Final Analysis Integrated Analysis Plan

Clinical Trial Protocol Identification No.	MS200527-0086
Title:	A Randomized, Double-Blind, Placebo-Controlled Phase II Study of M2951 with a Parallel, Open-Label, Active Control Group (Tecfidera), in Patients with Relapsing Multiple Sclerosis to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics, and Biological Activity.
Trial Phase	II
Investigational Medicinal Product(s)	Evobrutinib
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Integrated Analysis Plan Author	**Coordinating Author** Biostatistics, Merck **Function**: PPD, PPD **Author(s) / Data Analyst(s)**: PPD
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Integrated Analysis Plan Reviewers	Merck/EMD-Serono Reviewers: **Function**: PPD **Name**: PPD

PPD Reviewers:

Function	Name
PPD	PPD

1 Signature Page

Integrated Analysis Plan: MS200527-0086
A Randomized, Double-Blind, Placebo-Controlled Phase II Study of M2951 with a Parallel, Open-Label, Active Control Group (Tecfidera), in Patients with Relapsing Multiple Sclerosis to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics, and Biological Activity.

Approval of the Final Analysis IAP by Merck Responsible is documented within BREEZE via eSignature.

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2 Table of Contents

3 List of Abbreviations and Definition of Terms

ALC	Absolute lymphocyte count
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine Amino-Transferase
ARR	Annualized Relapse Rate
AST	Aspartate Amino-Transferase
ATC	Anatomical Therapeutic Class
BEA	Blinded extension analysis
BID	twice daily
BMI	Body Mass Index
BOA	Biostatistics Outputs Assembly
CCI	[redacted]
CCI	[redacted]
BCP	Business Continuity Plan
CFB	Change from Baseline
CI	confidence interval
CTP	Clinical Trial Protocol
DBP	Double-blind period
DMT	Disease Modifying Therapy
EAIR	Exposure Adjusted Incidence Rate
eCRF	electronic Case Report Form
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EEA	European Economic Area
EOT	End of Treatment
FA	Final Analysis
Gd+	Gadolinium-positive
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
CCI	[redacted]
IA	Interim Analysis

IAP	Integrated Analysis Plan
Ig	Immunoglobulin
IMP	Investigational Medical Product
IPD	Important Protocol Deviation
IV	Intravenous
IWRS	Interactive Web Response System
LLN	Lower limit of normal
CCI	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention to Treat
MMRM	Mixed Effect Model for Repeated Measures
MRI	Magnetic Resonance Imaging
MS	Multiple sclerosis
NB	Negative binomial
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
OLE	Open-label extension
PA	Primary Analysis
CCI	[redacted]
CCI	[redacted]
Pdev	Protocol deviation
CCI	[redacted]
PT	Preferred Term
QD	Once daily
Q1	25th Percentile
Q3	75th Percentile
RMS	Relapsing multiple sclerosis
RoW	Rest of the World
SAF	Safety Analysis Set
SAF-OLE	Safety Open-Label Extension Analysis Set
SAF-SWOLE	Safety Switch Open-Label Extension Analysis Set
SCR	Screening Analysis Set
SD	Standard Deviation

SDTM	Study Data Tabulation Model
SE	Standard Error
CCI	[redacted]
SMC	Safety Monitoring Committee
SOC	System Organ Class
SPMS	Secondary progressive multiple sclerosis
TEAE	Treatment Emergent Adverse Event
TBILI	Total Bilirubin
TLF	Table/Listing/Figure
ULN	Upper Limit of Normal
VS	Vital signs
WHO-DD	World Health Organization Drug Dictionary

4 Modification History

Unique Identifier for IAP Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	25 April 2024	PPD	NA – first version
2.0	03 June 2024	PPD	Section 17.3: Add Kaplan-Meier plot for time to first increase in ALT ≥ 3, update analysis to include DBP + OLE Section 16.3: added two more percentiles summary (35th, 40th) in the KM estimates of the cumulative probability of experiencing qualified relapse

5 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the Final Analysis (FA) of data collected for protocol MS200527-0086 considering the early termination of the study; the primary endpoints of the phase 3 MS200527_0080 and MS200527_0082 studies were not met). The IAP is based upon Section 8 (Statistics) of the trial protocol dated 06 July 2023 (Version 8.0) and is prepared in compliance with International Conference on Harmonization E9.

This FA data report will include summaries of participant disposition, demographics, baseline characteristics, medical history, previous and concomitant medications, treatment exposure, efficacy evaluations, adverse events (AEs), deaths, selected laboratory parameters, vital signs, ECGs, and other endpoints related to safety monitoring up to the end of the study.

6 Objectives/Endpoints of the Final Analysis

The objective of the OLE Period of this study is to evaluate the long-term safety, efficacy, and HRQoL of M2951 for an additional 8 years, at an initial dose of 75 mg once daily which was eventually switched to 75 mg twice daily.

Endpoints for OLE Period:

- Efficacy and CCI endpoints at Week 48, 96, 144, 192, 240, 288, 336 and 384.
  - Number of gadolinium-enhancing T1 lesions;
  - ARR, based on protocol-defined qualified relapses;
  - Qualified relapse-free status;
  - Change from baseline in disability score based on EDSS score;

CCI

- Safety as assessed by the nature, severity, and occurrence of AEs; vital signs; ECGs; absolute concentrations and change from Baseline in Ig levels; CCI [redacted]; and clinical laboratory safety parameters.

For the Final Analysis, selected safety and efficacy endpoints based on data from OLE Day 1 to the end of the study will be evaluated.

For more details on the main study objectives please review section 4 Trial Objectives of the protocol.

7 Sample Size/Randomization

Sample size and randomization is described in the IAP for the primary analysis/blinded extension analysis performed after completion of the Double-Blind Period (DBP) of the study (Week 48/Week 52).

8 Overview of Planned Analyses

The protocol describes a total of 5 analyses that should be performed for this study. 4 of them have already been conducted according to the protocol. These are:

- Primary Analysis (when 100% of participants enrolled reached Week 24 of treatment, or prematurely discontinued from treatment)
- Blinded Extension Analysis (when 100% of participants enrolled either reached Week 52 (4-week Safety Follow-up Visit) and completed the study, enrolled in the OLE, or prematurely discontinued from study)
- Safety OLE W60 Interim Analysis (when 100% of participants enrolled in the OLE reached OLE Week 60 or discontinued prematurely from the OLE prior to OLE Week 60)
- OLE W240 Interim Analysis (timed to occur shortly before the primary analysis of the Phase 3 studies in RMS, to support the results of Phase 3 studies)

The last analysis is:

- Final Analysis (triggered when 100% of participants enrolled in the OLE will complete the OLE or will discontinue prematurely from the OLE)

This IAP covers the Final Analysis. Statistical analyses will be performed using cleaned electronic Case Report Form (eCRF) data, lab and MRI data collected up until end of study. All endpoints for the OLE period will be evaluated.

9 Changes to the Planned Analyses in the Clinical Trial Protocol

There are no changes to the planned analyses in the Clinical Trial Protocol (CTP) for the Final Analysis.

10 Protocol Deviations and Analysis Sets

10.1 Definition of Protocol Deviations and Analysis Sets

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect participants rights, safety, or well-being.

The following important deviations will be identified and confirmed prior to or at the Data Review Meeting at the latest.

- Participants who are dosed on the study despite not satisfying the inclusion criteria
- Participants who develop withdrawal criteria whilst on the study but are not withdrawn
- Participants who receive the wrong treatment or an incorrect dose
- Participants who receive an excluded concomitant medication
- Deviation from Good Clinical Practice
- Inclusion and exclusion criteria violations
- Concomitant medication violations
- Other violations/events that may have a relevant influence on the CCI analysis (e.g., adverse events (AEs), vomiting, sample processing errors, inaccurate dosing, etc.)

Protocol deviations will not lead to the exclusion of a participant from an analysis set for the Final Analysis.

All important protocol deviations should be documented in Clinical Data Interchange Standards Consortium Study Data Tabulation Model (SDTM) whether identified through sites monitoring, medical review and/or programming based on the inclusion/exclusion criteria presented in the protocol. Important protocol deviations are listed and described in the Monitoring Plan-PDMP-28Nov2022.pdf.

10.2 Definition of Analysis Sets and Subgroups

Screening Analysis Set (SCR)

The Screening (SCR) Analysis Set includes all participants who signed the informed consent.

Safety Analysis Set (SAF)

The Safety Analysis Set (SAF) consists of all participants who receive at least one dose of trial treatment. Participants will be analyzed according to the actual treatment they received during the DBP.

Modified Intent-To-Treat Analysis Set (mITT)

The mITT Analysis Set consists of all subjects randomly allocated to a treatment who belong to the Safety Analysis Set, and who have at least one baseline and one post-baseline MRI assessment. Subjects will be analyzed according to the treatment they were randomized to.

Modified Intent-To-Treat Open-Label Extension Analysis Set (mITT-OLE)

The modified ITT OLE Analysis Set (mITT-OLE) Analysis Set consists of all subjects randomly allocated to a treatment who belong to the Safety OLE Analysis Set, and who have at least one MRI assessment on or after OLE Week 0. Subjects will be analyzed according to their planned treatment during the DBP.

Safety Open-Label Extension Analysis Set (SAF-OLE)

The Safety OLE Analysis Set consists of all participants who receive at least 1 dose of Evobrutinib during the OLE. Participants will be analyzed according to the actual treatment they receive during the DBP.

Safety Switch Open-Label Extension Analysis Set (SAF-SWOLE)

The Safety Switch OLE Analysis Set consists of all participants who receive at least 1 dose of Evobrutinib 75 mg BID after a switch of dose from 75 mg QD during the OLE. Participants will be analyzed according to the actual treatment they receive during DBP.

The SAF and mITT analysis sets were pre-defined by the CTP and mainly used for PA/BEA. Specific safety OLE analysis sets (SAF-OLE, SAF-SWOLE) were defined in the IAP for OLE W60 Safety IA (version 1.0, 16Jan2020). The mITT-OLE analysis set was defined in the OLE W240 IA IAP.

The use of the analysis sets in the different analyses is summarized in the following table:

Table 1: Analysis set

Analyses	SCR Analysis Set	SAF Analysis Set	SAF- OLE Analysis Set	SAF-SWOLE Analysis Set	mITT Analysis Set	mITT–OLE Analysis Set
Subject Disposition	✓		✓			
Protocol Deviations			✓			
Demographic and Other Baseline Characteristics			✓			
Previous and Concomitant Medications/Procedures			✓			
Treatment Compliance and Exposure			✓	✓		
Efficacy					✓	✓
Safety Evaluation		✓	✓			

11 General Specifications for Statistical Analyses

All statistical analyses will be performed by PPD Inc.

11.1 Treatment groups and Investigational Medical Product (IMP)

Treatment groups are defined according to initial actual treatment received as placebo, Evobrutinib 25 mg QD, Evobrutinib 75 mg QD, Evobrutinib 75 mg BID, and Tecfidera. All participants who choose to continue the OLE period entered on the 75 mg once daily dose and have switched to the 75 mg twice daily dose following protocol amendment V5 dated 21 November 2018. Unless otherwise indicated, all analyses will be presented separately for the 5 initial treatment groups plus combined across treatment groups (i.e., "Total"). The IMP during the OLE phase is Evobrutinib.

11.2 Presentation of Tables/Listings/Figures

TLFs will be presented using initial treatment groups (i.e., true treatment groups as "Placebo+Evobrutinib 25 mg QD", "Evobrutinib 25 mg QD", "Evobrutinib 75 mg QD", "Evobrutinib 75 mg BID", and "Tecfidera") and total population. A footnote will be added to indicate that participants switched from Placebo to Evobrutinib 25 mg QD for the second 24-week treatment period. A second footnote will be added to indicate that all participants switched to Evobrutinib 75 mg QD on OLE Week 0 and following protocol amendment V5 dated 21 November 2018, all participants still ongoing in OLE switched to Evobrutinib 75 mg BID.

All data recorded during the trial will be presented in individual data listings performed on the Safety OLE Analysis Set (SAF-OLE), unless otherwise specified. All listings will be sorted by treatment group, participant, and scheduled time point (where applicable), if not otherwise stated. Further details are provided in the appropriate section for the analysis of the specific parameter.

Tables and figures will be presented by treatment group and scheduled time point during OLE period (where applicable), unless otherwise specified. Tables and figures will be sorted by treatment group and chronological scheduled time point (where applicable).

Summary statistics as displayed in tables and figures will include data until end of study.

11.3 Presentation by Time Period

Tables summarizing data from the overall OLE study period will be provided, unless otherwise specified.

Boxplots for laboratory parameters will be split in several periods to remain readable.

Some outputs will be split between the OLE period where the participants are taking 75 mg QD and the period where the participants are taking 75 mg BID.

Listings will be presented for both DBP and OLE period depending on the corresponding table or figure. All listings with assessments during OLE period will have a flag indicating either the first

visit where the switch to Evobrutinib 75 mg BID occurred, or all the events occurring on or after the date of the switch.

11.4 Data handling after cut-off date

Not applicable.

11.5 Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics, i.e.:

- number of participants (N)
- number and percentage of non-missing values
- number and percentage of missing values.
- mean, standard deviation (SD)
- median, 25th Percentile - 75th Percentile (Q1-Q3)
- minimum, and maximum

The number of digits for non-derived and derived data, presented in outputs or available in ADaM (Analysis Data Model) datasets, is specified in the Biostatistics Outputs Assembly (BOA) document.

For both continuous and qualitative variables, percentages as 0% or 100% should be reported with the same format used for the column and together with the count of values. For example, if the count of value is zero, then display '0 (0.0)'; if the percentage is 100% then display 'xx (100.0)'.

Qualitative variables will be summarized by counts and percentages. A missing category should always be displayed at baseline – even when no missing data. A missing category, at other endpoints than baseline, should only be displayed when there are missing data.

Unless otherwise stated, the calculation of proportions will be based on the number of participants in the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of participants in the analysis set of interest, unless otherwise specified. Total of missing and non-missing observations at each time-point will reflect the population still in the trial at that time. For example, if a participant is still in the trial at the time-point but with missing data, it should be counted in the number of missing observations.

11.6 Definition of baseline and change from baseline

For the purpose of statistical analysis, OLE baseline is defined as the last non-missing measurement (including those collected at an Unscheduled visit) prior to the first dose of IMP during OLE. Study baseline is defined as the last non-missing measurement (including those

collected at an Unscheduled visit) prior to the first dose of IMP in the study. If baseline cannot be defined, then the baseline value will be treated as missing. OLE baseline will be used in OLE tables and both baselines will be displayed in the listings based on DBP+OLE period, unless otherwise specified.

Definition of change from baseline (CFB)

CFB and percent CFB at a given post-baseline visit will be computed as follows:

- CFB = visit value – baseline value
- Percent CFB = 100 * (visit value – baseline value) / baseline value

At the baseline visit, the CFB will be equal to zero and the percent CFB will be missing.

11.7 Definition of duration

Duration will be calculated as the difference between start and stop dates plus 1 (e.g., AE duration (days) = AE end date - AE start date + 1).

The time since an event will be calculated as:

- reference date minus date of event +1 (eg, days in study at onset of AE = AE start date - date of randomization + 1) if date of event is equal or greater than reference date
- reference date minus date of event (eg, days in study at onset of AE = AE start date - date of randomization) otherwise.

11.8 Conversion factors

The following conversion factors will be used to convert days into months or years: 1 month = 30.4375 days, 1 year = 365.25 days.

11.9 Handling of missing data

Unless otherwise specified, missing data will not be replaced.

In all participant data listings, imputed values will be presented and flagged. Partial dates, which are not to be imputed according to this IAP, will be presented using the format "_____YYYY".

Missing statistics, eg, when they cannot be calculated, should be presented as 'nd', with 'nd' standing for 'not done'. For example, if n = 1, the measure of variability (SD) cannot be computed and should be presented as 'nd'.

In case of zero records available for presentation in a given TLF, then an empty output with 0 occurrence or a sentence stating that there are no data will be provided. For tables of Adverse Events and Deaths (outputs required for EudraCT and/or clinicaltrial.gov), if there is no observation, the output must contain the first line 'Participant with…' or 'Participant who died' displayed with 0 occurrence.

If a System Organ Class (SOC) or Anatomical Therapeutic Class (ATC) term is missing/not coded yet, then 'Uncoded SOC' (or 'Uncoded ATC') will be indicated at the TLF level. When a Preferred Term (PT) is missing, it will be set to 'Uncoded PT:' TEAE verbatim text.

Incomplete AE-related dates will be handled as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year, are equal to the start of IMP, then the onset date will be replaced by the minimum of the start of IMP date and the AE resolution date (if not missing).
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant death. In the latter case, the date of death will be used to impute the incomplete stop date.

Participants with study termination e-CRF form completed and treatment termination form missing at the time of the end of study will be handled as follows:

End of treatment status will be set to "Discontinued" and the following end of treatment information will be carried over from the study termination e-CRF form:

- Reason for discontinuation of treatment will be replaced by the reason for study discontinuation
- Reason for discontinuation of treatment - protocol non-compliance/withdrawal of consent/Other, specify free-text fields will be replaced by the corresponding free-text fields in the study termination form
- End of treatment date will be replaced by the discontinuation date from the study termination e-CRF form

11.10 Trial day / Treatment day

Trial day is defined relative to the date of randomization. Treatment day is defined relative to the date of start of treatment (i.e. treatment day 1 is the day of the first dose of IMP). There will be a second start of treatment on the day of first administration of Evobrutinib during OLE labeled OLE Treatment day.

The day before the start date of treatment is defined as treatment day -1, i.e., there is no treatment day zero.

11.11 Repeated and unscheduled measurements

Repeated and unscheduled measurements are included in the listings. Data collected at both scheduled and unscheduled visits will be used for shift analyses.

By-visit summary statistics should be programmed based on assessments at both scheduled and unscheduled visits. Assessments at unscheduled visits will be included according to the visit windowing approach described below. A by-visit summary table/figure will include a footnote indicating whether assessments from unscheduled visits are included in the analysis.

For by-visit tabulations, in case of multiple assessments (including unscheduled) linked to the same visit, the first available assessment (in chronological order) will be included in the summary of a visit. This rule doesn't apply to baseline where the latest assessment before day 1 or OLE day 1 is taken.

Repeated and unscheduled measurements will be reported in the listings.

11.12 Early treatment termination assessments

By-visit summary statistics should be programmed based on assessments slotted according to the visit windowing approach described below. A by-visit summary table/figure will include a footnote indicating whether assessments from early treatment termination visits are included in the analysis based on slotting the assessment into the appropriate analysis visit window. The summary for the Early Treatment Termination visit (for assessments not slotted according to a visit window approach) will be distinguished from the OLE Week 384 visit, and the Early Study Termination visit from the summary for the OLE Week 388 visit.

For analyses by time period, data from Safety Follow-up will be included in the period in which the participant has discontinued. Data from Safety Follow-up will also be included in shift table to derive worst grade or value.

11.13 Analysis visit windows

Assessments may be made at times other than the nominal times of planned visits, due to participant scheduling issues, unscheduled visits, or early treatment termination visits.

Analysis visit windows for efficacy and safety endpoints, will be used to incorporate unscheduled assessments in by-visit summaries. For participants discontinuing treatment during the OLE, the premature End of Treatment (EOT) assessment will be windowed appropriately, prior to the analysis, for safety.

For the calculation of analysis visit using the time windows, 1 month is expressed as 30 days.

As the schedule of assessments is different for each visit, specific time windows must be used for each endpoint. They are defined in Appendix 19.3.

For all biochemistry parameters, the same schedule of assessment is considered with all visits possible per protocol.

If there are multiple assessments within a same visit window, then the one closest to the target day will be used. If 2 assessments have the same difference with target day, the earlier one will be used.

11.14 Time since MS onset/diagnosis

Time in years since MS onset is calculated from date of informed consent – MS onset date / 365.25 days if the category of medical history is 'History of MS'.

Time in years since MS diagnosis is calculated from date of inform consent – MS Diagnosis date / 365.25 days.

11.15 Body Mass Index (kg/m²) at study Baseline

Is calculated as:

$$\text{Body Mass Index (BMI) [kg/m}^2\text{]} = \frac{weight\ [kg] at\ baseline}{height[cm]^2\ at\ screening} \times 10000$$

11.16 Software

All analyses will be performed using SAS® Software version 9.4 or higher.

12 Trial Subjects

The subsections in this section include specifications for reporting participant disposition and treatment/trial discontinuations.

12.1 Disposition of Subjects and Discontinuations

A table on screened participants describing the number and percent of participants in each of following disposition categories will be produced by treatment group:

- Total number of screened subjects, i.e. subjects that gave informed consent (overall summary only)
- Number of subjects who discontinued prior to randomization and reason (overall summary only)
- Number of randomized subjects
- Number of randomized subjects who did not start treatment
- Number of randomized subjects who completed the first 24 weeks of treatment
- Number of randomized subjects who permanently discontinued treatment prior to Week 24 and reason
- Number of randomized subjects who permanently discontinued treatment after Week 24 and prior to OLE and reason
- Number of randomized subjects who completed 48 weeks of treatment
  - Number of randomized subjects who signed the OLE Informed Consent
  - Number of randomized subjects who did not sign it
- Number of randomized subjects who entered OLE at dose 75 mg QD and switched to 75 mg BID during the OLE

- Number of subjects who discontinued treatment after OLE Week 0 and prior to OLE Week 48
- Number of subjects still on treatment at OLE Week 48
- Number of subjects who discontinued treatment after OLE Week 48 and prior to OLE Week 96
- Number of subjects who completed the OLE treatment at OLE Week 96
- Number of subjects who entered a gap period at OLE Week 96
- Number of subjects still on treatment at OLE Week 96
- Number of subjects who discontinued treatment after OLE Week 96 and prior to OLE Week 144
- Number of subjects still on treatment at OLE Week 144
- Number of subjects who discontinued treatment after OLE Week 144 and prior to OLE Week 192
- Number of subjects still on treatment at OLE Week 192
- Number of subjects who discontinued treatment after OLE Week 192 and prior to OLE Week 240
- Number of subjects still on treatment at OLE Week 240
- Number of subjects who discontinued treatment after OLE Week 240 and prior to OLE Week 288
- Number of subjects still on treatment at OLE Week 288
- Number of subjects who discontinued treatment after OLE Week 288 and prior to OLE Week 336
- Number of subjects still on treatment at OLE Week 336
- Number of subjects who completed treatment during OLE. A participant is considered to have completed the OLE if he/she completed the End of Treatment Visit for the OLE Period and was assigned the status 'Completed', or if the main reason for treatment discontinuation was "Other, specify: Study terminated by Sponsor".
- Number of randomized subjects who permanently discontinued treatment during OLE and reason. COVID-19 related reason for discontinuation will be reported separately from the "Other" reason.
- Number of randomized subjects in the follow-up phase who have not completed the trial (ie, treatment completed or discontinued without documented Safety Follow-up/End of Trial Visit)
- Number of randomized subjects who completed the trial
  - Number of randomized subjects who completed the trial at Week 52
  - Number of randomized subjects who completed the trial at OLE Week 100
  - Number of randomized subjects who completed the trial at OLE Week 340
  - Number of randomized subjects who completed the trial at end of trial

- Number of randomized subjects who discontinued from trial after randomization and prior to OLE and reason.
- Number of randomized subjects who discontinued from trial during OLE overall, and by year of OLE (on or before OLE W48, OLE W48 - OLE W96 etc.) and reason. COVID-19 related reason for discontinuation will be reported separately from the "Other" reason.

A table based on screened subjects describing the number and percent of subjects in each analysis set by treatment groups will be produced:

- Number of screened subjects
- Number of subjects included in the SAF
- Number of subjects included in the SAF-OLE
- Number of subjects included in the SAF-SWOLE
- Number of subjects included in the mITT
- Number of subjects included in the mITT-OLE

A table describing the number of participants by region, country within region and site will be produced by analysis set. A listing with participants by analysis set will be provided.

Study and treatment discontinuation/completion status will be listed for all participants in the SAF-OLE analysis set. The details of who discontinued/completed treatment or study will be provided with their reason for discontinuation (if applicable) as well as, treatment group, subject ID, First Date (relative day)/ Last Date (relative day) of dosing, first date of dosing in OLE, date of the switch during OLE (if switch performed), treatment and study discontinuation dates (relative day).

Participants with study participation impacted by the Ukraine crisis will also be listed with a description of the different events and impacts. This could include study intervention discontinuation, study discontinuation, protocol deviations, missed doses and missed visits.

12.2 Protocol Deviations

12.2.1 Important Protocol Deviations

The following summary tables and listings of important protocol deviations (IPDs) during the DBP and the OLE period will be provided:

- Table providing frequency of subjects with at least one IPD and frequency for each type of IPD; Ukraine crisis related IPDs will also be summarized as a separate category within the table.
- Table providing frequency for each type of minor Ukraine crisis related PDev.
- Listing of important protocol deviations
- A specific listing for Ukraine crisis related IPDs/PDevs.

Ukraine crisis related PDevs will include all PDevs including the mention "BCP22" or "BCP" within their description.

12.2.2 Reasons Leading to the Exclusion from an Analysis Set

Not applicable.

13 Demographics and Other Baseline Characteristics

Demographics, baseline disease characteristics, and other baseline characteristics at study baseline will be summarized based on the SAF-OLE analysis set, presented by treatment group plus combined across treatment groups (i.e. "Total").

Supportive listings will be based on the SAF-OLE analysis set, with subjects flagged according to membership in the SAF-SWOLE analysis sets.

13.1 Demographics

- Demographic characteristics
  - Sex: male, female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other
  - Ethnicity: Hispanic or Latino, Not Hispanic or Latino
  - Age (years) at informed consent: summary statistics
- Pooled Region (US or Western Europe, Eastern Europe, Rest of the World)
- Geographic/Capability Region (US, Western Europe, Eastern Europe and CCI, Eastern Europe and not CCI, Rest of the World)
- European Economic Area (EEA)
- A listing with actual treatment group, subject ID, analysis set, age, sex, race, ethnicity, height, weight, BMI, country and region will also be presented.

Specifications for computation:

- Age (years):
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of missing day for at least one date, but month and year available for both dates, the day of informed consent and the day of birth will be set to 1 and the formula above will be used.
  - In case of missing month for at least one date, but year available for both dates, the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used.
- Site codes will be used for the determination of the participants geographic region.

13.2 Medical History

Relevant past and present medical conditions at study baseline will be summarized from the "Medical History Details" eCRF page.

For this analysis, the Medical Dictionary for Regulatory Activities (MedDRA), current version, PT as event category and MedDRA SOC body term as Body System category will be used. The MedDRA version used will be indicated in a footnote. Medical history will be tabulated by SOC and PT. SOC and PT will be alphabetically sorted. Medical history will be also listed.

13.3 Other Baseline Characteristics

13.3.1 Disease history

Information on MS baseline disease characteristics, based on data collected at study baseline will be summarized in total and by treatment group for participants enrolled in the OLE and they will also be listed.

Descriptive statistics will be presented for:

- Type of MS, either relapsing-remitting MS or secondary progressive MS
- Time (years) since MS onset (first symptom)
- Time (years) since MS diagnosis
- Major systems affected
- Number of relapses in the year prior to randomization
- Number of relapses in the last 2 years before screening
- EDSS score
- Scores for each of the 7 Functional Systems (Visual, Brainstem, Pyramidal, Cerebellar, Sensory, Bowel/Bladder, Cerebral) and score for Ambulation used to derive EDSS score.
- Presence of at least 1 T1 Gd+ lesion within 6 months prior to randomization
- Number of T1 Gd+ lesions
- Volume of T1 Gd+ lesions
- Volume of T2 lesions

For time since MS onset or MS diagnosis, a missing onset day/month will be replaced by 1 for duration derivation.

13.3.2 Other

Descriptive statistics will be presented for physical examination as continuous variables: Height (cm), Weight (kg) and BMI (kg/m^2).

Analyses of baseline characteristics with respect to ECGs and clinical laboratory evaluations are discussed in Section 17 Safety.

14 Previous or Concomitant Medications/Procedures

Medications/procedures will be presented on the SAF-OLE Analysis Set.

Concomitant medications are medications, other than IMPs, which are taken by participants any time on-trial (on or after the first day of IMP treatment for each participant). Concomitant medications include those started prior to and continued during administration of IMP, as well as those that were started after first administration of IMP. If the date values do not allow a medication to be classified as a non-concomitant medication, the medication will be considered as a concomitant medication.

Concomitant medications during OLE treatment period are defined as medications starting on or after the first IMP administration during OLE period or starting before first administration during OLE but ending or ongoing after first administration during OLE period.

Previous medications are medications, other than trial medications, which started before first administration of IMP during the DBP. Previous medications include those that were continued during administration of IMP during the DBP, as well as those discontinued prior to first administration of IMP during the DBP. If the date values do not allow a medication to be classified as concomitant medication, the medication will be considered as a previous medication.

Concurrent procedures are procedures which were undertaken any time on trial. If the date values do not allow a procedure to be classified as a non-concomitant procedure, the procedure will be considered as a concomitant procedure.

Concurrent procedures during OLE treatment period are defined as procedures starting on or after the first IMP administration during OLE period or starting before first administration during OLE but ending or ongoing after first administration during the OLE period.

Concomitant medications and concurrent procedures occurring during the OLE period will be tabulated.

For concomitant medication during the OLE the ATC-second level and preferred term will be tabulated as given from the World Health Organization Drug Dictionary (WHO-DD) current version. In case multiple ATCs are assigned to a drug, all ATC-2nd level terms will be used for reporting.

Concurrent procedures during the OLE period will be classified by medical review. Number of participants with concomitant procedures (starting prior to first dose of trial treatment, on or after the first day of IMP and prior to first dose during the OLE period and starting after first dose during the OLE period) and by type of procedure (as classified by medical review) will be summarized by treatment group and listed.

Listings of concomitant medications and concomitant procedures during the OLE will be provided.

Disease Modifying Therapy (DMT) is not captured in the eCRF but is of interest for the analysis. In order to identify DMTs, the list of all previous medications was reviewed by the Merck medical team and the flag for DMT was assigned retrospectively (refer to Appendix 19.7 for list of identified DMTs). Flags were then created from this list in ADaM:

- Prior DMTs from Prior Medications eCRF (see definition for previous medication in section above),
- subjects with at least one prior DMT,
- subjects with more than one prior DMT,
- number of prior DMTs per subject.

Tables for Prior DMT will be created based on the SAF and SAF-OLE analysis sets with selection on the previous medications and presenting number of subjects with at least one prior DMT, number of subjects with more than one prior DMT and number of subjects per prior DMT (WHO-DD preferred term).

15 Treatment Compliance and Exposure

Exposure and compliance will be presented on the SAF-OLE and SAF-SWOLE Analysis Sets.

Planned administration of Evobrutinib during OLE

Each kit contains 24 tablets of 25 mg of Evobrutinib which is enough medication for the administration of 3 tablets per day (so 75 mg in total) for 8 days. On OLE Day 1, participants not treated with Tecfidera during the DBP received 12 kits. From OLE Week 12 until OLE Week 84, these participants received between 11 and 13 kits depending on the quantity of kits carried over from last visit. On OLE Day 1, participants treated with Tecfidera during the DBP received 5 kits. From OLE Week 4 until OLE Week 8, they received between 4 and 6 kits depending on the quantity of kits carried over from last visit. At each trial visit from OLE Week 12, participants were given treatment kits containing the number of tablets needed up to the next planned trial visit depending on the kits carried over from last visit. Participants received 75 mg of Evobrutinib QD (once a day) until they switched to the dose of 75 mg of Evobrutinib BID.

Once a participant switched to the new dose of 75 mg BID and new kits were available, each kit contained 48 tablets of 25 mg of Evobrutinib which was enough medication for the administration of 6 tablets per day (3 in the morning and 3 in the evening) for 8 days. At each trial visit, a participant was given treatment kits containing the number of tablets needed up to the next planned trial visit. Number of kits dispensed was the same as before the switch of dose. After the switch, participants received 75 mg of Evobrutinib BID (twice a day) for the remainder of the OLE.

Exposure

Exposure time in weeks during the OLE will be calculated according to the following formula:

exposure (weeks) =
(date of last dose during OLE period - date of first dose during OLE period + 1)/7

If the end date of the last dose is missing, then the date of last dose will be replaced by the last visit date. If a participant is lost to follow up and hasn't performed the EOT visit, then end of study date will be considered as the end of treatment date.

Exposure time will be presented by summary statistics during the OLE period and according to the categories ≤ 1 week, > 1 to 12 weeks, > 12 to 24 weeks, > 24 to 36 weeks, > 36 to 48 weeks, > 48 to 60 weeks, > 60 to 72 weeks, > 72 to 84 weeks, > 84 to 96 weeks, > 96 to 108 weeks, >108 to 120 weeks, >120 to 132 weeks, >132 to 144 weeks >144 to 156 weeks, >156 to 168 weeks, > 168 to 180 weeks, >180 to 192 weeks, >192 to 216 weeks, >216 to 240 weeks, >240 to 264 weeks, > 264 to 288 weeks, > 288 to 312 weeks, >312 weeks. For this analysis the SAF-OLE analysis set will be used. Tables about exposure time before or after the switch during the OLE period will be provided, the day of switch will be considered in the period after the switch. For tables about exposure time after the switch, the SAF-SWOLE analysis set will be used.

The cumulative actual dose (mg) per participant is the number of tablets taken during the OLE period, multiplied by 25 mg (dosage of 1 tablet). The number of tablets ingested will be deduced from the "M2951 Box Number (BATCH3)" electronic case report form (eCRF) page. Descriptive statistics for cumulative actual dose will be presented during OLE period using the SAF-OLE analysis set. Descriptive statistics for cumulative actual dose received before and after the switch during the OLE period will be also provided. Descriptive statistics after the switch will be restricted to SAF-SWOLE Analysis Set.

Compliance

$$\text{Compliance with treatment during OLE period} = 100*(\frac{(N_{1bs})}{3 * N_{2bs}} + \frac{(N_{1as})}{6 * N_{2as}})$$

where

- N_{1bs} = number of tablets given minus number of tablets returned before dose switch,
- - N_{2bs} = number of days between treatment start and switch visit (or treatment termination visit if participant discontinued before the switch),
- - N_{1as} = number of tablets given minus number of tablets returned after dose switch,
- - N_{2as} = number of days between switch visit and treatment termination visit. For participants who are lost to follow-up the end of study visit date will be used.

Compliance with treatment before the switch during OLE period is defined as

$$100*(\frac{(N_{1bs})}{3 * N_{2bs}})$$

Compliance with treatment after the switch during OLE period is defined as

$$100*(\frac{(N_{1as})}{6 * N_{2as}})$$

If the subject didn't switch the dose, $\frac{(N_{1as})}{6*N_{2as}}$ is set to 0. If a kit is received by the participant but no information about the number of tablets returned is available because of lost to follow-up, the kit is not considered in the calculation of compliance.

Compliance with treatment will be presented by summary statistics during the OLE period and according to the categories < 60%, ≥ 60% to < 80%, ≥ 80% to < 90%, ≥ 90% to < 110%, ≥ 100%. For this analysis the SAF-OLE analysis set will be used. Tables about compliance before or after the switch during OLE period will be also provided. Tables after the switch will be restricted to SAF-SWOLE Analysis Set.

The following listings will be provided:

- listing of Evobrutinib start/end dates of the single administration with number of ingested tablets (from EXPOSUREDT3 eCRF page), for the study drug administration during the OLE period.
- listing with exposure time, cumulative dose, and compliance during the OLE period.

16 Efficacy Evaluation

All efficacy analyses will be based on the mITT and mITT-OLE analysis sets, as specified in below sections. All analyses are descriptive, there is no hypothesis testing.

16.1 MRI

Descriptive statistics for the number of T1 Gd+ lesions, new/enlarging T2 lesions and T2 volume at each visit (early treatment discontinuers during OLE will be presented at 'EOT' visit) during the OLE will be provided by treatment group and overall on the mITT-OLE analysis set.

Mean number of T1 Gd+ lesions and new/enlarging T2 lesions will be presented as a by-visit line plot for each treatment group during the OLE on the mITT-OLE analysis set, with a vertical line segment at each visit representing ± standard error (SE) (jittered if needed for legibility), and with all treatment groups included in a single figure.

A listing will be provided for the MRI assessment data, by participant and by timepoint for the OLE treatment period.

16.2 Relapses

Annualized Relapse Rates (ARR)

Descriptive statistics on relapses during the OLE period will be provided by treatment group and overall on the mITT-OLE analysis set. In particular, at the treatment-group-level, number of qualified relapses, total number of relapses (qualified or not), follow-up on treatment (in participant-years), and unadjusted ARR based on protocol-defined qualified relapses (number of qualified relapses divided by follow-up on treatment) and confidence intervals will be reported. In addition, descriptive statistics of participant-level ARR (number of qualified relapses experienced

by a participant, divided by the follow-up experienced by a participant) will be summarized for each treatment group, in terms of mean, SD, median, Q1, Q3, min, and max.

Subjects discontinuing early are analyzed according to number of years of follow-up on treatment and number of qualified relapses observed at the time of discontinuation, including data (both follow-up time and number of relapse events) from the 4-week Safety Follow-up period.

The summary will be presented for the overall OLE period (OLE Baseline – last OLE visit), for each 48-week period during the OLE, between OLE Baseline and Dose Switch during OLE, and between Dose Switch during OLE to the last OLE visit.

A listing will be provided for relapse data, by participant for the DBP and OLE treatment period combined.

16.3 Time to First Qualified Relapse and estimates

Time to first qualified relapse will be represented by a Kaplan-Meier (KM) plot on the mITT for the DBP + OLE period with orientation "increasing left to right", and with labels "Time from randomization (Weeks)" vs "Cumulative probability of qualified relapse". 1 curve will be provided for each of the 5 treatment groups. The cumulative probability of an event is estimated with PLOTS=SURVIVAL(FAILURE) option of PROC LIFETEST.

The horizontal axis should extend as far as needed to include follow-up from all participants, regardless of whether the time to an event is observed or censored.

A qualified relapse event will be counted even if it occurs after the participant has discontinued treatment.

Participants who have qualified relapse during DBP + OLE period, will have the time to first qualified relapse (weeks) calculated as "([date of first qualified relapse] – [date of first dose] + 1)/7".

Participants who do not have qualified relapse, or are lost to follow up, will be censored at the date of the last relapse assessment for this analysis. The censoring time (weeks) will be calculated as "([date of censoring] – [date of first dose] + 1)/7".

KM estimates (product-limit estimates) of the cumulative probability of experiencing qualified relapse over time will be presented in a table by treatment group, together with a summary of percentiles (5^{th}, 10^{th}, 15^{th}, 20^{th}, 25^{th}, 30^{th}, 35^{th}, 40^{th}, median) and corresponding 2-sided 95% CIs, as well as number of participants at risk, number of participants with an event, number of censored participants.

Number and percentage of subjects with qualified relapse-free status will be provided by treatment group and overall.

16.4 Expanded Disability Status Scale (EDSS)

Descriptive statistics for the EDSS score and EDSS CFB at each visit during the DBP and the OLE period combined will be provided by treatment group and overall on the mITT analysis set.

In addition, descriptive statistics for the EDSS score and EDSS CFB at each visit during the OLE period only will be provided by treatment group and overall on the mITT-OLE analysis set (early treatment discontinuers during OLE will be presented at 'EOT' visit).

Descriptive statistics for categorical EDSS CFB, i.e., number and proportion improving, stable, or worsening, will also be reported for each time point. Here improvement is defined as a decrease of 1.0 point or more, stable condition as a change of no more than half a point in either direction and worsening as an increase of 1.0 point or more.

Mean CFB in EDSS will be presented on mITT analysis set as a by-year line plot during DBP and OLE period combined. The plot will be provided for each treatment group and overall, with a vertical line segment at each visit representing ± SE (jittered if needed for legibility), and with all treatment groups included in a single figure.

Additionally, the plot of mean CFB in EDSS will be presented for OLE period only (OLE Week 48 to OLE Week 336 and EOT) on mITT-OLE analysis set.

A listing will be provided for EDSS data, by participant and by timepoint for the DBP and OLE treatment period combined.

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17 Safety Evaluation

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical trials such as adverse events, laboratory tests and vital signs.

All outputs will be provided on the OLE period if not otherwise indicated.

Safety analyses will be based on the SAF for summaries on the DBP + OLE period and on the SAF-OLE for summaries on the OLE period, according to the as-treated principle.

17.1 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as those AEs with an onset date on or after the date of first IMP administration or with an onset date prior to first IMP administration, but an exacerbation date after. For the DBP the reference date is first study IMP administration date. For the OLE period, the reference date is first administration of Evobrutinib during the OLE period.

TEAEs occurring during the 4 weeks of Safety Follow-up will be included in the tables.

TEAEs occurring during the wash-out period for participant treated with Tecfidera during the DBP will be flagged in the listing of TEAEs from the overall study.

In case a subject entered the gap period allowed at OLE Week 96, the AE starting during this period will be considered as starting also during the OLE period and then considered as TEAE in the analyses. These AEs will be flagged in the listing of all TEAEs.

Trial drug related Adverse Events are those AEs with relationship to study treatment reported by the investigator as related or those of unknown relationship.

Serious Adverse Events are those events reported on the AE eCRF form with the serious field ticked "Yes" or with unknown seriousness.

Adverse Events leading to study withdrawal of IMP are those AEs with action taken regarding study treatment as "Drug withdrawn" (as recorded on the AEs eCRF page).

Adverse Events leading to study termination are those AEs with other action taken as "Led to study termination" (as recorded on the AEs eCRF page).

Adverse Events leading to death are those AEs with outcome "Fatal" (as recorded on the AEs eCRF page).

Adverse events will be coded according to the latest MedDRA version available at the time of analysis. The severity of AEs will be graded using National Cancer Institute - Common Terminology Criteria for AEs (NCI-CTCAE version 4.03) toxicity grades.

All Adverse Events recorded during the course of the trial (i.e., assessed from signature of informed consent until the end of the Follow-up/End of Trial visit) will be coded according to the MedDRA and assigned to a SOC and PT.

Group/SOC terms will be sorted alphabetically. Preferred terms within each group/SOC will be sorted by the Total column descending frequency, and alphabetically if multiple preferred terms have the same frequency.

If a participant experiences more than one occurrence of the same TEAE during the trial for a given trial period of interest, the participant will only be counted once for that treatment (the worst severity and the worst relationship to trial treatment will be tabulated).

In case a participant had events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. AEs with missing classification concerning study intervention relationship will be considered related to the study intervention.

Incomplete AE-related dates will be handled as described in Section 11.9.

17.1.1 All Adverse Events

17.1.1.1 Overview of TEAEs

The overall summary of TEAEs occurring during the OLE period table will include the frequency (number and percentage) of participants with each of the following:

- Any TEAE
- IMP-Related TEAE
- Serious TEAE
- IMP-Related serious TEAE
- TEAE by intensity (NCI-CTCAE grade 1 to 4)
- IMP-Related TEAE by intensity (NCI-CTCAE grade 1 to 4)
- TEAE leading to death
- Related TEAE leading to death

Additionally, a TEAE summary table by SOC by year of OLE will be presented: number and percentage of participants by SOC for each period ([OLE W0; OLE W48],]OLE W48; OLE W96],]OLE W96; OLE W144],]OLE W144; OLE W192],]OLE W192; OLE W240],]OLE W240; OLE W288], >OLE W288).

A TEAE summary table will include a row for the overall frequency of TEAEs occurring during the OLE period of the following types:

- TEAE leading to interruption of IMP
- IMP-related TEAE leading to interruption of IMP
- TEAE leading to withdrawal of IMP
- IMP-related TEAE leading to withdrawal of IMP
- TEAE leading to concomitant medication
- IMP-related TEAE leading to concomitant medication
- TEAE leading to concomitant procedure

- IMP-related TEAE leading to concomitant procedure
- TEAE leading to study termination
- IMP-related TEAE leading to study termination

In addition, TEAE tables to be prepared are listed in Table 2 below:

Table 2: TEAE Tables to be Produced

	Overall frequency	By primary SOC and PT	By PT only	By primary SOC, PT and worst grade	OLE Period
All TEAEs	✓	✓	✓	✓	✓
Serious TEAEs	✓	✓	*NA*	*NA*	✓
Non-serious TEAEs*	✓	✓	*NA*	*NA*	✓
TEAEs leading to study intervention withdrawal	✓	✓	*NA*	*NA*	✓
TEAEs leading to study termination	✓	✓	*NA*	*NA*	✓
TEAEs leading to death	✓	✓	*NA*	*NA*	✓
IMP-related TEAEs	✓	✓	✓	✓	✓
IMP-related serious TEAEs	✓	✓	*NA*	*NA*	✓
IMP-related TEAEs leading to treatment withdrawal	✓	✓	*NA*	*NA*	✓
IMP-related TEAE leading to study termination	✓	✓	*NA*	*NA*	✓
IMP-related TEAEs leading to death	✓	✓	*NA*	*NA*	✓

*A table with all TEAEs will be first provided and then only TEAEs exceeding a frequency of 5% in at least one of the treatment groups (>5%), by SOC and PT will be provided.

TEAEs will be listed by treatment group and participant during OLE.

In addition, a grouped count and percentage of participants experiencing Rash (i.e. all PTs containing Rash), a grouped count and percentage of participants experiencing Anaemia (i.e. all PTs containing Anaemia) and a grouped count and percentage of participants experiencing Leukocytosis (i.e. PTs 'Leukocytosis' and 'White blood cell count increased') will be presented for OLE period only for "Total".

17.1.1.2 EAIR of TEAEs

EAIR of TEAEs are calculated as the number of participants with TEAE divided by the sum of the individual times of all participants in the treatment group from start of treatment to first onset of TEAE in the corresponding time period. The incidence rate multiplied with 100 would give the number of AEs expected in 100 participants within 1 time unit (year). EAIR of TEAEs will be presented by SOC and PT. Confidence interval of incidence rate will be calculated using the GENMOD procedure from SAS ® with lsmeans instruction using a Poisson binomial model. If a participant has multiple events, the exposure period of the first event will be used. For a participant with no event, the exposure period will be censored at the last follow-up time within the AE summarization period.

The EAIR of TEAE tables to be prepared are listed in Table 3 below:

Table 3: EAIR of TEAE Tables to be Produced

	Overall frequency	By primary SOC and PT	By primary SOC, PT and worse grade	OLE Period	OLE Period by year
TEAEs	X	X	X	X	X
IMP-related TEAEs	X	X	NA	X	NA
Serious TEAEs	X	X	NA	X	NA
IMP-related Serious TEAEs	X	X	NA	X	NA
TEAEs of Special Interest	X	NA (by AESI category, CMQ/SMQ and PT)	NA	X	NA

17.1.1.3 Adverse Events Leading to Treatment Discontinuation or Other Action Taken

Summary tables will be provided as detailed in Section 17.1.1.1.

A listing of TEAEs leading to withdrawal of IMP and a listing of TEAEs leading to study termination during the OLE period, will be provided.

17.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

17.2.1 Deaths

A summary of deaths occurring during OLE period will be provided including (clinicaltrials.gov requirement):

- Number and percentage of (all) deaths
- Number and percentage of the primary cause of death (categories: progressive disease and/or disease related condition, event unrelated to IMP, event related to IMP, unknown)

TEAEs leading to death and IMP-related TEAEs leading to death will be tabulated by SOC and PT along with overall frequency as described in Section 17.1.1.1. A listing of deaths occurring during the DBP and OLE period, if any, will be provided. In case there is no death in the trial, only the summary of death required by clinicaltrials.gov will be performed, neither tabulation of TEAE leading to death will be edited, nor the listing of death.

17.2.2 Serious Adverse Events

The tabulation of serious TEAEs is described in Section 17.1.1.1. A participant listing of serious TEAEs during the OLE period will be provided.

17.2.3 TEAEs of Special Interest

The following events are defined as AEs of Special Interest (AESI):

- Liver related AEs
- Infections:
    - All Infections reported as Serious AEs or Grade ≥ 3
    - All opportunistic infections
- Amylase and lipase elevations including acute pancreatitis
- Seizures

AESI will be identified using Standardized MedDRA query (SMQ) if available or sponsor-defined list of search term (refer to Appendix 19.5). AESI terms will be summarized under all categories they fall under.

An overview of AESI will be presented by treatment group showing number and percentage of participants experiencing AESI for the OLE period. Study intervention related AESI will also be presented. AESIs will be flagged in the AE listings.

Additional analysis on the infections will be performed.

The following output will be provided:

Kaplan-Meier figure for time to onset of infections. An event is defined as first occurrence of any PT in the SMQ "Severe Infections" or AESI "Opportunistic infections" from first day of exposure with Evobrutinib (i.e. for patients in the Placebo and Tecfidera groups the time period starts after switch to Evobrutinib 25 mg QD (week 25) and switch to Evobrutinib 75 mg QD, respectively. For all other patients the time period starts at study start (with first intake of Evobrutinib)). An overall Kaplan-Meier curve will be displayed.

17.3 Clinical Laboratory Evaluation

The clinical laboratory safety parameters measured in this trial and reported as part of the safety evaluation of hematology, biochemistry, and urinalysis, are specified in the protocol (Table 8 of the Clinical Trial Protocol, Section 7.4.3). The entire clinical laboratory section will be analyzed for OLE period. Some outputs not produced at time or Primary analysis and Blinded Extension analysis will also be repeated on the DBP for participants of the SAF analysis set.

Summaries of Clinical Laboratory Data

Laboratory values (including corresponding normal ranges) converted in standard units will be used for summary statistics, shift tables and boxplots. Gradable laboratory results will be classified according to the grades defined in NCI-CTCAE Version 4.03 as provided by the central laboratory. If a laboratory parameter has bi-directional toxicities (e.g., Potassium), both directions will be presented for the given parameter (i.e., Potassium Low and Potassium High). On-treatment values are defined as results of assessments made after the first IMP administration on Day 1. Laboratory results containing a modifier such as "<" or "≥" will be handled case by case for summary statistics and will be reported both as collected in the database and as imputed in participant data listings. Data until the Safety Follow-up included will be used to derive the worst on-treatment values.

All parameters will also be presented according to the categories based on normal ranges: below normal limits (Low), within normal limits (Normal) and above normal limits (High).

Shift tables of baseline value (low, normal, high) versus worst on-treatment value, presented by treatment group, will be provided for hematology and biochemistry parameters.

Shift tables of baseline grade versus worst post-baseline grade, presented by treatment group, will be provided for hematology and biochemistry parameters.

Shift tables will be displayed using the OLE Baseline and worst on-treatment value or worst post-baseline grade during OLE period.

Directional laboratory tests (hematology, biochemistry) (Appendix 19.1) will be summarized by worst on-treatment value and by treatment group.

Protocol-specified clinical laboratory hematology, biochemistry and urinalysis parameters will be summarized using descriptive statistics appropriate to continuous-valued random variables (see Section 11.5) by time point and by treatment group during the OLE period. At each time point, both observed value and CFB value will be summarized.

Graphical Display of Clinical Laboratory Data

Boxplots of laboratory values by treatment group and timepoint will be provided for the hematology and biochemistry parameters displayed in Table 4.

Table 4: Parameters for boxplots

Category	Laboratory parameter	Conventional Unit	SI Units
Hematology	Hemoglobin	g/dL	g/L
	Red blood cell count	$10^6/\mu L$	$10^{12}/L$
	Reticulocyte count	$10^3/\mu L$	$10^9/L$
	White blood cell count	$10^3/\mu L$	$10^9/L$
	Neutrophil count	$10^3/\mu L$	$10^9/L$
	Lymphocyte count	$10^3/\mu L$	$10^9/L$
	Eosinophils	$10^9/L$	$10^9/L$
	Basophils	$10^9/L$	$10^9/L$
	Platelet count	$10^3/\mu L$	$10^9/L$
Biochemistry	Alanine aminotransferase (ALT)	U/L	U/L
	Albumin	g/dL	g/L
	Aspartate aminotransferase (AST)	U/L	U/L
	Gamma-glutamyl transferase (GGT)	U/L	U/L
	Alkaline phosphatase	U/L	U/L
	Total bilirubin	mg/dL	µmol/L
	Amylase	U/L	U/L
	Lipase	U/L	U/L
	eGFR	mL/min	mL/min
	Blood urea nitrogen (BUN)	mg/dL	mmol/L
	Creatinine	mg/dL	µmol/L
	Glucose	mg/dL	µmol/L
	Sodium	mEq/L	mmol/L
	Potassium	mEq/L	mmol/L

Boxplots will be displayed from the OLE Baseline up to OLE Week 48 and from OLE Week 52 to OLE Week 96 etc. to remain readable.

The ULN and LLN will be added to the lab parameter boxplot, for any lab parameter where the normal range is the same for all participants in the analysis set. All graphical displays will be shown on a log-scale when needed to make the plot readable. All plots of a given parameter will have the same scale to allow comparison between groups and periods.

Liver function tests

AST, ALT and total bilirubin are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these 3 parameters during the OLE period.

Summary of liver function tests will include the following categories. The number and percentage of participants with each of the following categories during the OLE period will be summarized by treatment group:

- AST ≥ 3×ULN, AST ≥ 5xULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- TBILI ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP ≤ 2×ULN or missing

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, i.e., a participant with an elevation of AST ≥ 10×ULN will also appear in the categories ≥ 5×ULN and ≥ 3×ULN.

ALT values over time will be presented in a spaghetti plot for participants with on-treatment ALT grade 2 or higher elevation (i.e. grade ≥ 2) during the OLE period, by treatment group. There will be 1 panel by treatment group. All plots by parameter will have the same scales to allow comparison between groups.

Kaplan-Meier estimates of proportion surviving event-free as a function of time will be presented for the following 4 types of events based on the ALT and eGFR parameters:

- Time from OLE first dose to first occurrence of ≥ grade 2 ALT (days) (for participants with OLE baseline grade < 2)
- Time from OLE first dose to first increase in ALT ≥ 1 grade above OLE baseline grade (days)

- Time from first Evobrutinib dose to first increase in ALT ≥ 2 grade above baseline grade (days) in DBP+OLE
- Time from first Evobrutinib dose to first increase in ALT ≥ 3 grade above baseline grade (days) in DBP+OLE.
- Time from OLE first dose to first occurrence of eGFR assessment equal to less than (<) 60 mL/min for participants with OLE baseline eGFR ≥ 60 mL/min by treatment group (days)

For the above figures based on OLE: time-to-event figures will be based on data from OLE weeks 0-end of treatment; a participant reaching end of treatment, without experiencing the event will have his/her event time right-censored at the time of the last ALT/eGFR assessment. A separate KM curve will be estimated for each of the 5 initial groups: Placebo + Evobrutinib 25 mg QD, Evobrutinib (any dose) and Tecfidera. For the figures based on DBP+OLE: the start time will be the first Evobrutinib dose irrespective of its occurrence during DBP or OLE phase.

To be included in a time-to-event figure, a group must have at least one event. Below the horizontal axis of the time-to-event figure, number of events and number of participants at risk will be displayed every 56 days (OLE period). The vertical axis may be restricted to 0.50 – 1.0, if none of the curves reach 50%.

eDISH (Evaluation of Drug-Induced Serious Hepatotoxicity) figures, as described in Merz *et al* (2014), will be presented for the OLE period. The figure produced will include 6 panels: 1 for each initial dose group and 1 pooled for all the participants who received Evobrutinib during DBP.

Listings containing Lab Test, Analysis Visit, Visit, Date of Measurement (Days under Treatment/ Days under OLE), Time Measurement, Result, Change from Baseline/OLE Baseline, Reference Range Low – High and NCI-CTCAE Grade for ALT, AST, Total Bilirubin and ALP for participants with a post-baseline LFT elevation will be provided for the OLE period.

Listings of Clinical Laboratory Data

By-participant listings of all individual hematology, biochemistry and urinalysis values present in the database will be provided. Only data during the OLE period (including OLE Baseline) will be displayed. A flag will indicate the first visit of switch from Evobrutinib 75 mg QD to Evobrutinib 75 mg BID during OLE period.

Laboratory values that are outside the normal range will be flagged in the data listings, along with corresponding normal ranges.

In this study, clinically significant lab abnormalities were recorded as adverse events. In lieu of a listing of clinically significant lab abnormalities for each domain, the following by-participant lab value listings will be provided:

- Listing of Grade ≥ 3 hematology values with data from DBP and OLE period
- Listing of Grade ≥ 3 biochemistry values with data from DBP and OLE period

- Listing of urinalysis values with Grade ≥ 3, value ≥ 2 times ULN (excluding values for Specific Gravity or pH parameters), or an increase of "++" for non-gradable parameters when applicable with data from DBP and OLE period

Additional analysis on the pancreatic and liver enzymes elevations will be performed.

The following outputs will be provided:

1. Kaplan-Meier figure for time to first occurrence of Lipase increased > 2 x ULN and Amylase increased > 2 x ULN separately for DBP and OLE.

2. Abnormalities in lipase and amylase (i.e. higher the ULN). For the DBP information to be displayed by original treatment groups. For the OLE period only "Total" is needed.

3. Summary of potential DILI by R-Values and Periods for subjects with any ALT or AST elevation for DBP+OLE.

17.4 Vital Signs

The SAF-OLE analysis set will be used in presenting the vital signs results. Vital signs (height (cm), weight (kg), BMI (kg/m²), body temperature (°C), Systolic Blood Pressure (SBP) (mmHg), Diastolic Blood Pressure (DBP) (mmHg), respiratory rate (breaths/min) and pulse rate (beats/min)) will be summarized by treatment group using descriptive statistics (see Section 11.5).

The descriptive statistics will be presented as follows:

- The OLE baseline will be presented first
- Then each scheduled time point will be presented on participants who have reached this time point: absolute values and OLE CFB will be displayed (except for height and BMI as they are only present at screening visit).

Body temperature, SBP, DBP, respiratory rate and pulse rate will be analyzed with shift tables of maximum CFB using the categories defined in Table 5:

Table 5: Vital Signs Categories

Parameter	Unit	Shift	Baseline categories	Post-baseline categories (absolute change)
Temperature	°C	Increase	<37 / ≥37 - <38 / ≥38 - <39 /≥39 - <40 / ≥ 40	≤0* / >0 - <1 / ≥1 - <2 /≥2 - <3 / ≥3
Pulse rate	bpm	Increase and decrease	<100 / ≥100	≤0* / >0 - ≤20 / >20 - ≤40 / >40
SBP	mmHg	Increase and decrease	<140 / ≥140	≤0* / >0 - ≤20 / >20 - ≤40 / >40
DBP	mmHg	Increase and decrease	<90 / ≥90	≤0* / >0 - ≤ 20 / >20 - ≤40 / >40
Respiratory rate	breaths/min	Increase and decrease	<20 / ≥20	≤0* / >0 - ≤5 / >5 - ≤10 / >10

* This category will include the participants with no changes or decrease/increase in the increase/decrease part of the table respectively.

In addition, 2 scatter plots on OLE period will be provided presenting:

- OLE baseline SBP value versus maximum (highest) post-baseline SBP value
- OLE baseline Diastolic BP value versus maximum (highest) post-baseline Diastolic BP value

Line for linear regression will be included. The figures will be produced overall, i.e., for all participants pooled.

A listing of maximum CFB for OLE period and a listing of all vital signs data for OLE period will be provided.

17.5 12-Lead Electrocardiogram (ECG)

The 12-lead ECG data will be listed and summarized for the OLE period for observed values and change from OLE baseline values by treatment group using descriptive statistics:

- Ventricular rate (beats/min)
- Pulse rate interval (msec)
- QRS (msec)
- QT (msec)
- Fridericia corrected QT (QTcF) (msec).

The QTcF parameter will be categorized by observed value into the categories

- $\leq$ 430 msec,
- > 430 – 450 msec,
- > 450 – 480 msec,
- > 480 – 500 msec,
- > 500 msec

and by CFB value into the categories

- $\leq$ 30 msec,
- > 30 – 60 msec,
- > 60 msec.

Number and percentage of participants within each category listed above, based on their post-OLE baseline QTcF data, will be presented by treatment group.

A shift table of rhythm results (Sinus rhythm, Atrial fibrillation, Other, Missing) from OLE baseline to last on treatment category, presented by treatment group, will be provided for the OLE period.

Shift tables of morphological assessments (Normal, Abnormal, Missing) from OLE baseline to maximum on treatment value will be provided for the OLE period.

Listings of ECG quantitative values, morphological and rhythm results will be produced on OLE period.

17.6 Physical Examination

No summary table will be provided since physical examination findings during screening will be recorded as medical history events and findings during the study as AEs.

17.7 Pregnancy Test

Results of pregnancy test (urine or serum) will be listed for OLE period based on SAF-OLE.

17.8 Immunoglobulin Levels, and CCI [redacted] ;CCI CCI

Analyses will be performed for the DBP+OLE period based on the SAF analysis set and for OLE period based on the SAF-OLE.

Data on immunoglobulin (Ig) levels, and CCI [redacted] (see list of parameters in Appendix 19.2) will be summarized for the OLE period for observed values, change from OLE baseline values, and percent change from OLE baseline by treatment group and overall using descriptive statistics.

In addition, number and percent of subjects falling above, below, and within normal range will be summarized where applicable. Assessments made at the End of Treatment visit for treatment discontinuers will be windowed appropriately. Assessments made at the End of Trial visit for study discontinuers will be summarized separately from assessments made at Safety follow-up visit at OLE Week 388 End of Trial visit for study completers.

Additionally, descriptive statistics of absolute values of CCI [redacted] CCI [redacted] will be provided for subjects falling above, below, and within normal range of the specific laboratory parameter. Summaries will be provided on OLE period for observed values, change from OLE baseline values, and percent change from OLE baseline by treatment group and overall.

Shift tables from OLE baseline value (low, normal, high) to end of OLE Period will be presented by treatment group and overall, for each Ig class and subclass, and CCI [redacted] parameters where applicable (see list of parameters in Appendix 19.2), using SAF-OLE analysis set.

Boxplots for each Ig class and subclass, (g/L), and CCI [redacted] (see list of parameters in Appendix 19.2) by treatment group and time point will be provided, for OLE period.

Line plots of median percent change from baseline will be provided by time point and treatment group on DBP and OLE combined periods for each Ig class and subclass, and CCI [redacted] (see list of parameters in Appendix 19.2).

CCI [redacted] (see list of parameters in Appendix 19.2) and Ig class and subclass levels will be listed by treatment group, participant and time point (where applicable). IgG values < 3 g/L (severe hypogammaglobulinemia) and IgG values < 6 g/L (hypogammaglobulinemia) will be flagged in the listing.

EAIR of infections

For definition of severe infections AESI, see Section 17.2.3 and Appendix 19.5.

EAIR of infections will be provided in subjects with and without at least one occurrence of CCI [redacted] lower than LLN during the DBP and OLE period combined. This analysis will be based on SAF. Among subjects who experienced CCI [redacted] lower than LLN at least once during the DBP and OLE period combined (on-treatment assessments considered only), EAIR will be computed separately considering the time between the first treatment administration and the first occurrence of CCI [redacted] lower than LLN and the time after the first occurrence of CCI [redacted] lower than LLN.

Confidence interval of incidence rate will be calculated using the Garwood method for Poisson mean.

17.9 Urinalysis Microscopic Evaluation

Urinalysis Microscopic Evaluation data will be listed by treatment group and time point (where applicable) for the OLE period.

17.10 Columbia- Suicide Severity Rating Scale (C-SSRS)

Analyses will be performed on SAF-OLE.

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a numerical score derived from 10 categories. The C-SSRS assesses the suicidal behavior and suicidal ideation in participants.

The C-SSRS outcome categories are provided below. Each category has a binary response (yes/no) and are numbered, providing a score. A score of 0 is assigned if there is no suicidal ideation or suicidal behavior present.

Ideation:

1. Wish to be Dead
2. Non-specific Active Suicidal Thoughts
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
5. Active Suicidal Ideation with Specific Plan and Intent

Behavior:

6. Preparatory Acts or Behavior

7. Aborted Attempt
8. Interrupted Attempt
9. Actual Attempt (non-fatal)
10. Completed Suicide

Occurrence of suicidal behavior is defined as having answered "yes" to a least 1 of the 4 suicidal behavior subcategories for baseline/screening assessments and to at least 1 of the 5 suicidal behavior subcategories for post-baseline "since last visit" assessments. Note that non-suicidal self-injurious behavior is not considered in the derivation of suicidal behavior and occurrence will be reported separately.

Occurrence of suicidal ideation is defined as having answered "yes" to at least one of the suicidal ideation sub-categories.

Occurrence of suicidality is defined as having at least one occurrence of suicidal ideation or at least one occurrence of suicidal behavior.

The number and percentage of participants with occurrence of suicidal behavior at any time during OLE period, occurrence of suicidal ideation at any time during treatment, occurrence of suicidality at any time during treatment and occurrence of self-injurious behavior without suicidal intent at any time during treatment will be summarized.

Shifts from study baseline (maximum score from "baseline/screening" assessment) and from OLE baseline to the worst on treatment outcome (maximum score from "since last visit" assessments) will be presented. The following categories will be summarized:

- No ideation (score 0)
- Non-serious suicidal ideation (score 1-3)
- Serious suicidal ideation (score 4-5)
- Suicidal behavior (score 6-10).

Participant data listings will be also provided.

18 References

US Department of Health and Human Services. Common Terminology Criteria for Adverse Events Version 4.0. 2009 (v4.03: June 14, 2010).

CCI [redacted]

Crowe BJ, Xia HA, Berlin JA, et al. Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. Clin Trials. 2009;6(5):430-40.

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Hoepner R, Miclea A, Popovic J, et al. Immunoglobulin levels may aid in the prediction treatment response in anti-CD20 treatment of multiple sclerosis. Clinical & Translational Neuroscience 2018, 1-6.

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19 Appendices

19.1 Appendix 1: Worst on treatment value based on normal range of laboratory evaluations

Names of Clinical Safety Laboratory Evaluations in Protocol version 6.0, 08 November 2019	If gradable parameter, corresponding evaluation names in NCI-CTCAE 4.03	Worst on treatment value based on normal range
Albumin	Hypoalbuminemia	LOW
Aspartate aminotransferase	Aspartate aminotransferase increased	HIGH
Alanine aminotransferase	Alanine aminotransferase increased	HIGH
Alkaline phosphatase	Alkaline phosphatase increased	HIGH
γ-Glutamyl-transferase	GGT increased	HIGH
Lactate dehydrogenase		HIGH
Bilirubin (total)	Blood bilirubin increased	HIGH
Protein (total)		LOW
Creatinine	Creatinine increased	HIGH
Estimated Glomerular Filtration Rate	Chronic kidney disease	LOW
Amylase	Serum amylase increased	HIGH
Lipase	Lipase increased	HIGH
Total carbon dioxide		LOW
Blood urea nitrogen		HIGH
Glucose	Hyperglycemia	HIGH
Glucose	Hypoglycemia	LOW
Sodium	Hypernatremia	HIGH
Sodium	Hyponatremia	LOW
Potassium	Hyperkalemia	HIGH
Potassium	Hypokalemia	LOW
Chloride		NA
Calcium	Hypercalcemia	HIGH
Calcium	Hypocalcemia	LOW
Magnesium	Hypermagnesemia	HIGH
Magnesium	Hypomagnesemia	LOW
Phosphate	Hypophosphatemia	LOW
Hematocrit		LOW/HIGH
Hemoglobin	Hemoglobin increased	HIGH
Hemoglobin	Anemia	LOW
Red blood cell count		NA
Mean corpuscular volume		NA
Mean corpuscular hemoglobin		NA
Mean corpuscular hemoglobin concentration		NA
Reticulocyte count		NA
Platelet count	Platelet count decreased	LOW

Names of Clinical Safety Laboratory Evaluations in Protocol version 6.0, 08 November 2019	If gradable parameter, corresponding evaluation names in NCI-CTCAE 4.03	Worst on treatment value based on normal range
White blood cell count	Leukocytosis	HIGH
White blood cell count	White blood cell decreased	LOW
CCI [redacted] cell count		LOW
White blood cell differentials and absolute counts: Basophils		NA
White blood cell differentials and absolute counts: Eosinophils		NA
White blood cell differentials and absolute counts: Lymphocytes	Lymphocyte count increased	HIGH
White blood cell differentials and absolute counts: Lymphocytes	Lymphocyte count decreased	LOW
White blood cell differentials and absolute counts: Monocytes		NA
White blood cell differentials and absolute counts: Neutrophils	Neutrophil count decreased	LOW

19.2 Appendix 2: List of parameters for Immunoglobulin Levels and Immune cell subset counts

Immunoglobulin classes and subclasses

Parameter	Units
Immunoglobulin A	g/L
Immunoglobulin M	g/L
Immunoglobulin G	g/L
Immunoglobulin G subclass 1	g/L
Immunoglobulin G subclass 2	g/L
Immunoglobulin G subclass 3	g/L
Immunoglobulin G subclass 4	g/L

CCI [redacted]

CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

CCI [redacted]	[redacted]
[redacted]	[redacted]

19.3 Appendix 3: Analysis visit windows for Safety and Efficacy Endpoints

Analysis visit windows for biochemistry parameters through OLE Period

Analysis visit	Nominal analysis visit day	Analysis visit window (days)	
		Evobrutinib/Placebo during main study	Tecfidera during main study
OLE Week 0	1	[1, 1]	[1, 1]
OLE Week 1	7		[2, 11)
OLE Week 2	14	[2, 21)	[11, 18)
OLE Week 3	21		[18, 25)
OLE Week 4	28	[21, 35)	[25, 32)
OLE Week 5	35		[32, 39)
OLE Week 6	42	[35, 49)	[39, 46)
OLE Week 7	49		[46, 53)
OLE Week 8	56	[49, 63)	[53, 60)
OLE Week 9	63		[60, 67)
OLE Week 10	70	[63, 77)	[67, 74)
OLE Week 11	77		[74, 81)
OLE Week 12	84	[77, 91)	[81, 88)
OLE Week 13	91		[88, 95)
OLE Week 14	98	[91, 105)	[95, 102)
OLE Week 15	105		[102, 109)
OLE Week 16	112	[105, 126)	[109, 126)
OLE Week 20	140	[126, 154)	
OLE Week 24	168	[154, 182)	
OLE Week 28	196	[182, 210)	
OLE Week 32	224	[210, 238)	
OLE Week 36	252	[238, 266)	
OLE Week 40	280	[266, 294)	
OLE Week 44	308	[294, 322)	
OLE Week 48	336	[322, 350)	
OLE Week 52	364	[350, 378)	
OLE Week 56	392	[378, 406)	
OLE Week 60	420	[406, 434)	
OLE Week 64	448	[434, 462)	
OLE Week 68	476	[462, 490)	
OLE Week 72	504	[490, 518)	
OLE Week 76	532	[518, 546)	
OLE Week 80	560	[546, 574)	

Analysis visit	Nominal analysis visit day	Analysis visit window (days)	
		Evobrutinib/Placebo during main study	Tecfidera during main study
OLE Week 84	588	[574, 602)	
OLE Week 88	616	[602, 630)	
OLE Week 92	644	[630, 658)	
OLE Week 96	672	[658, 714)	
OLE Week 108	756	[714, 798)	
OLE Week 120	840	[798, 882)	
OLE Week 132	924	[882, 966)	
OLE Week 144	1008	[966, 1050)	
OLE Week 156	1092	[1050, 1134)	
OLE Week 168	1176	[1134, 1218)	
OLE Week 180	1260	[1218, 1302)	
OLE Week 192	1344	[1302, 1428)	
OLE Week 216	1512	[1428, 1596)	
OLE Week 240	1680	[1596, 1764)	
OLE Week 264	1848	[1764, 1932)	
OLE Week 288	2016	[1932, 2100)	
OLE Week 312	2184	[2100, 2268)	
OLE Week 336	2352	[2268, 2366)	

Analysis visit windows for biochemistry parameters through DBP

Analysis visit	Nominal analysis visit day	Analysis visit window (days)
		All treatment groups
Day 1	1	[1, 1]
Week 4	28	[2, 42)
Week 8	56	[42, 63)
Week 10	70	[63, 77)
Week 12	84	[77, 91)
Week 14	98	[91, 105)
Week 16	112	[105, 119)
Week 18	126	[119, 133)
Week 20	140	[133, 147)
Week 22	154	[147, 161)
Week 24	168	[161, $X^{[1]}$]
Week 26	182	($X^{[1]}$, $X^{[1]}$ + 21)
Week 28	196	[$X^{[1]}$ + 21, $X^{[1]}$ + 35)
Week 30	210	[$X^{[1]}$ + 35, $X^{[1]}$ + 49)
Week 32	224	[$X^{[1]}$ + 49, $X^{[1]}$ + 63)
Week 34	238	[$X^{[1]}$ + 63, $X^{[1]}$ + 77)
Week 36	252	[$X^{[1]}$ + 77, $X^{[1]}$ + 91)
Week 38	266	[$X^{[1]}$ + 91, $X^{[1]}$ + 105)

Week 40	280	[X[1] + 105, X[1] + 119)
Week 42	294	[X[1] + 119, X[1] + 133)
Week 44	308	[X[1] + 133, X[1] + 147)
Week 46	322	[X[1] + 147, X[1] + 161)
Week 48	336	[X[1] + 161, X[1] + 171)

X[1] corresponds to the time + 30 minutes where subjects are exposed for the first time to Evobrutinib in the second 24-week treatment period.

Analysis visit windows for Ig levels, including both DBP and OLE Period

Analysis visit	Nominal analysis visit day	Analysis visit window (days)	
		Evobrutinib/Placebo during main study	Tecfidera during main study
Day 1	1	[1, 1]	*same*
Week 4	28	[2, 70)	*same*
Week 16	112	[70, 140)	*same*
Week 24	168	[140, 189)	*same*
Week 48	336	[189, OLE 22)	[189, OLE 1)
OLE W0	OLE 1	*Same as W48 window*	[OLE 1, OLE 1]
OLE W24	OLE 168	[OLE 22, OLE 252)	[OLE 2, OLE 252)
OLE W48	OLE 336	[OLE 252, OLE 420)	*same*
OLE W72	OLE 504	[OLE 420, OLE 588)	*same*
OLE W96	OLE 672	[OLE 588, OLE 756)	*same*
OLE W120	OLE 840	[OLE 756, OLE 924)	*same*
OLE W144	OLE 1008	[OLE 924, OLE 1092)	*same*
OLE W168	OLE 1176	[OLE 1092, OLE 1260)	*same*
OLE W192	OLE 1344	[OLE 1260, OLE 1428)	*same*
OLE W216	OLE 1512	[OLE 1428, OLE 1596)	*same*
OLE W240	OLE 1680	[OLE 1596, OLE 1764)	*same*
OLE W264	OLE 1848	[OLE 1764, OLE 1932)	*same*
OLE W288	OLE 2016	[OLE 1932, OLE 2100)	*same*
OLE W312	OLE 2184	[OLE 2100, OLE 2268)	*same*
OLE W336	OLE 2352	[OLE 2268, 2366)	*same*

Analysis visit windows for immune cell subset counts, including both DBP and OLE Period

Analysis visit	Nominal analysis visit day	Analysis visit window (days)	
		Evobrutinib/Placebo during main study	Tecfidera during main study
SCR[1]			
Day 1	1	[1, 1]	*same*
Week 4	28	[2, 98)	*same*
Week 24	168	[98, 189)	*same*
Week 48	336	[189, OLE 22) for patients who enter OLE	[189, OLE 1) for patients who enter OLE

		[189, 350) for patients who do not enter OLE	[189, 350) for patients who do not enter OLE
Week 52	364	[350, ∞)	*same*
OLE W0	OLE 1	*Same as W48 window*	[OLE 1, OLE 1]
OLE W48	OLE 336	[OLE 22, OLE 504)	[OLE 2, OLE 504)
OLE W96	OLE 672	[OLE 504, OLE 840)	*same*
OLE W144	OLE 1008	[OLE 840, OLE 1176)	*same*
OLE W192	OLE 1344	[OLE 1176, OLE 1512)	*same*
OLE W240	OLE 1680	[OLE 1512, OLE 1848)	*same*
OLE W288	OLE 2016	[OLE 1848, OLE 2184)	*same*
OLE W336	OLE 2352	[OLE 2184, OLE 2366)	*same*

[1] Ignore SCR assessment unless needed to replace missing D1 assessment

Analysis visit windows for ECG though OLE Period

Analysis visit	Nominal analysis visit day	Analysis visit window (days)
		All treatment groups
OLE Week 0	1	[Main period day 189, OLE30]
OLE Week 48	336	[30,504)
OLE Week 96	672	[504,840)
OLE Week 144	1008	[840,1176)
OLE Week 192	1344	[1176,1512)
OLE Week 240	1680	[1512,1848)
OLE Week 288	2016	[1848,2184)
OLE Week 336	2352	[2184,2382)

Analysis visit windows for hematology through OLE Period

Analysis visit	Nominal analysis visit day	Analysis visit window (days)	
		Evobrutinib/Placebo during main study	Tecfidera during main study
OLE Week 0	1	[1, 1]	[1, 1]
OLE Week 4	28		[2, 35)
OLE Week 6	42		[35, 49)
OLE Week 8	56		[49, 63)
OLE Week 10	70		[63, 77)
OLE Week 12	84		[77, 98)
OLE Week 16	112		[98, 140)
OLE Week 24	168	[2, 210)	[140, 210]
OLE Week 36	252	[210, 294)	
OLE Week 48	336	[294,378)	
OLE Week 60	420	[378, 462)	
OLE Week 72	504	[462, 546)	
OLE Week 84	588	[546, 630)	

OLE Week 96	672	[630, 714)
OLE Week 108	756	[714, 798)
OLE Week 120	840	[798, 882)
OLE Week 132	924	[882, 966)
OLE Week 144	1008	[966, 1050)
OLE Week 156	1092	[1050, 1134)
OLE Week 168	1176	[1134, 1218)
OLE Week 180	1260	[1218, 1302)
OLE Week 192	1344	[1302, 1428)
OLE Week 216	1512	[1428, 1596)
OLE Week 240	1680	[1596, 1764)
OLE Week 264	1848	[1764, 1932)
OLE Week 288	2016	[1932, 2100)
OLE Week 312	2184	[2100, 2268)
OLE Week 336	2352	[2268, 2366)

Analysis visit windows for hematology parameters through DBP

Analysis visit	Nominal analysis visit day	Analysis visit window (days)
		All treatment groups
Day 1	1	[1, 1]
Week 4	28	[2, 42)
Week 8	56	[42, 70)
Week 12	84	[70, 98)
Week 16	112	[98, 126)
Week 20	140	[126, 154)
Week 24	168	[154, 210]
Week 36	252	[210, 294)
Week 48	336	[294, 339)

Analysis visit windows for urinalysis parameters through DBP

Analysis visit	Nominal analysis visit day	Analysis visit window (days)
		All treatment groups
Week 12	84	[2, 126)
Week 24	168	[126, 252)
Week 48	336	[252, 350)

Analysis visit windows for urinalysis parameters through OLE Period

Analysis visit	Nominal analysis visit day	Analysis visit window (days)
		All treatment groups
OLE Week 0	1	[1, 1]
OLE Week 24	168	[2, 294)

OLE Week 60	420	[294, 546)
OLE Week 96	672	[546, 714)
OLE Week 108	756	[714, 798)
OLE Week 120	840	[798, 882)
OLE Week 132	924	[882, 966)
OLE Week 144	1008	[966, 1050)
OLE Week 156	1092	[1050, 1134)
OLE Week 168	1176	[1134, 1218)
OLE Week 180	1260	[1218, 1302)
OLE Week 192	1344	[1302, 1428)
OLE Week 216	1512	[1428, 1596)
OLE Week 240	1680	[1596, 1764)
OLE Week 264	1848	[1764, 1932)
OLE Week 288	2016	[1932, 2100)
OLE Week 312	2184	[2100, 2268)
OLE Week 336	2352	[2268, 2366)

Analysis visit windows for vital signs through OLE Period

Analysis visit	Nominal analysis visit day	Analysis visit window (days)	
		Evobrutinib/Placebo during main study	Tecfidera during main study
OLE Week 0	1	[1, 1]	[1, 1]
OLE Week 4	28		[2, 42)
OLE Week 8	56		[42, 70)
OLE Week 12	84	[2, 126)	[70, 126)
OLE Week 24	168	[126, 210)	
OLE Week 36	252	[210, 294)	
OLE Week 48	336	[294, 378)	
OLE Week 60	420	[378, 462)	
OLE Week 72	504	[462, 546)	
OLE Week 84	588	[546, 630)	
OLE Week 96	672	[630, 714)	
OLE Week 108	756	[714, 798)	
OLE Week 120	840	[798, 882)	
OLE Week 132	924	[882, 966)	
OLE Week 144	1008	[966, 1050)	
OLE Week 156	1092	[1050, 1134)	
OLE Week 168	1176	[1134, 1218)	
OLE Week 180	1260	[1218, 1302)	
OLE Week 192	1344	[1302, 1428)	
OLE Week 216	1512	[1428, 1596)	
OLE Week 240	1680	[1596, 1764)	
OLE Week 264	1848	[1764, 1932)	

Analysis visit	Nominal analysis visit day	Analysis visit window (days)	
		Evobrutinib/Placebo during main study	Tecfidera during main study
OLE Week 288	2016	[1932, 2100)	
OLE Week 312	2184	[2100, 2268)	
OLE Week 336	2352	[2268, 2366)	

Analysis visit windows for EDSS through DBP

Analysis visit	Nominal analysis visit day	Analysis visit window (days)
		All treatment groups
Day 1	1	[1, 1]
Week 12	84	[2, 126)
Week 24	168	[126, 189)
Week 36	252	[189, 294)
Week 48	336	[294, 339)

Analysis visit windows for EDSS through OLE Period

Analysis visit	Nominal analysis visit day	Analysis visit window (days)
		All treatment groups
OLE Week 0	1	[Main period day 294, OLE 169]
OLE Week 48	336	[169, 504)
OLE Week 96	672	[504, 840)
OLE Week 144	1008	[840, 1176)
OLE Week 192	1344	[1176, 1512)
OLE Week 240	1680	[1512, 1848)
OLE Week 288	2016	[1848, 2184)
OLE Week 336	2352	[2184, 2382)

Analysis visit windows for MRI through OLE Period

Analysis visit	Nominal analysis visit day	Analysis visit window (days)
		All treatment groups
OLE Week 0	1	[Main period day 189, OLE 30)
OLE Week 48	336	[30, 504)
OLE Week 96	672	[504, 840)
OLE Week 144	1008	[840, 1176)
OLE Week 192	1344	[1176, 1512)
OLE Week 240	1680	[1512, 1848)
OLE Week 288	2016	[1848, 2184)
OLE Week 336	2352	[2184, 2382)

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CCI [redacted]

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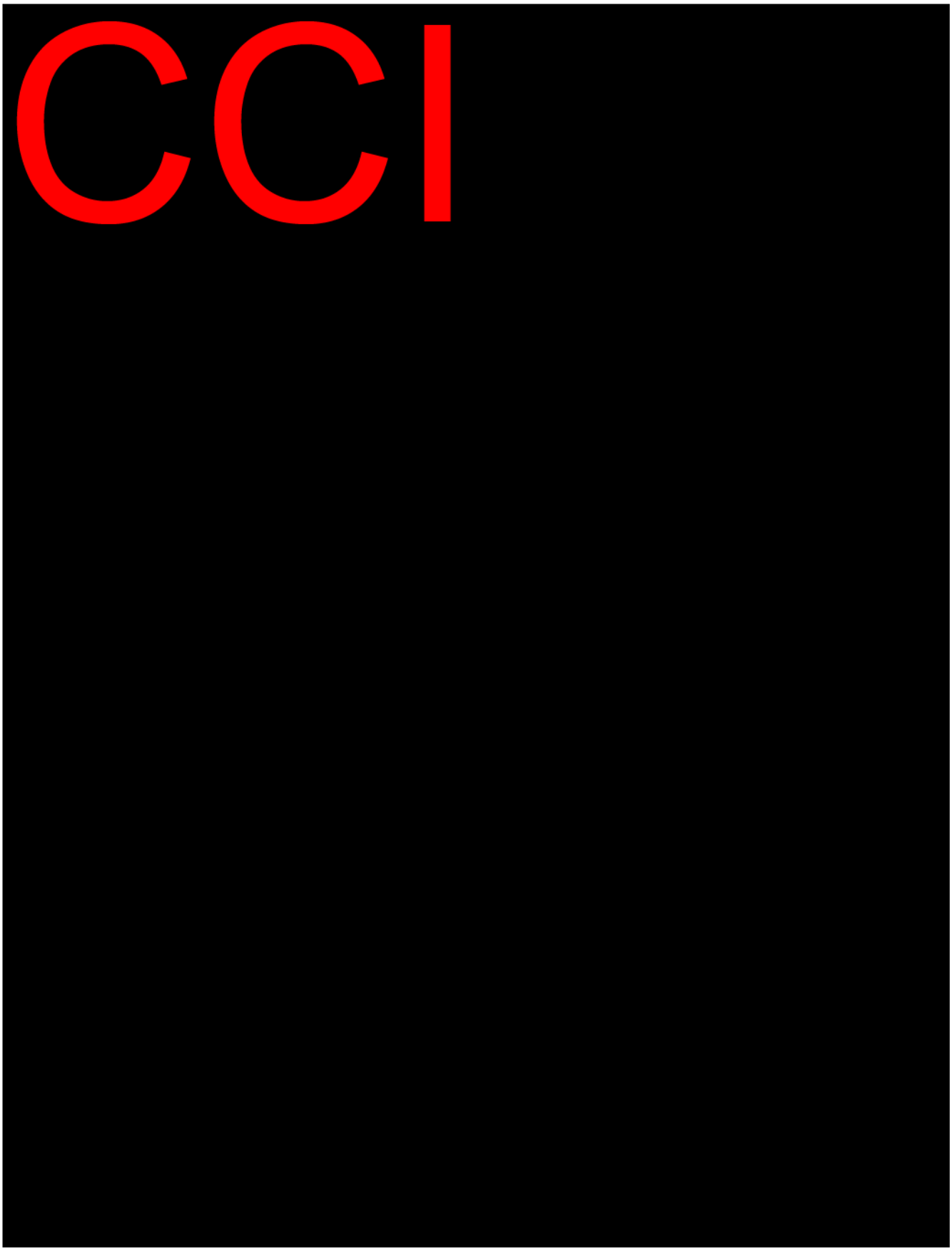
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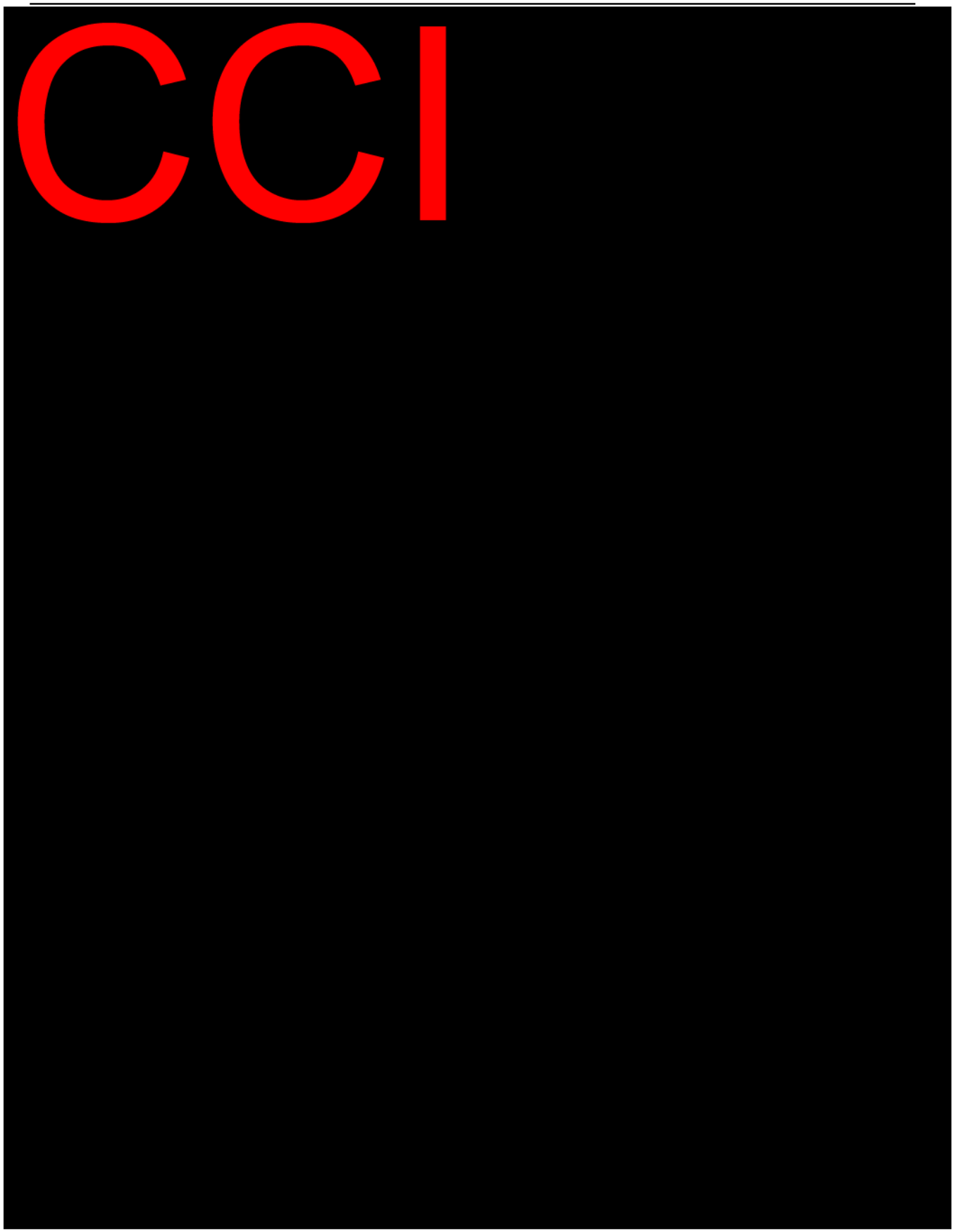
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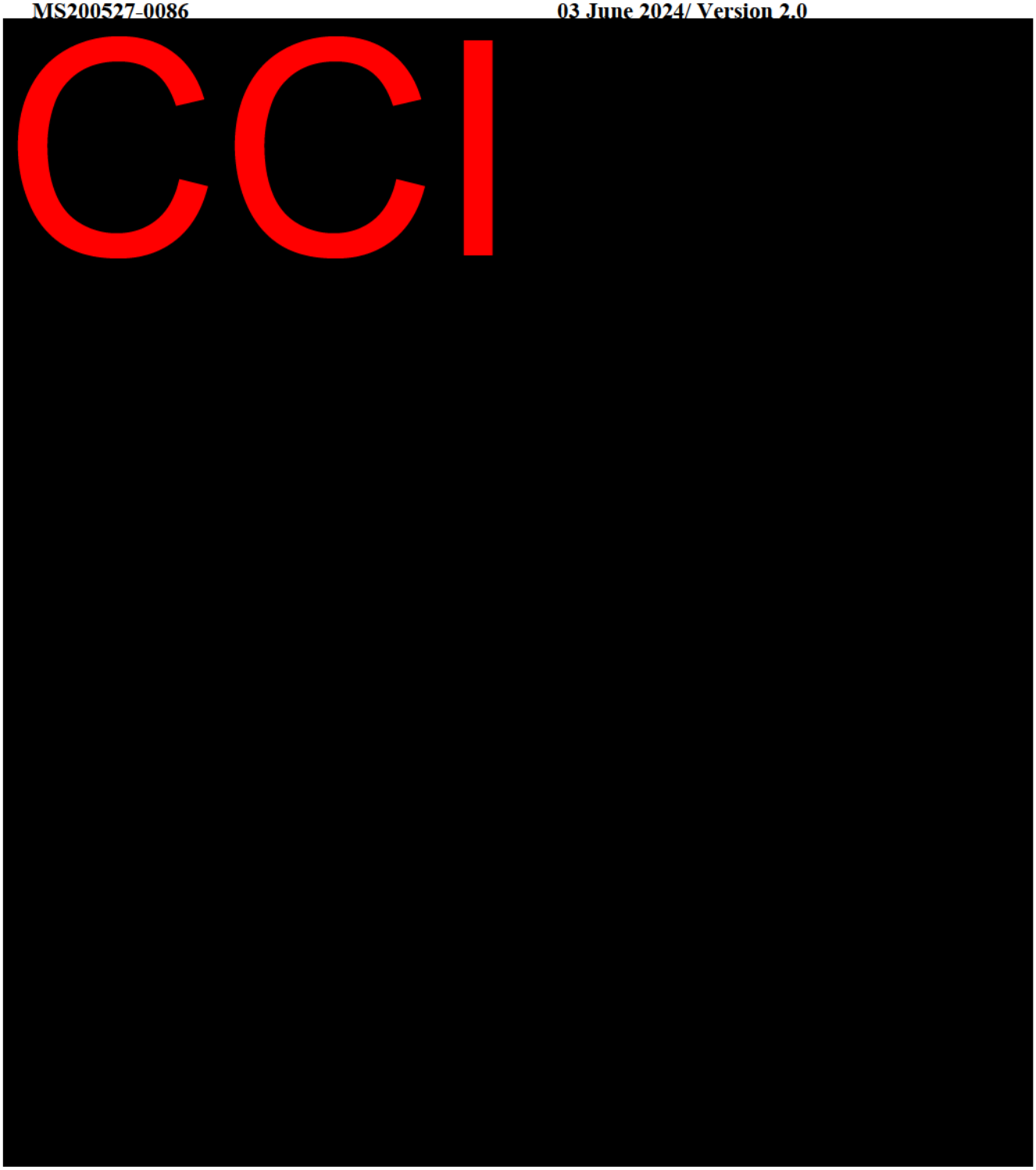

19.5 Appendix 5: AEs of Special Interest

A reference spreadsheet containing the list of AE terms to programmatically flag participants with AEs of special interest is shared by the Safety Team and regularly updated according to MedDRA version update.

The latest version of the file at time of analysis will be used.

19.6 Appendix 6: Data handling after cut-off date

Not applicable

19.7 Appendix 7: List of Prior DMT

Unique_prev_med_GCD_v2.1

Signature Page for VV-CLIN-359910 v3.0

Approval Task	PPD Clinical 10-Jun-2024 21:00:59 GMT+0000

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