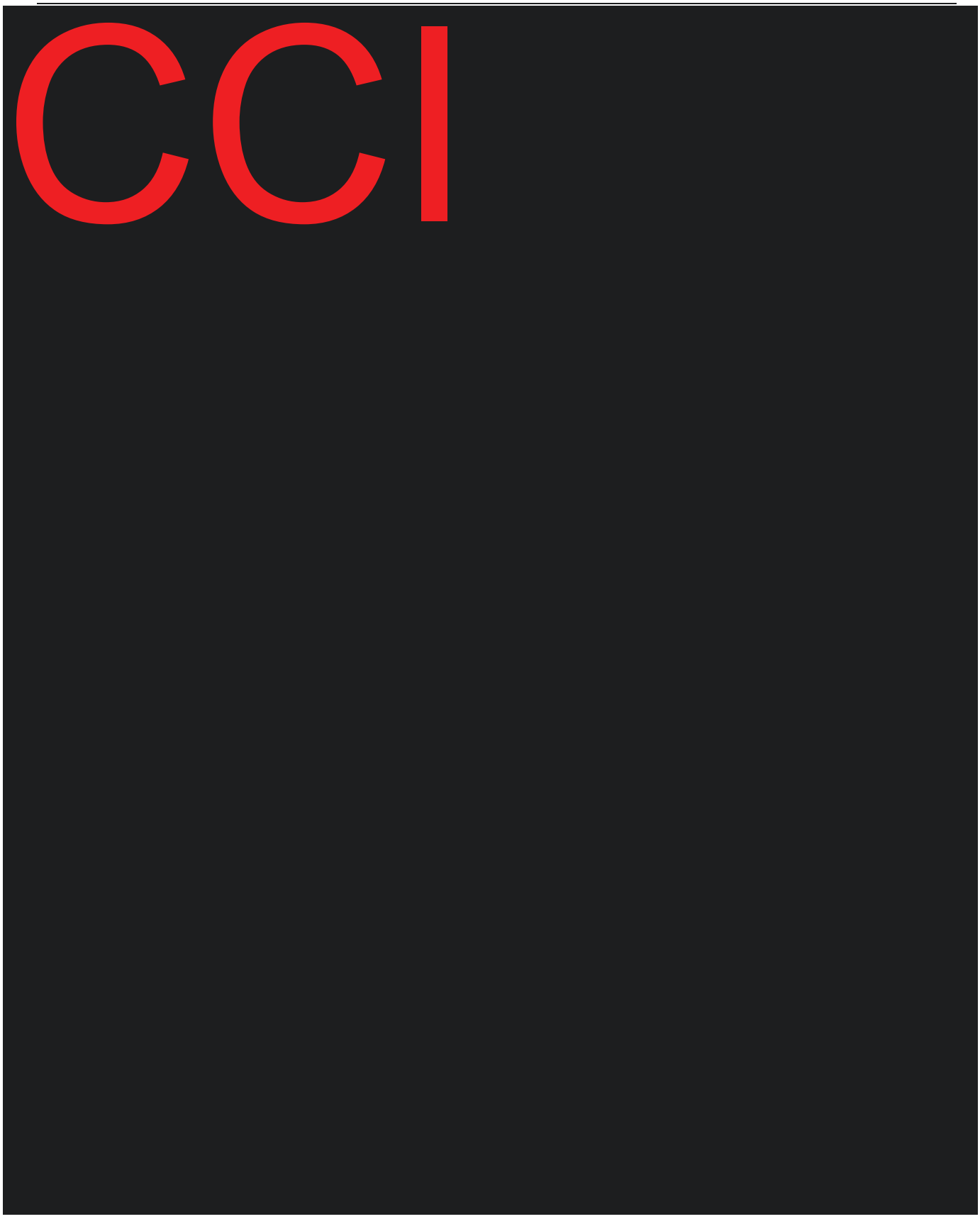
- QT, or QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from baseline of > 30 ms to ≤ 60 ms
  - Increase from baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS

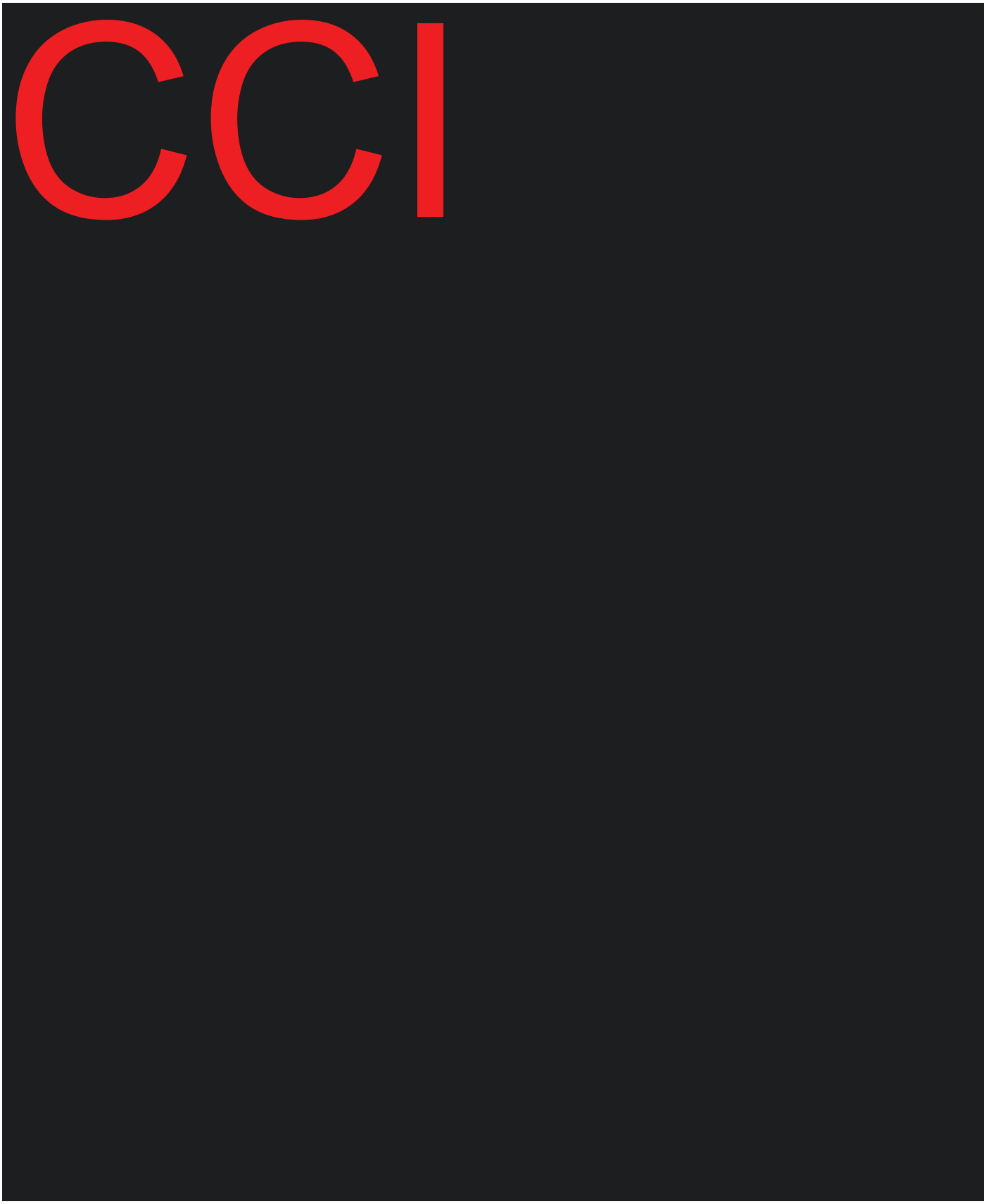
- Increase from baseline >25% and to a value > 120 ms
- New values of QRS > 120 ms

A summary of newly occurring notable ECG values will be provided. A listing of notable ECG values will be produced and notable values will be flagged.

2.8 Exploratory analyses

Some of the exploratory analyses may be conducted in an independent document outside of CSR.


CCI


CCI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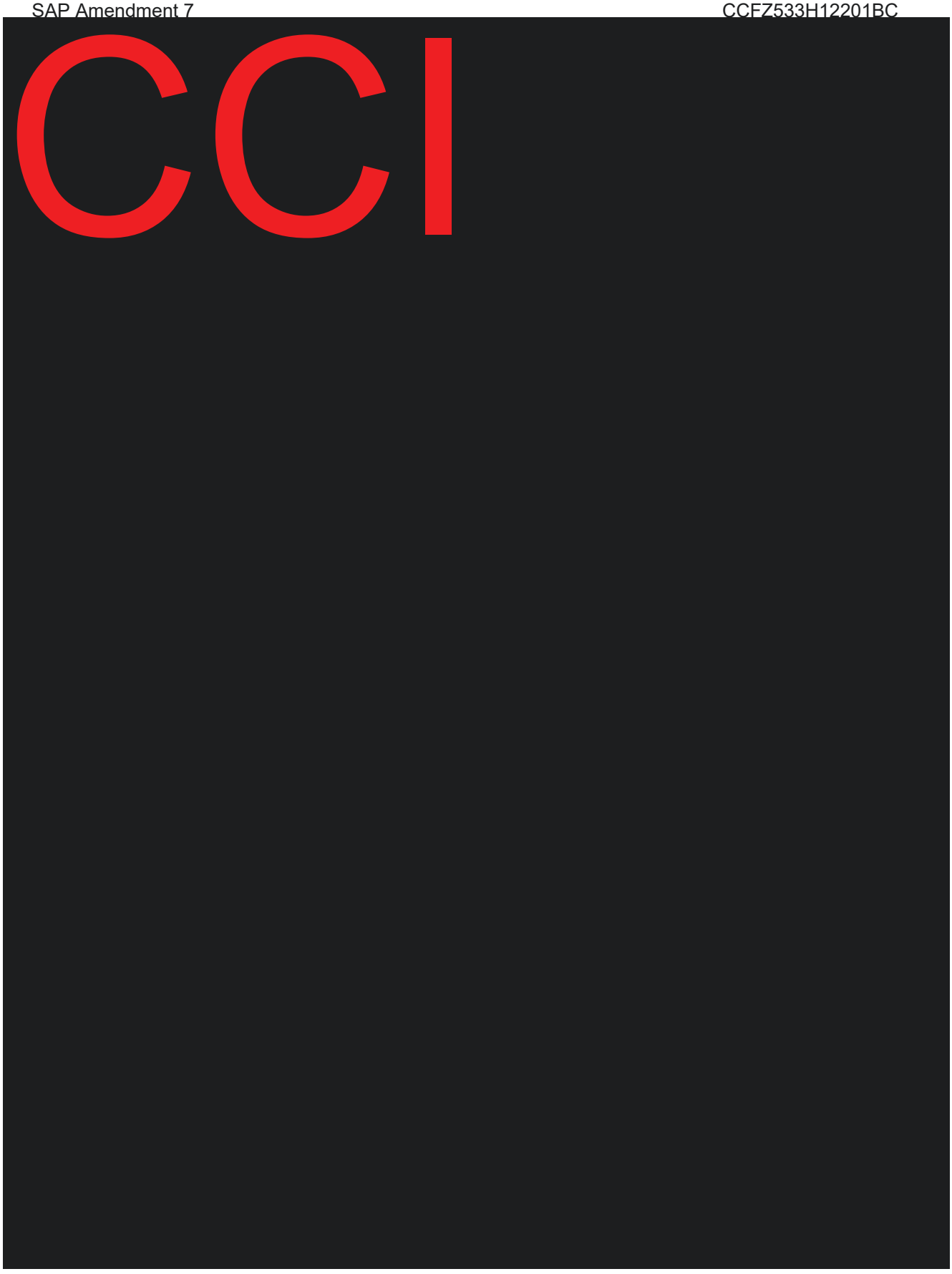
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2.9 CCI

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3 Sample size calculation

3.1 Primary endpoint

Approximately CCI subjects are to be recruited, with approximately CCI in each of Cohort A and B, approximately CCI in Cohort C, approximately CCI in Cohort D (approximately CCI subjects will receive remibrutinib CCI mg CCI., approximately CCI subjects will receive remibrutinib CCI mg CCI and approximately CCI subjects corresponding placebo), and approximately CCI in Cohort E. Within the analysis set of the primary endpoint, if more than 10% treatment withdrawals/discontinuations are observed before completion of 12 weeks of treatment, the discontinued subjects may be replaced to ensure enough data are available to effectively assess the treatment effect. Subjects will be randomized in a 2:1 ratio to the investigational treatment or placebo within Cohorts A and B, 3:1 ratio for Cohorts C and E, and 3:3:1 ratio for Cohort D.


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Figure 3-1 CCI


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3.2 Secondary endpoint

Not Applicable.

4 Change to protocol specified analyses in consideration due to COVID-19

Due to the COVID-19 pandemic, it may not be possible to perform some procedures as per protocol. All deviations due to COVID-19 will be listed separately to other deviations and may also be tabulated.

Observations that were impacted due to COVID-19, may be excluded from the primary analyses, for example including (but not limited to) observations taken at participant's house instead of site, and separately explored to identify if there is an impact of them on the analyses.

5 Appendix

5.1 Imputation rules

5.1.1 Date imputation

5.1.1.1 Date of last drug administration

The following rule should be used for the imputation of date of last administration for a given study treatment component:

Scenario 1: If the date of last administration is completely missing and there is no EOT eCRF page, the subject is considered as on-going:

The subject should be treated as on-going and the cut-off date should be used as the last dosing date.

Scenario 2: If the date of last administration is completely or partially missing and the EOT eCRF page is available (prior to any death date or withdrawal of consent date, if available):

Case 1: The date of last administration is completely missing, and the EOT visit date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for the date of last administration, and yyyy = the year of EOT date and mm < the month of EOT visit:

Use last day of the Month (mm).

After imputation, compare the imputed date with the start date of that specific record, if the imputed date is < start date of that record

Use the start date of that record.

5.1.1.2 Date of first drug administration

Subjects with missing start dates are generally considered missing for all study treatment component related calculations and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

However, if the dosing information at day 1 is entered on the PK DAR page, the date on this page will be used to impute the first administration date. Before imputing the date, it will be checked that the date is not after the second administration or after the end date of the first record.

5.1.1.3 First HS diagnosis date

1. If the first diagnosis or Symptom onset day/ month are missing and the year is nonmissing:
   a. If the year part of the date is equal to the year part of the inform consent date, then the imputed date is set to the year start point (01JANYYYY).
   b. Otherwise the imputed date is set to the mid-year point (01JULYYYY).
2. If the first diagnosis or Symptom onset day is missing and the month/year are nonmissing:
   a. If the month and year part of date is equal to the month and year part of the inform consent date, then the imputed date is set to the month start point (01MONYYYY).
   b. Otherwise the imputed date is set to the mid-month point (15MONYYYY).

5.1.2 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.

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

5.1.3 Concomitant medication date imputation

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Appendix Section 5.1.2). No imputation will be performed for concomitant medication end dates.

5.1.4 CCI

5.1.5 Multiple Imputation (MI) for Primary Efficacy

To address the concern that treatment withdrawals could be due to safety/tolerability of the study drug, MI will be performed to impute intermittent or monotonic missingness on the underlying abscess, nodule and fistula counts of the primary efficacy response, sHiSCR. The procedure is described as below:

Assume a dataset ***A*** with longitudinal data that includes:

- ***n*** subjects with response as defined at the primary timepoint and without intercurrent event (IE) (potentially missing data in-between, but this doesn't matter)
- ***m*** subjects with an IE for whom non-response is imputed in a composite strategy
- ***r*** subjects with an IE for whom multiple imputations are applied

1. For the reduced dataset (***A*** minus the ***m*** subjects), apply multiple imputations (say 100 times), separately for each treatment group assuming that the IE is non-informative (like treatment discontinuation due to COVID or due to administrative reasons, like moving to a

different region). This reflects a hypothetical strategy. (In SAS you would either use a "by treatment" statement or add treatment in the model statement in PROC MI)

2. Arrange the dataset in long format i.e. stack the response counts for each **type** (abscess, nodule, fistula) such that the response variable is $\boldsymbol{Y_{ijk}}$ where $\boldsymbol{i}$ is subjId, $\boldsymbol{j}$ is visit number, $\boldsymbol{k}$ is count type. Below is the proposed organization of data on which MI should be implemented:

Subjid	visit	countType	respCount	BLcovariates
1	1	1	Y111	x
1	1	2	Y112	x
1	1	3	Y113	x
1	2	1	Y121	x
1	2	2	Y122	x
1	2	3	Y123	x

3. Fit a model to $\boldsymbol{Y_{ijk}}$ including including visit*type as covariate along with other baseline covariates that exhibit difference between the treatment arms based on preliminary descriptives.
4. Of note, the variables to be imputed in the MI model should be "normally" distributed, however, it has also worked well for 5-point categorical varables in the past.
5. In each of the 100 imputed datasets, derive the response HiSCR, add the $\boldsymbol{m}$ subjects, and run the primary analysis. This would result in 100 posterior distributions. The averaging of the results will be in line with the approach recommended by Zhou and Reiter et al, 2010.
6. In case the algorithm is computationally unstable for full model, consider modeling with fewer covariates (Hurley score, weight); or, consider modeling abscesses, nodules, fistula separately.
7. Produce a table presenting treatment effect estimates from the non-imputed data and imputed data along with credible intervals.

5.2 Definitions of Efficacy Response Endpoints

5.2.1 HiSCR and its Derivatives

The HiSCR is defined by the status of three types of HS specific lesions, which are abscesses (fluctuant, with or without drainage, tender or painful), inflammatory nodules (tender, erythematous, pyogenic granuloma lesion), and draining fistulae (sinus tracts, with communications to the skin surface, draining purulent fluid, also called tunnel). The proposed definition of responders to treatment (HiSCR achievers) is at least a 50% reduction in abscesses and nodules (ANs), no increase in the number of abscesses, and no increase in the number of draining fistulas from baseline (Kimball et al 2014, Kimball et al 2018).

A **simplified HiSCR50** (sHiSCR) is proposed for this study as primary endpoint and is defined as follows:

1. at least a 50% reduction in abscesses and inflammatory nodules (ANs),
2. no increase in the number of draining fistulas from baseline

This definition is used to reflect the difficulty in clinically distinguish abscesses reliably from inflammatory nodules. The score will be derived from the individual lesion counts of abscesses

and nodules (and fistulae) at scheduled visits as indicated in Assessments schedule and as such will not be recorded in the CRF.

Additionally to facilitate comparisons with other trials, the following HiSCRs will be derived:

- The simplified HiSCR90 (sHiSCR90)
    a. at least a 90% reduction in abscesses and inflammatory nodules (ANs), and
    b. no increase in the number of draining fistulas from baseline.
- The simplified HiSCR75 (sHiSCR75)
    a. at least a 75% reduction in abscesses and inflammatory nodules (ANs), and
    b. no increase in the number of draining fistulas from baseline.
- The original HiSCR (or HiSCR)
    a. at least a 50% reduction in abscesses and inflammatory nodules (ANs),
    b. no increase in the number of draining fistulas from baseline, and
    c. no increase in the number of abscesses.
- HiSCR75:
    a. at least a 75% reduction in abscesses and inflammatory nodules (ANs),
    b. no increase in the number of draining fistulas from baseline, and
    c. no increase in the number of abscesses.
- HiSCR90:
    a. at least a 90% reduction in abscesses and inflammatory nodules (ANs),
    b. no increase in the number of draining fistulas from baseline, and
    c. no increase in the number of abscesses.


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5.3 Laboratory parameters derivations

Table 5-4 lists all laboratory parameters that are collected. Table 5-5 lists CTC grade for the laboratory parameters to be summarised.

Table 5-4 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), MCH, MCHC, MCV, For Cohort E only: CCI [redacted]
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose, CCI [redacted] (Cohort C only) CCI [redacted]. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated
Coagulation	International normalized ratio [INR]), activated Partial thromboplastin time (aPTT), Prothrombin time (PT)
Serology	HbsAg, HbcAb, hepatitis C antibodies, HIV, CMV, Lupus anticoagulant, Quantiferon
Additional tests	hsCRP, IgA, IgG, IgM, sBAFF
Pregnancy Test	Serum / Urine pregnancy test

Table 5-5 Laboratory parameters CTC grade as per EASE standards

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Hematology								
WBC ↓	10^9/L	WBC	**3.9 – 10.7 x 10^9/L**	≥ LLN	< LLN - 3.0 x 10^9/L	< 3.0 – 2.0 x 10^9/L	< 2.0 – 1.0 x 10^9/L	< 1.0 x 10^9/L
WBC [2] (Leukocytosis)	10^9/L	WBC			-	-	> 100 x 10^9/L	-

Hemoglobin [2] (Anemia) Hemoglobin ↑	g/L g/L	HGB HGB	**120 - 160 g/L** or 7.4 - 9.9 mmol/L (F) **140 - 170 g/L** or 8.7 – 10.6 mmol/L (M) *(16.113 x mmol/L = g/L)*	≥ LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L Increase >0-20 g/L above ULN	< 100 - 80 g/L < 6.2 - 4.9 mmol/L Increase >20-40 g/L above ULN	< 80 g/L < 4.9 mmol/L Increase >40 g/L above ULN	- -
Platelets ↓	10^9/L	PLAT	**150 - 350 x 10^9/L**	≥ LLN	< LLN - 75.0 x 10^9/L	< 75.0 - 50.0 x 10^9 L	< 50.0 - 25.0 x 10^9/L	< 25.0 x 10^9 /L
Neutrophils [3]↓	10^9/L	NEUT		≥2x10^9 /L	< 2.0 - 1.5 x 10^9 /L	< 1.5 - 1.0 x 10^9 /L	< 1.0 - 0.5 x 10^9 /L	< 0.5 x 10^9 /L
Lymphocytes [3]↓ Lymphocytes ↑	10^9/L 10^9/L	LYM LYM		≥1.5x10^9 /L	< 1.5 - 0.8 x 10^9 /L -	< 0.8 - 0.5 x 10^9 /L > 4 - 20 x 10^9 /L	< 0.5 - 0.2 x 10^9 /L > 20 x 10^9 /L	< 0.2 x 10^9 /L -
Biochemistry								
AST ↑	U/L	AST	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Total bilirubin ↑	umol/L	BILI	**5.1 – 20.5 umol/L** or 0.3 – 1.2 mg/dL	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	**36 - 92 U/L** or 0.5 - 1.5 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine [4]↑	umol/L	CREAT	**61.9 - 115 umol/L** or 0.7 – 1.3 mg/dL	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Albumin [2] (Hypoalbuminemia)	g/L	ALB	**35 - 55 g/L** or 3.5 to 5.5 g/dL	≥ LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-
Lipase ↑	U/L	LIPASE	**<95 U/L** or <1.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	**0 - 130 U/L** or 0 – 2.17 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Uric acid [2] (Hyperuricemia)	umol/L	URATE	**150 - 470 umol/L** or 2.5 – 8 mg/dL *(59.48 x mg/dL = umol/L)*	≤ ULN	> ULN – 10 mg/dL > ULN – 595 umol/L	-	-	> 10 mg/dL > 595 umol/L
Calcium (corrected) [2] (Hypercalcemia) Calcium (corrected) [2] (Hypocalcemia)	mmol/L mmol/L	CACALC CACALC	**2.2 - 2.6 mmol/L** or 9 - 10.5 mg/dL *(0.2495 x mg/dL = mmol/L)*	≤ ULN ≥ LLN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L < LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	> 11.5 - 12.5 mg/dL > 2.9 - 3.1 mmol/L < 8.0 - 7.0 mg/dL < 2.0 - 1.75 mmol/L	> 12.5 - 13.5 mg/dL > 3.1 - 3.4 mmol/L < 7.0 - 6.0 mg/dL < 1.75 - 1.5 mmol/L	> 13.5 mg/dL > 3.4 mmol/L < 6.0 mg/dL < 1.5 mmol/L
Magnesium [2] (Hypermagnesemia) Magnesium [2] (Hypomagnesemia)	mmol/L mmol/L	MG MG	**0.62 – 0.99 mmol/L** or 1.5 – 2.4 mg/dL *(0.4114 x mg/dL = mmol/L)*	≤ ULN ≥ LLN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L < LLN - 1.2 mg/dL < LLN - 0.5 mmol/L	- < 1.2 - 0.9 mg/dL < 0.5 - 0.4 mmol/L	> 3.0 – 8.0 mg/dL > 1.23 – 3.3 mmol/L < 0.9 - 0.7 mg/dL < 0.4 - 0.3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L < 0.7 mg/dL < 0.3 mmol/L

Glucose (non-fasting) [2] (Hyperglycemia)	mmol/L	GLUCSN	**<7.8 mmol/L** or <140 mg/dL *(0.05551 x mg/dL = mmol/L)*	≤ ULN	-	> ULN - 250 mg/dL > ULN - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose (fasting) [2] (Hyperglycemia)	mmol/L	GLUCSF	**3.9 – 5.8 mmol/L** or 70 - 105 mg/dL	≤ ULN	> ULN - 160 mg/dL > ULN - 8.9 mmol/L	> 160 - 250 mg/dL > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dL > 13.9 - 27.8 mmol/L	> 500 mg/dL > 27.8 mmol/L
Glucose [2] (Hypoglycemia)	mmol/L	GLUCSN/ GLUCSF	*(0.05551 x mg/dL = mmol/L)*	≥ LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3.0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Potassium [2] (Hyperkalemia)	mmol/L	K	**3.5 - 5.0 mmol/L** *(0.2558 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium [2] (Hypokalemia)	mmol/L	K		≥ LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium [2] (Hypernatremia)	mmol/L	SODIUM	**136 - 145 mmol/L** *(0.435 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Sodium [2] (Hyponatremia)	mmol/L	SODIUM		≥ LLN	< LLN - 130 mmol/L	-	< 130 - 120 mmol/L	< 120 mmol/L
Coagulation								
INR [2]↑	1	INR	**0.8 – 1.2**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Activated partial thromboplastin time [2,5]↑	sec	APTT	**25 - 35 sec**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

(1) = **LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria**, e.g. if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ≤ ULN.

(2) = **Life-threatening consequences and/or hospitalization are <u>not</u> considered** for determination of LAB CTC grades 3 and 4. Concomitant usage of anticoagulation therapy (for INR and Fibrinogen) is not considered either.

(3) = Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, ≥ **1.5 x 10^9 /L (lymphocytes) and** ≥ **2 x 10^9 /L (neutrophils) are considered as LAB CTC grade 0**

(4) = For Creatinine and Fibrinogen, the **comparison with baseline is <u>not</u> considered** for derivation of LAB CTC grades

(5) = In this study, partial thromboplastin time is collected. The ranges for the CTC grading will be provided in the TFLs shells, since the ranges for grading may not be the same as the ranges for grading of activated partial thromboplastin time.

Table 5-6 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≥ 5 x ULN 1.5 x ULN < TBL ≥ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN
	• ALP > 2 × ULN (in the absence of known bone pathology)
	• TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	• ALT or AST > 3 × ULN and INR > 1.5
	• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	• Any clinical event of jaundice (or equivalent term)
	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	• Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

NOVARTIS

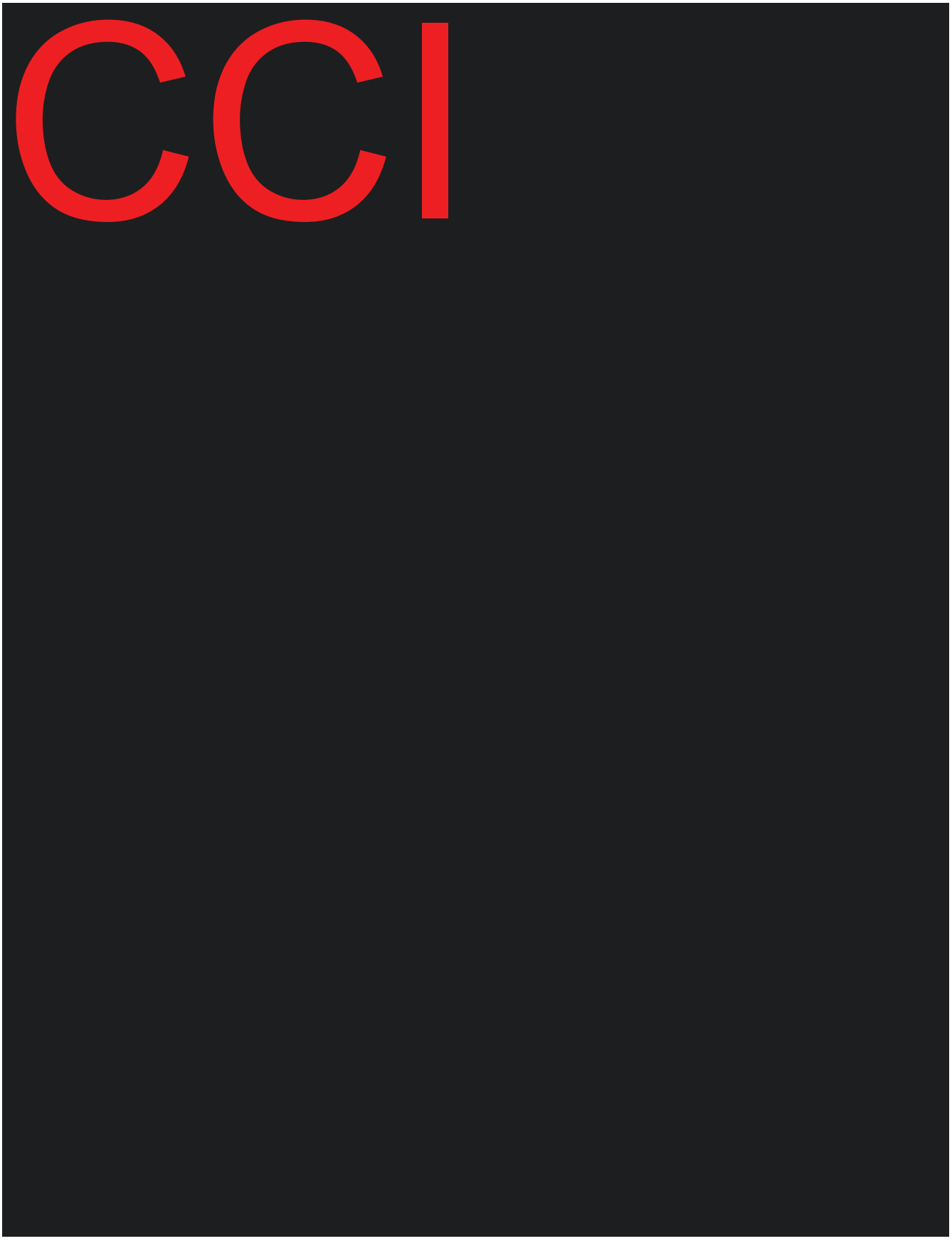
5.4 CCI

CCI

CCI

5.5 CCI

CCI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