STATISTICAL ANALYSIS PLAN	
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A Phase II Randomized, Double-blind Study to Evaluate the Safety, Neutralizing Activity and Efficacy of AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants having an Increased Risk for Inadequate Response to Active Immunization (NOVELLA)

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Class
BMI	Body Mass Index
CI	Confidence Interval
COVID-19	COronaVIrus Disease
CSP	Clinical Study Protocol
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
Gm	Geometric Mean
GMFR	Geometric Mean Fold Rise (GMT Ratio of Post-Treatment Titer to Baseline Titer)
GMT	Geometric Mean Titer
gSD	Geometric Standard Deviation
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IPD	Important Protocol Deviation
LLN	Lower Limit of Normal
M	Mean
MAAE	Medically Attended Adverse Event
max	Maximum
Me	Median
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
N	Number of (Valid) Observations
NA	Not Applicable

Abbreviation or Specialized Term	Definition
nAb	Neutralizing Antibody
PD	Protocol Deviation
PDMP	Protocol Deviations Management Plan
PT	Preferred Term
Q1–Q3	1st And 3rd Quantiles
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Software for Statistical Analysis
SD	Standard Deviation
SOC	System Organ Class
TBL	Total Bilirubin
ULN	Upper Limit of Normal
WHO	World Health Organization
WHO Drug	World Health Organization Drug Dictionary

AMENDMENT HISTORY

Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	10/12/2023	Initial approved SAP	NA	NA
4.1.6.1	19/02/2024	Description of calculation of "time (days) from last COVID-19 infection reported" added	YES	Clarification
4.1.7.2	19/02/2024	Description of table of prior COVID-19 infections removed	YES	This table described in section 4.1.6.1
4.2.1.3	19/02/2024	In description of tables of AESIs the SOC replaced with category	YES	Category is more informative for AESI than SOC
4.2.1.3	19/02/2024	Description of listings of AEs of participants who died, who had serious AEs and who discontinued study removed, description of listing of AEs leading to death added.	YES	Decided that these listings are redundant, to present AEs leading to death will be more suitable.
4.2.2.3	19/02/2024	Clarified that outputs of SARS-CoV-2 Neutralizing Antibody assessments will be presented separately for each dominant variant	YES	Clarification
4.2.3.3	19/02/2024	Clarification of table of symptomatic COVID-19 cases.	YES	Clarification
4.3.1.2	19/02/2024	Presentation of cases of IP administration interruption	YES	Clarification
4.3.3.2	19/02/2024	Description of shift tables for blood parameters updated: the table will be based on maximum CTCAE grades separately for low and high abnormal results	YES	Such presentation of abnormal results is more informative and suitable.
4.3.4.1	19/02/2024	The rules of dealing with multiple VS measurements added.	YES	Clarification
4.3.5.2	19/02/2024	Description of listing of physical examination removed.	YES	Physical examination findings register and present as AEs
5	19/02/2024	The rule of selecting data for the interim analysis added. Typos corrected	YES	Clarification
3.3.1	24/06/2024	The rule of rounding log-transformed data is added	YES	Clarification
4.1.5.1	24/06/2024	Presentation of number of participants previously vaccinated is added	YES	Clarification
4.2	24/06/2024	Typos in section numbers in the table were corrected	YES	Clarification

CSP – clinical study protocol; NA – not applicable; SAP – statistical analysis plan.

1 INTRODUCTION

The purpose of the current statistical analysis plan (SAP) is a detailed (in comparison to Section 9 of the Clinical Study Protocol (CSP)) description of basic principles of statistical analysis, description of methods used to analyse the primary and secondary endpoints, and other data obtained during the study.

This plan provides for compliance of the planned and conducted statistical analysis with the CSP, including the definition of data sets for analysis, transformations and calculations for endpoints, the required number of observations, etc. All discrepancies with the CSP should be clarified.

The current statistical analysis plan is prepared in compliance with:

- ICH harmonised tripartite guideline. Statistical principles for clinical trials (E9). Step 5 finalized guideline February 1998
- ICH harmonised tripartite guideline. Structure and Content of Clinical Study Reports (E3). Step 5 finalized guideline dated November 1995
- Good Clinical Practice of the Eurasian Economic Union, adapted by the decision of the Council of Eurasian Economic Commission on 3 November 2016, N 79
- Recommendation of the Board of the Eurasian Economic Commission No. 19 "On Guidelines for the Application of Biostatistics principles in Clinical trials of Medicinal Products", dated 3 November 2020

This SAP is based on version 3.0 of the CSP dated 2 August 2023. In case of future amendments to the protocol, the SAP may be modified to account for changes relevant to the statistical analysis.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable for the current version of statistical analysis plan.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

An interim analysis is planned after all participants have completed Visit 4 (Day 29) or have withdrawn from the study. A final analysis will occur after all participants have completed Visit 6 (Day 181) or have withdrawn from the study.

3.2 Analysis Populations

The following populations are defined:

Table 1 Populations for Analysis

Population/Analysis set	Description
Screened Set	All participants who provided the Informed Consent
Full analysis set (FAS)/ Safety analysis set	All randomized participants who received part or all of study intervention. Participants in the FAS will be classified according to the assigned treatment. The safety analysis set will include participants from the FAS but report participants according to the actual treatment received regardless of the assigned treatment.
SARS-CoV-2 neutralizing antibody analysis set	All participants in the FAS with baseline and post-dose antibody measurements (i.e. at least one post-dose antibody measurement with a measurable SARS-CoV-2 titer in serum). Participants will be classified according to the actual received treatment. Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded or have data collected after the protocol deviations set to missing.

3.3 General Considerations

The data analyses will be conducted using SAS® System (SAS Institute Inc., Cary, NC), version 9.4 or higher.

In general, all data will be listed, sorted by treatment arm and participant, and when appropriate by visit number within participant.

Unless otherwise noted, data will be presented in tables by treatment arm (i.e. AZD3152 and placebo) using descriptive statistics.

3.3.1 General Study Level Definitions

The study will consist of 2 periods: a screening period of up to 7 days (Day -7 through Day -1), and a treatment and follow-up period lasting 6 months after the administration of study intervention which consist of Visit 1 (Day 1), Visit 2 (Day 8), Visit 3 (Day 15), Visit 4 (Day 29), Visit 5 (Day 91) and Visit 6 (Day 181). Acceptable visit windows presented in Section 3.3.2. More detailed description of study visits and procedures presented in the Schedule of Activities (Table 1) of the CSP.

Categorical variables will be summarized using frequency, percentages (where the denominator for calculation is the underlying analysis set population, unless otherwise stated).

Continuous (quantitative) data will be presented as:

- Number of valid observations (n);
- Arithmetic Mean (M) or Geometrics Mean (gM) if appropriate;

- Standard deviation (SD) or Geometric standard deviation (gSD) if appropriate;
- 95% confidence interval (CI) if appropriate;
- Minimum value (Min.);
- Maximum value (Max.);
- Median (Me);

Data after log transformation will be rounded up to 3 decimals.

For continuous data, descriptive statistics will be rounded according to rules:

Mean, geometric mean, median and quartiles will be represented with an accuracy of 1 decimal place greater than the measured values. Standard deviation and geometric standard deviation will be represented with an accuracy of 2 decimal places greater. Minimum and maximum will have the accuracy of the measured values.

For categorical data, percentages will be rounded to 1 decimal place.

Data will be provided in data listings sorted by treatment arm and participant number. Tabular summaries will be presented by the actual treatment received for safety analysis and by the assigned for efficacy analysis.

3.3.2 Visit Window

Period	Visit	Nominal Day	Windows			
			SARS-CoV-2 serology	SARS-CoV-2 nAb serum samples	Labo-ratory assess-ments	Vital signs
Screening	Screening	(-7) – (-1)	(-7) – (-1)	(-7) – (-1)	(-7) – (-1)	(-7) – (-1)
Treatment and Follow-up Period	Visit 1	1	1	1	1	1
	Visit 2	8	–	5 – 11	2 – 18	2 – 94
	Visit 3	15	–	12 – 18	–	–
	Visit 4	29	2– 60	26 – 32	19 – 195	–
	Visit 5	91	61 – 136	86 – 96	–	–
	Visit 6	181	137 – 195	167 – 195	–	95 – 195

When one or more results are available for the same visit window, the result with the date closest to the expected visit date will be used in the analysis. If two observations are equidistant from the expected visit date, the later observation will be used in the analysis. Visits outside the specified visit windows will not be part of the by-visit summaries (i.e., no mapping will be applied to such data points).

3.3.3 Handling of Unscheduled Visits

Unscheduled, retest (with the same visit number assigned), and early discontinuation measurements will be included in by-visit summaries per Section 3.3.2

In the case of a missing value at a scheduled visit, which is then followed by a non-missing value at an unscheduled assessment within the same visit window, the non-missing value at the unscheduled assessment will be used.

Data collected at unscheduled assessments might be included in baseline definitions, and in any definitions of maximum value, minimum value where appropriate.

3.3.4 Multiplicity/Multiple Comparisons

All analyses will be performed in descriptive manner, no hypothesis testing will be performed.

3.3.5 Handling of Protocol Deviations in Study Analysis

Protocol deviations will be collected, reviewed, and reconciled throughout the study. Important protocol deviations (IPDs) will be identified from the complete set of protocol deviations. IPDs are those which may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a participant's rights, safety, or wellbeing.

All decisions on importance will be made throughout the study and finalised before clinical data base lock.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers participants disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical history, prior and concomitant medication and study drug compliance.

4.1.1 Participants Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Participants disposition and completion status will be comprised of the following:

- Enrolled (screened) participants;

- Non-randomized participants (screen failures);
- Randomized participants;
- Participants who were randomized but no dosed;
- Participants who received study intervention;
- Participants who were randomized and ongoing in study (applicable to primary analysis)
- Randomized participants who completed the study.
- Randomized participants who withdrew from the study;
    - Reasons for withdrawal;

4.1.1.2 Presentation

Number and percentage of participants in the following categories will be reported: participants who were screened, non-randomized, randomized, randomized but not dosed, received study intervention, randomized and ongoing in study (applicable to primary analysis), withdrew from the study (with reasons) and who completed the study.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Refer to Section 3.2 for definition of analysis sets:

- Screened set
- Full analysis set
- Safety analysis set
- SARS-CoV-2 neutralizing antibody (nAb) analysis set.

4.1.2.2 Presentation

The number of participants included in each analysis set will be reported by treatment arm. In addition, for each analysis set, the number of participants excluded, including the reasons, will be reported.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

A detailed list of possible important protocol deviations (IPDs) and the process for reviewing them by the clinical study team will be outlined in the protocol deviations management plan (PDMP).

The medical and statistical team members will review the protocol deviation categories in a blinded fashion before the clinical database lock and be classified as important per the PDMP.

At a minimum, the following deviations categories will be included for review and classified as important for the evaluation and implementation of the study:

- Inclusion Criteria Deviations
- Exclusion Criteria Deviations
- Discontinuation Criteria for study product met but participant not withdrawn from study treatment
- Discontinuation Criteria for overall study withdrawal met but participant not withdrawn from study
- Investigational Product Deviation
- Excluded Medications taken
- Deviations to study procedure
- Other Important Protocol Deviations

4.1.3.2 Presentation

The number and percentage of participants with IPDs will be provided per protocol deviation category. The summary will be based on the Safety Analysis Set.

All important protocol deviations will be presented in a listing.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographics will be comprised of age, sex, race and ethnicity.

4.1.4.2 Presentation

All Demographic data will be summarized for all participants in the Safety Analysis Set.

4.1.5 Baseline Characteristics

4.1.5.1 Presentation

Following baseline characteristics will be summarized for all participants in the Safety Analysis Set:

- Weight (kg)
- Height (cm)
- Body mass index (BMI, kg/m^2)
- Sufficient medical conditions:
    - Obese, (BMI ≥ 30 kg/m2)
    - Congestive heart failure
    - Chronic obstructive pulmonary disease
    - Chronic kidney disease, (GFR < 30 mL/min/1.73 m2)

  - Intolerant of vaccine
  - Immunocompromised state
- Previous COVID-19 vaccinations:
  - Participants previously vaccinated
  - Brand of last COVID-19 vaccine
  - Number of prior COVID-19 vaccinations received
  - Whether any bivalent booster was received or not
- Age group:
  - <60 years
  - ≥60 years

4.1.6 Disease Characteristics

4.1.6.1 Presentation

The following data on prior COVID-19 infections will be summarized for Safety Analysis Set:

- Time (days) from last COVID-19 infection reported (calculated as date of IMP dosing – date of last COVID-19 infection reported)
- Number of prior confirmed COVID-19 Infections
- Whether the previous COVID-19 infection led to hospitalization in the past 6 month or not

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Clinically significant abnormal physical examination findings at screening will be recorded as medical history.

Medical history and relevant surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or later. The version used will be indicated in the data summaries and listings.

4.1.7.2 Presentation

Medical history and Concomitant disease will be grouped by MedDRA system organ class and preferred term and will be summarized in the Safety Analysis Set as number and percentage of participants in each treatment arm.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Medications will be coded using World Health Organization Drug dictionary (WHO Drug) version Mar 2023 B3 or later. The version used will be indicated in the data summaries and listings.

Prior medications are any medications which stopped being taken prior to the study treatment.

Medication is considered concomitant if the start date is on or after the first IMP dosing date or if it started before the IMP dose and is ongoing after the IMP dose.

The algorithm for imputing missing or partial medication start and stop dates is provided in Appendix A.

4.1.8.2 Presentation

Prior and Concomitant therapy will be grouped by Anatomical Therapeutic Class (ATC) Level 2 and preferred drug name and will be summarized for all participants in the Safety Analysis Set as number of participants in each treatment arm and number of events.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

There is only single study intervention administration in this study.

4.1.9.2 Presentation

Compliance will be reported in the disposition table as participants who were randomized but no dosed, and participants who received study intervention.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses.

Statistical category	Endpoint	Popu-lation	Intercurrent event strategy	Population level summary (analysis)	Details in Section
Objective 1: To evaluate the safety of AZD3152 compared with Placebo					
Primary	Occurrence of AEs collected throughout the study Occurrence of SAEs, MAAEs, and AESIs collected throughout the study	Safety analysis set	Treatment policy will be applied, i.e., all observed events collected will be included in the analysis.	The number and proportion of participants with of AEs, SAEs, MAAEs, AESIs.	4.2.1
Objective 2: To compare the nAb responses to the SARS-CoV-2 emerging dominant variant(s) of concern circulating during the course of the study in serum following AZD3152 or Placebo administration					
Secondary	Titer for SARS-CoV-2 emerging dominant variant(s) nAbs	SARS-CoV-2 nAb analysis set	Participants who experience protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of this endpoint (i.e., while-on-treatment strategy is applied).	Geometric mean titer (GMT) and geometric mean fold rise (GMFRs) (from baseline value through **Day 181** after the single IM dose) of SARS-CoV-2 nAbs. Descriptive statistics for the log-transformed titer will include the number of participants, GMT and GMFR, corresponding gSD, 95% CI, minimum, and maximum and summarized by treatment arm.	4.2.2
Objective 3: To compare the incidence of symptomatic COVID-19 cases in participants receiving study intervention.					
Secondary	Incidence of a post-treatment symptomatic COVID-19 case (negative RT-PCR at baseline to	Full analysis set	Participants who become unblinded to treatment assignment and/or take other non-investigational product(s) for COVID-19	Incidence of a post-treatment symptomatic COVID-19 case.	4.2.3

Statistical category	Endpoint	Popu-lation	Intercurrent event strategy	Population level summary (analysis)	Details in Section
	positive RT-PCR or positive antigen test at any time up to 6 months AND symptoms specified in the modified WHO definition of symptomatic COVID-19).		prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will have data collected after the intercurrent event set to missing for analysis of this endpoint (i.e., while-on-treatment strategy is applied).		
Objective 4: CCI					
Exploratory	CCI				
Objective 5: CCI					
Exploratory	CCI				

AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; GMFR = geometric mean fold rise; GMT = geometric mean titer; gSD = geometric standard deviation; IMP = investigational medicinal product; MAAE = medically attended adverse event; nAb = neutralizing antibody; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WHO = World Health Organization

4.2.1 Primary Endpoints

Primary endpoints are:

- Occurrence of AEs collected through the study
- Occurrence of SAEs, MAAEs, and AESIs collected throughout the study

4.2.1.1 Definition

For definition of AEs, SAEs, MAAEs, and AESIs see Section 8.3 of the CSP.

Adverse events will be collected from the time of study intervention administration through the last study visit.

MAAE, AESI will be recorded from the time of study intervention administration throughout the study, up to and including the last visit.

SAEs will be recorded from the time of signing of the ICF throughout the study, up to and including the last visit.

4.2.1.2 Derivations

AEs will be coded using the latest version of the MedDRA dictionary.

4.2.1.3 Primary Analysis of Primary Endpoint

Summaries of AEs, SAEs, MAAEs and AESIs per MedDRA System Organ Class (SOC) and Preferred Term (PT) will include the number and percentage of participants reporting at least one event and number of events.

Also all AEs will be presented in following tables:

- Overall summary of AEs
- AEs by SOC and PT
- AEs by SOC, PT, and maximum intensity
- Possibly related AEs by SOC and PT
- Immediate AEs after study intervention dose by SOC and PT
- COVID-19-related AEs by SOC and PT
- AESIs by category and PT
- Medically attended AEs by SOC and PT
- Serious AEs by SOC and PT
- Possibly related AESIs by category and PT
- Possibly related medically attended AEs by SOC and PT
- Possibly related serious AEs by SOC and PT

- Serious AESIs by category and PT
- Medically attended serious AEs by SOC and PT
- Possibly related serious AESIs by category and PT
- Possibly related medically attended serious AEs by SOC and PT
- AESIs – PT mapping (according to Appendix D)

The following listings will be presented:

- All AEs
- SAEs
- MAAEs
- AESIs
- AEs leading to death
- COVID-19 Initial Assessment AEs

4.2.2 Secondary Endpoint - SARS-CoV-2 Neutralizing Antibody Assessments

4.2.2.1 Definition

Serum samples to measure SARS-CoV-2 Neutralizing Antibody (nAb) levels will be collected according to planned visits. Authorized laboratory will measure nAbs to the SARS-CoV-2 emerging dominant variant(s) circulating during the course of the study.

The SARS-CoV-2 nAb responses include the nAb titer levels and fold rise of nAb titers collected over time. The fold rise will be calculated as the ratio of the post-dose titer and the baseline nAb titer levels.

This secondary endpoint will be analyzed in the SARS-CoV-2 neutralizing antibody analysis set.

4.2.2.2 Derivations

The geometric means will be calculated as the mean of the assay results after taking the logarithm transformation and then anti-logarithm transformation the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking log transforms of assay results, calculating the 95% CI with reference to Student's t-distribution, and then anti-logarithm transforming the confidence limits.

Geometric mean fold rises (GMFRs) will be reported and limited to participants with non-missing values at both time points.

Dealing with missing and undetectable results (<LLOQ and >ULOQ) described in Appendix C. Participants who experience an important protocol deviation that can interfere with an antibody response or violate adherence to the assigned dose, become infected, receive COVID-19 treatment or vaccination that can alter nAb levels will have data collected after the intercurrent event set to missing for analysis of this endpoint (i.e., while-on-treatment strategy is applied).

4.2.2.3 Analysis

GMT and GMFRs, corresponding gSD, 2-sided 95% CIs, minimum and maximum will be presented for each visit by treatment arm in tables separately each dominant variant of SARS-CoV-2. Also box and whiskers plots (separately for each dominant variant) will be presented in the following manner: dots show geometric means, lines within boxes are medians, box bounds are quartiles and whiskers are minimums and maximums.

Also all data will be presented in listings.

4.2.3 Secondary Endpoint - Symptomatic COVID-19 Case

4.2.3.1 Definition

Incidence of a post-treatment symptomatic COVID-19 case (negative RT-PCR at baseline to positive RT-PCR or positive antigen test at any time up to 6 months AND symptoms specified in the modified WHO definition of symptomatic COVID-19).

This secondary endpoint will be analyzed in the FAS.

4.2.3.2 Derivations

The following criteria adapted from the WHO COVID-19 case definition clinical criteria (WHO 2022) will be used to determine a symptomatic COVID-19 case:

- Any two of the following: fever (subjective definition to be used for fever), cough, positive COVID-19 test (rapid antigen test or RT-PCR)

OR

- Acute onset of ANY THREE OR MORE of the following signs or symptoms: fever (subjective definition to be used for fever), cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, nausea/diarrhea/anorexia, conjunctivitis, positive COVID-19 test, symptom as judged by the Investigator to be related to COVID-19.

To properly link the onset of symptoms with the laboratory results, a window will be applied to the symptom onset date. For participants who meet the symptomatic criteria listed above, a positive of RT-PCR test or positive antigen test collected within 10 days of COVID-19 symptoms is required to consider the participant meeting the symptomatic COVID-19 case criteria.

Participants who become unblinded to treatment assignment and/or take other non-investigational product(s) for COVID-19 prevention, in both cases prior to having met the criteria for the COVID-19 endpoint, will have data collected after the intercurrent event set to missing for analysis of this endpoint (i.e., while-on-treatment strategy is applied).

4.2.3.3 Analysis

The following results will be presented with descriptive statistics by treatment arm:

- Participants who has symptomatic COVID-19
- Time to event of symptomatic COVID-19
- Participants with COVID-19 symptoms up to Visit 6 (Day 181)

Also all data will be presented in listings.

4.2.4 Other Endpoints

4.2.4.1 Definition

The following exploratory variables will be assessed:

[redacted]

4.2.4.2 Derivations

[redacted]

4.2.4.3 Handling of Dropouts and Missing Data

[redacted]

4.2.4.4 Primary Analysis of Other Endpoint

CCI [redacted]

4.3 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, and ECG. Safety Analyses will be conducted in the Safety Analysis Set.

4.3.1 Exposure

4.3.1.1 Definitions and Derivations

The study treatment will be administered using single injection. Possible reasons of incomplete injection or other abnormal study drug administration will be collected.

Duration of follow up period will be calculated as difference (in days) of date of last contact with participant – date of study treatment + 1 day.

4.3.1.2 Presentation

Data on the injection results will be listed for the Safety analysis set.

Duration of follow up period and cases of IP administration interruption will be summarized by treatment arm.

4.3.2 Adverse Events

Analysis of adverse events descripted in details in Section 4.2.1

4.3.3 Clinical Laboratory, Blood Sample

4.3.3.1 Definitions and Derivations

The serum chemistry, haematology, coagulation and other laboratory analyses will be performed.

Detailed list of safety laboratory parameters is presented in the CSP, Section 8.2.4.

4.3.3.2 Presentations

Laboratory data will be assessed and presented per parameter, treatment arm and analysis visit in summary tables using descriptive statistics for continuous variables. Changes from baseline in continuous laboratory parameters will be summarized over all participants by treatment arm and visit. Also cross (shift) tables for changes from baseline according to the maximum CTAE grade will be provided for each parameter separately for low and high abnormal results. Listings of all laboratory parameters will be provided.

4.3.4 Vital Signs

4.3.4.1 Definitions and Derivations

The following vital signs (VS) will be measured according to Section 8.2.2 of the CSP: pulse rate, respiratory rate, blood pressure, and body temperature.

For multiple VS assessments on Visit 1 the following rules will be used for analysis:

- If a participant has multiple VS assessments before IMP dosing, then the last assessment before dosing should be used as baseline and included into the table, but all records should be reported in a listing
- If a participant has multiple VS assessments after dosing then:
    - If a participant has record in “10-15 min window after dosing" then this record should be included in analysis as correct assessment
    - If a participant does not have records in "10-15 min window after dosing" then the first post-dosing assessment should be included in analysis

For multiple VS assessments on Visits 2 and 6 the earliest assessment within a visit window will be used for analysis.

4.3.4.2 Presentations

Vital signs will be summarized following a similar procedure as described above for laboratory values. Will be assessed and presented in Safety analysis set in summary tables using descriptive statistics for continuous variables. Changes from baseline will be summarized over all participants by treatment arm and visit. A listing of all vital signs will be provided.

4.3.5 Electrocardiogram and Physical Examination

4.3.5.1 Definitions and Derivations

Electrocardiogram (ECG) and physical examination will be conducted on the screening and during the study if indicated.

4.3.5.2 Presentations

A listing of ECG data will be provided.

4.3.6 Liver Signs and Symptoms

4.3.6.1 Presentations

The following laboratory data on liver toxicity for each treatment arm will be provided in the Safety Analysis Set:

- A table for the highest recorded values of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) after baseline, grouped into the following

categories: less than 3 times the upper limit of normal (ULN), from 3 up to but not including 5 times the ULN, from 5 up to but not including 10 times the ULN or 10 times or greater than the ULN. These values will be cross-referenced with the highest recorded total bilirubin (TBL) values post-baseline, categorized as less than 2 times the ULN or 2 times the ULN and above.

- A listing of participants who had at least one recorded post-baseline value of ALT or AST 3 times the ULN or greater or a TBL value 2 times the ULN or greater
- A listing of participants who had at least one recorded post-baseline value of ALT or AST 3 times the ULN or greater and simultaneously a TBL value 2 times the ULN or greater

5 INTERIM ANALYSIS

Two planned statistical analyses will be performed:

Interim analysis (unblinded and performed by a separate unblinded team)

An interim analysis is planned after 116 participants have completed Visit 4 (Day 29) (or early withdrawal from the study) to evaluate early safety at Day 29. All available data by the the date when the last participant completed (or withdrew from) Visit 4 will be included in the interim analysis. Efficacy data may be presented as appropriate at interim analysis if adequate data allows.

This interim analysis will include primary endpoint variables: all AEs, SAEs, MAAEs, and AESIs. If available, nAb responses to the SARS-CoV-2 emerging dominant variant(s) will be analysed.

This interim analysis will be unblinded and will be performed by a separate unblinded team. Disposition, demographic, baseline characteristics, occurrence of AEs collected through the study and occurrence of SAEs, MAAEs, and AESIs collected throughout the study will be provided by treatment arms.

Final analysis (unblinded)

The final analysis will be performed once all participants complete Visit 6 (Day 181) or early withdrawal from the study.

No multiplicity correction is expected as there are no formal statistical tests planned, only descriptive data.

6 REFERENCES

- ICH harmonised tripartite guideline. Statistical principles for clinical trials (E9). Step 5 finalized guideline February 1998;
- ICH harmonised tripartite guideline. Structure and Content of Clinical Study Reports (E3). Step 5 finalized guideline dated November 1995;
- Good Clinical Practice of the Eurasian Economic Union, adapted by the decision of the Council of Eurasian Economic Commission on 3 November 2016, N 79.

APPENDIX A MISSING MEDICATION DATES IMPUTATION

The imputation rules for missing or partial medication start/stop dates are as follows:

- Missing or partial medication start dates:
  - If only the day is missing, use the first day of the month.
  - If both the day and month are missing, use the first day of the year.
  - If only the month is missing, use the year's first month.
  - If day and month are present and the year is missing, use the year of the informed consent date.
  - Use the informed consent date if the day, month, and year are missing.
- Missing or partial medication end dates:
  - Use the earliest of the data cutoff date and the end-of-study date as the reference date for the imputation rules below.
  - If the year is the same as the reference date's year:
    - If the day is missing and the month is the same as the reference date's month, use the day of the reference date.
    - If the day is missing and the month is different from the reference date's month, use the last day of the month.
    - If the day is present and the month is missing, use the month of the reference date.
  - If the year is different from the reference date's year:
    - If only the day is missing, use the last day of the month.
    - If both the day and month are missing, use the last day of the year.
  - If the date is completely missing, use the reference date.

APPENDIX B MISSING SAFETY DATA

Missing safety data is generally not imputed. However, safety assessments of the form of "<x" (ie, below the lower limit of quantification [LLOQ]) or ">x" (ie, above the upper limit

of quantification [ULOQ]) are imputed as “x” in the calculation of summary statistics but are displayed as “<x” or “>x” in the listings.

APPENDIX C MISSING DATA ON NEUTRALIZING ANTIBODIES

The analysis of GMTs will use the following imputation methods:

- Missing titer values will not be imputed.
- Titer values measured below the LLOQ will be imputed with half the LLOQ in summaries and analyses but will be listed as reported in the raw data listings.
- Titer values measured above the ULOQ will be imputed at the ULOQ value.

APPENDIX D AESI – PT MAPPING

AESI Category	Preferred Term
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	CCI


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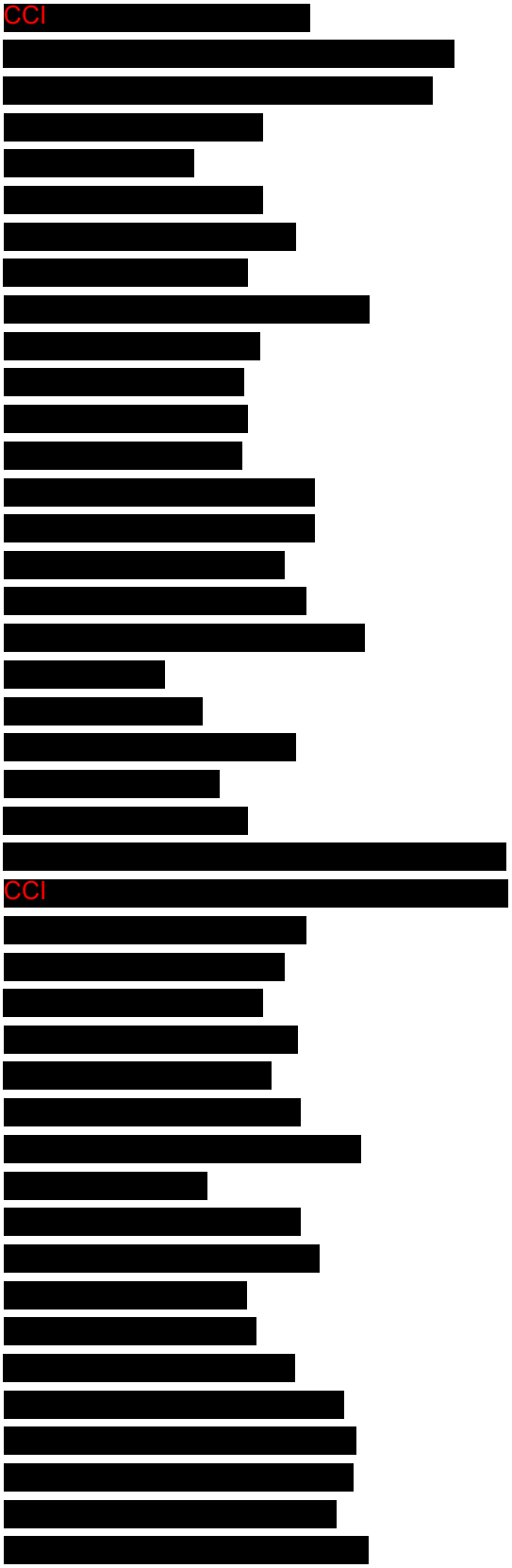
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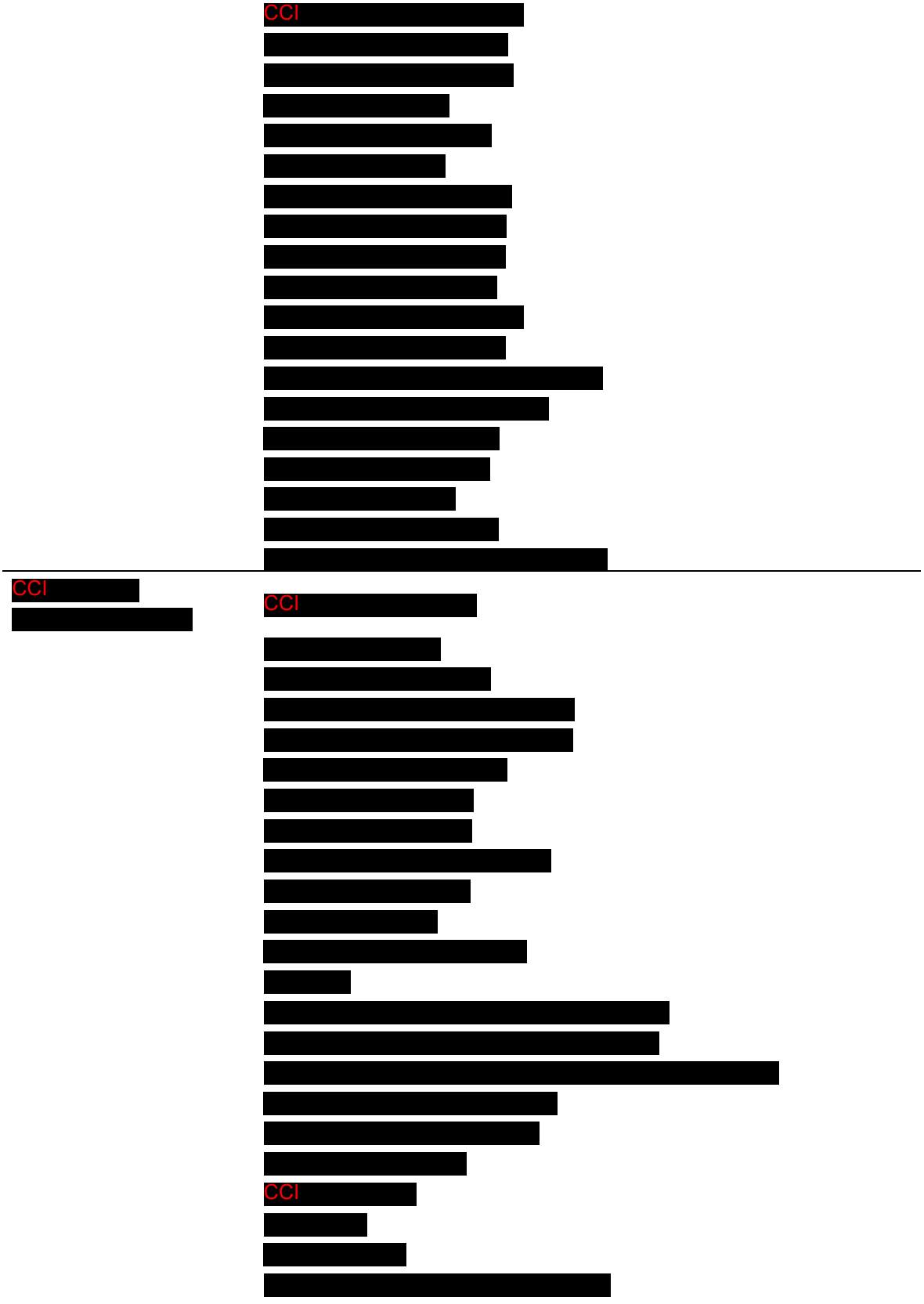
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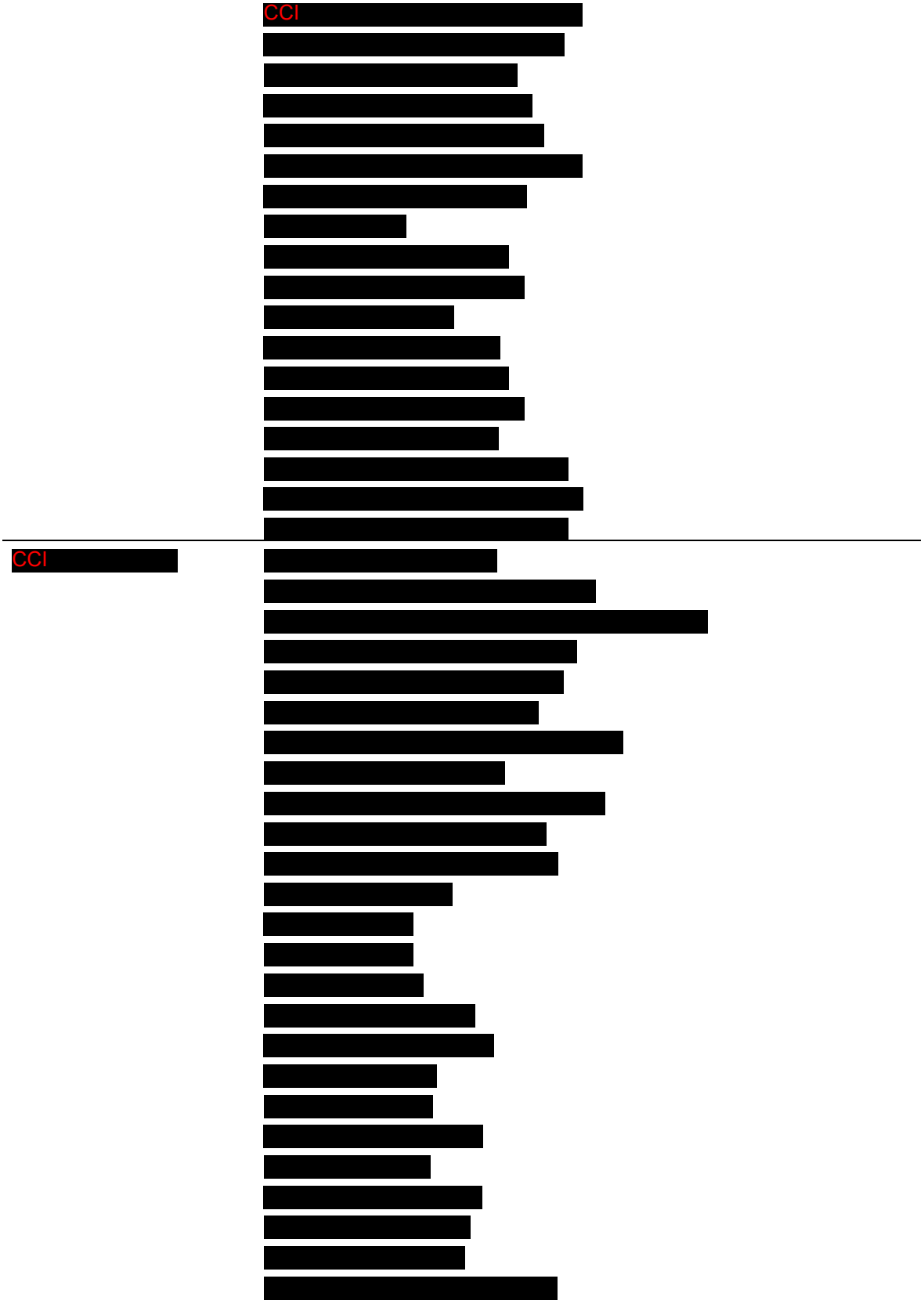
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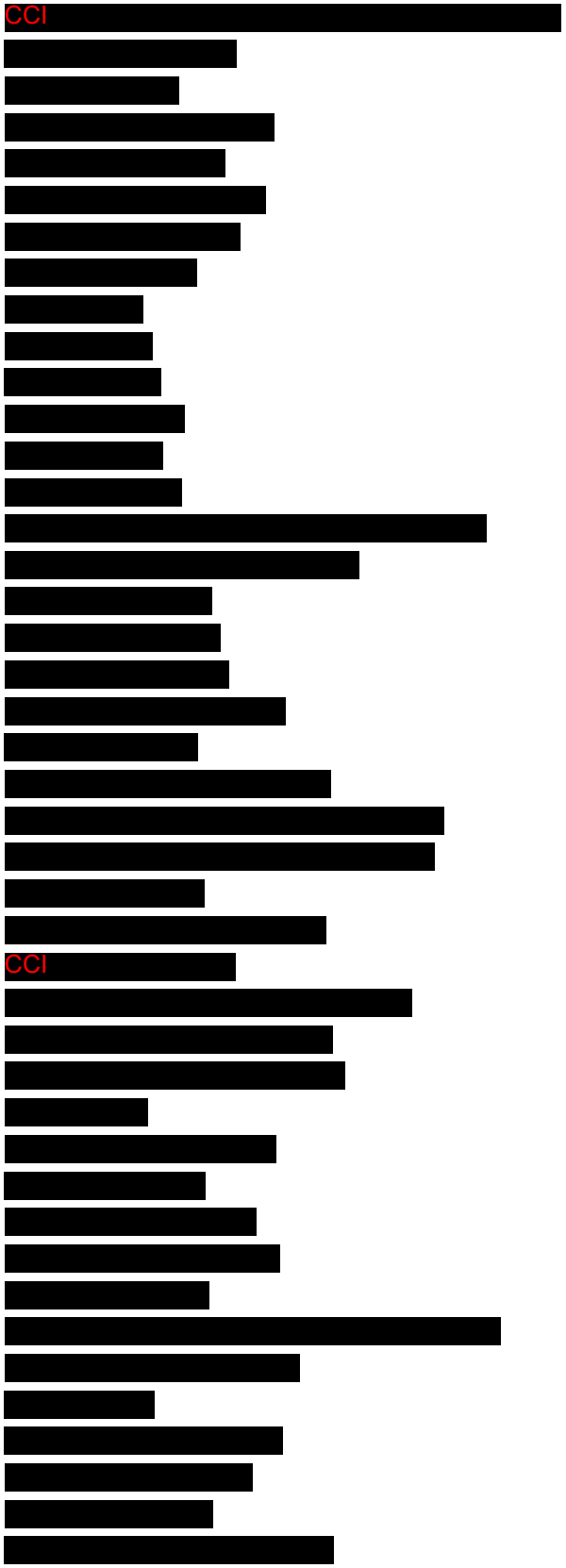
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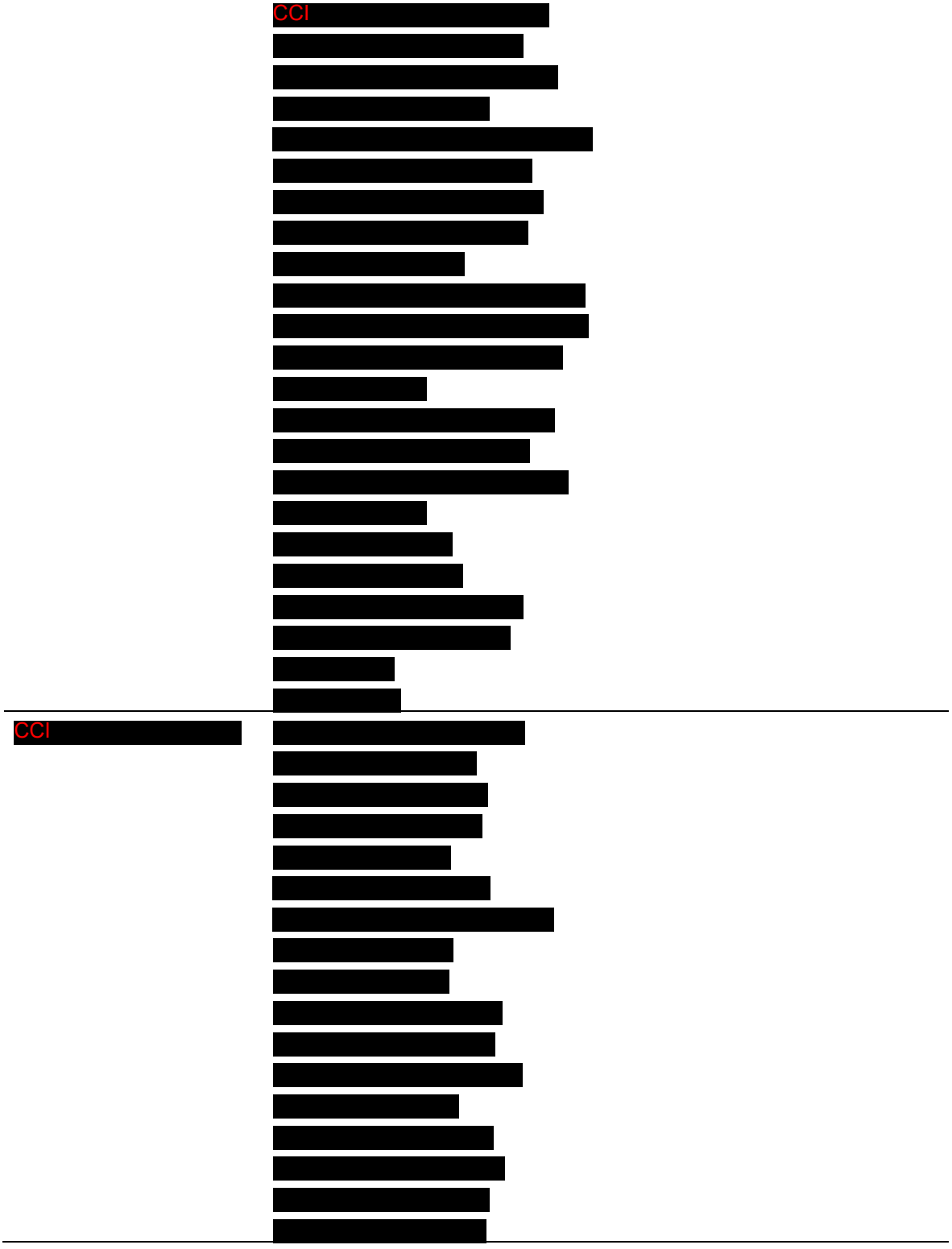
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