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STATISTICAL ANALYSIS PLAN

Long-term extension safety and efficacy study of tolebrutinib in participants with relapsing multiple sclerosis

SAR442168-LTS16004

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ARR:	annualized relapse rate
AST:	aspartate aminotransferase
BTK:	Bruton's tyrosine kinase
[redacted]	[redacted]
CI:	confidence interval
COVID-19:	coronavirus disease 2019
C-SSRS:	Columbia suicide severity rating scale
DMC:	Data Monitoring Committee
ECG:	electrocardiogram
eCRF:	electronic case report form
EDSS:	expanded disability status scale
HLGT:	high level group term
HLT:	high level term
ICF:	informed consent form
IDMC:	independent data monitoring committee
IMP:	investigational medicinal product
LLT:	lower level term
LTS:	long-term safety
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	modified intention to treat
MRI:	magnetic resonance imaging
MS:	multiple sclerosis
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamics
PT:	preferred term
RMS:	relapsing multiple sclerosis
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	standard deviation
[redacted]	[redacted]
SoA:	schedule of activities
SOC:	system organ class
TEAE:	treatment emergent adverse event
ULN:	upper limit of normal
WHO-DD:	World Health Organization Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

This SAP provides a comprehensive and detailed description of strategy and statistical techniques to be used to realize the analysis of data for tolebrutinib study protocol LTS16004. The purpose of the SAP is to ensure the credibility of the study findings by prespecifying the statistical approaches to the analysis of study data prior to data base lock for interim or final analysis.

1.1 STUDY DESIGN AND RANDOMIZATION

The LTS16004 study is a long-term, multicenter, follow-up study to determine the safety and efficacy of tolebrutinib. Participants who completed treatment with tolebrutinib in the previous DRI15928 study are eligible for enrollment. Participants will start the treatment as soon as possible after informed consent. The study consists of 2 parts:

Part A: Double-blind period of continued treatment with the respective tolebrutinib dose (ie, 5, 15, 30, or 60 mg/day) administered in the DRI15928 study.

Until the dose of tolebrutinib to be used in Phase 3 is determined, participants will continue treatment with their same tolebrutinib dose used in the DRI15928 study. Cohort 1 of the DRI15928 study that exits the trial receiving placebo from Weeks 13 to 16 will receive the active treatment dose assigned to them at randomization and administered during Weeks 1 to 12. The double-blind will be maintained until the selection of the Phase 3 dose is made.

Part B: Open-label period of a single-group treatment with the Phase 3 dose, selected as 60 mg/day tolebrutinib.

All participants providing consent to Part B of the study will be switched to open-label treatment with the selected dose. If the participant is not willing to switch to the selected dose of tolebrutinib, the participant will be withdrawn from the study and a follow-up visit will be performed 4 to 6 weeks after the last study intervention.

After the end of this study, participants who successfully complete the trial on tolebrutinib may be offered the option to participate in a Phase 3 LTS study for up to an additional 3 years, or until tolebrutinib is approved in their respective country, whichever comes first. If this program is terminated earlier, other available RMS treatments will need to be considered at discretion of the treating physician.

An IDMC will follow safety data periodically as detailed in the DMC charter.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to determine the long-term safety and tolerability of tolebrutinib in RMS patients.

1.2.2 Secondary objectives

The secondary objective of this study is to evaluate efficacy of tolebrutinib on disease activity, assessed by clinical and imaging methods.

1.3 DETERMINATION OF SAMPLE SIZE

There are no sample size calculations for this long-term extension study.

All participants who completed the DRI15928 study were eligible for enrollment in the LTS16004 study. The Sponsor enrolled 130 participants in the DRI15928 study, 129 completed the study treatment, and 126 enrolled in LTS16004.

1.4 STUDY PLAN

The SoA for up to Year 1, during Years 2 to 4, and for Year 5 can be found in Section 1.3 of the study protocol, Tables 1-3. The graphical study design is provided in Figure 1 of the study protocol.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The major changes in the protocol which are related to the statistical analysis are listed in this section.

Amendment Number	Approval Date	Description of statistical changes	Rationale
4	28-Oct-2020	Appendix 10 was added, containing contingency measures for a regional or national emergency that is declared by a governmental agency. Section 10.9.4 mentioned the methods of handling the impact of the emergency such as missing data would be detailed in the Statistical Analysis Plan.	To account for the impact of regional or national emergency such as COVID-19

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

SAP Version	Approval Date	Changes	Rationale
2	10-Jul-2023	Changed SAR442168 to tolebrutinib throughout.	Subsequent availability of the INN - international nonproprietary name could be added to abbreviations.
		Added opportunity to enroll in Phase 3 LTS17043 after completing the current study.	Since the LTS16004 study will end in 2024 and the phase 3 LTS is scheduled to start in 2024, participants will have the opportunity to continue tolebrutinib treatment.

SAP Version	Approval Date	Changes	Rationale
		Deleted study schedule and graphical study design.	They are already detailed in the protocol and so replaced with a reference to the protocol sections.
		Added missing MRI parameters as efficacy endpoints and the corresponding analysis methods.	Several exploratory MRI parameters were missed in the previous SAP version.
		Added safety findings on MRI to safety endpoints. Added the contents about reporting of safety findings from MRI.	Based on Protocol Amendment 02 & 05.
		Added summary tables for AEs occurring in Part A only.	To assess for any dose relationship in adverse events in Part A.
		Extended disposition summary.	To cover treatment and study status in both parts (A and B) of the study.
		Removed the mITT DRI15928+LTS16004 population in Section 2.3.1	Considering that miTT LTS16004 population is already defined and that there is no difference between these two populations.
		Added supplementary analysis of ARR on 60 mg tolebrutinib including data from all dose groups after the switch to the 60 mg dose.	Since all participants switch to tolebrutinib 60 mg in Part B, a better estimate of the ARR at this dose level can be provided by grouping participants together.
		Added a summary of COVID-19 related AEs in Section 2.4.5.1	Grouping PTs to get the overall incidence of COVID-19.
		Added methods of addressing missing data issue due to regional or national emergency.	According to Protocol Amendment 04.
		Added a table describing the selection criterion for each AESI category	To give a more explicit description of all AESI categories and to be aligned with the SAPs of the tolebrutinib phase 3 studies.
		Reformatted existing content when necessary. Did minor, editorial, stylistic changes as necessary. Updated table of contents, section numbers, abbreviations as necessary.	Accordance with Sponsor's standards.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the baseline value from the DRI15928 study. Data for demographic and baseline characteristics will be from study DRI15928 database for participants who enrolled in LTS16004.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the on-treatment summary statistics in the safety and efficacy sections.

Demographic characteristics

Demographic variables are gender (Male, Female), race (Caucasian/white, Black, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, other), age in years (quantitative and qualitative variable: ≤40, >40 years), and ethnicity (Hispanic, non-Hispanic).

Medical or surgical history

Medical and surgical history data in DRI15928 will be recoded to PT and associated primary SOC using the version of MedDRA in use at Sanofi at the time of LTS16004 database lock. Any new past and/ or concomitant diseases or past surgeries since the end of DRI15928 will also be included.

Substance use - alcohol habit

The frequency of alcohol use in the last 12 months prior to entry into DRI15928.

Multiple sclerosis history and disease characteristics at baseline

MS history and disease characteristics as defined in DRI15928 including time since first symptoms of MS (years), time since diagnosis of MS (years), time since most recent relapse onset (months), MS type (relapsing remitting, secondary progressive), number of relapse(s) within the past year and within the past 2 years (quantitative and qualitative: 0, 1, 2, ≥3), baseline EDSS score (quantitative and qualitative). All are relative to DRI15928 randomization visit.

MRI parameters at baseline

MRI parameters at DRI15928 baseline include count of Gd-enhancing T1 hyperintense, T2, and T1 non-enhancing (hypointense) lesions, volume of T2 and T1 non-enhancing (hypointense) lesions, and normalized brain, cerebral cortex, and thalamic volume.

2.1.2 Prior and concomitant medications

All medications ongoing at the end of the DRI15928 study, new medications taken since the end of the DRI15928 study, and any medications taken during the LTS16004 study including MS related treatment(s) are to be reported in the eCRF pages.

All medications will be coded using the WHO-DD using the version currently in effect at Sanofi at the time of database lock.

Prior medications are those the participant used prior to first IMP intake in LTS16004, including those in both DRI15928 and LTS16004. These prior medications can be discontinued before first dosing or can be ongoing during treatment phase.

Concomitant medications are those the participant used at any time during the LTS16004 treatment period, from the first IMP intake in LTS16004 to the day of last IMP intake in LTS16004. A given medication can be classified both as a prior medication and as a concomitant medication. Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

Baseline for efficacy endpoints assessed for long-term tolebrutinib treatment by change from baseline is defined as the last non-missing value prior to the first administration of randomized study intervention in the DRI15928 study, unless otherwise specified. All efficacy evaluations up to the closeout measurement will be included for analysis unless otherwise specified.

2.1.3.1 MRI parameters

For MRI parameters, data from both DRI15928 and LTS16004 will be examined. The last MRI obtained in the DRI15928 study, if performed within 6 weeks prior to Day 1 of the LTS16004 study, will be acceptable as the Day 1 MRI for the LTS16004 study.

MRI assessment will be performed at visits as specified in the protocol Section 1.3 SoA.

MRI parameters include:

- Number of new Gd-enhancing T1 hyperintense lesions (secondary)
- Number of new or enlarging T2 lesions (secondary)
- Total number of Gd-enhancing T1-hyperintense lesions (secondary)
- Volume of T2 and new/enlarging T2 lesions (tertiary/exploratory)
- Number of new T1 non-enhancing (hypointense) lesions (tertiary/exploratory)
- Volume of T1 non-enhancing (hypointense) lesions (tertiary/exploratory)
- Percent change from baseline in sum of brain volume (tertiary/exploratory)
- Percent change from baseline in sum of thalamus volume (tertiary/exploratory)

- Percent change from baseline in sum of cerebral cortex volume (tertiary/exploratory)
- Change in myelin integrity and other features of MRI lesions as measured by magnetization transfer ratio (MTR) and susceptibility-weighted imaging MRI (tertiary/exploratory):
  - Number of slowly enlarging lesions
  - Volume of slowly enlarging lesions
  - Number of phase rim lesions
  - MTR recovery in Gd-enhancing lesions
- Proportion of participants with no new MRI disease activity through the end of the study defined as 0 new Gd-enhancing T1-hyperintense lesions and 0 new or enlarging T2 lesions. (tertiary/exploratory)
- Normalized T1 intensity evolution in slowly evolving lesions
- Normalized T1 intensity evolution in screening unenhancing T2 lesions
- Normalized T1 intensity evolution in phase rim regions of interest

In the DRI15928 study and the LTS16004 study Part A the central reader is blinded and in the LTS16004 study Part B the central reader is not blinded.

2.1.3.2 MS relapse

MS relapse events are clinical events that met the protocol defined criteria (protocol Section 8.1.2.2).

ARR:

Defined as the number of confirmed relapses per participant-year (secondary) in LTS16004.

Proportion of relapse free participants

The proportion of participants without confirmed relapse in LTS16004 will be estimated based on the Kaplan-Meier curve at yearly time points (1, 2, 3, 4 and 5 years since first IMP in LTS16004).

2.1.3.3 EDSS

EDSS is an ordinal clinical rating scale which ranges from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments. EDSS consists in rating of 7 functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual rating, and cerebral functions) and ambulation. Change from baseline at each visit in LTS16004 will be presented (secondary).

[redacted]

2.1.4 Safety endpoints

The safety analyses will be based on the reported AEs, including safety findings on MRI, and other safety information, such as clinical laboratory, ECG, vital signs, and C-SSRS data collected in LTS16004.

Magnetic resonance imaging scans should be reviewed locally for any non-MS pathology. In case of such findings, the relevant information needs to be provided to the Investigator for appropriate safety reporting and to ensure the appropriate management of the participant's identified safety finding. When available, a diagnosis of pathology as a cause of such MRI findings or the findings themselves will be reported as an AE until the diagnosis is clear.

MS relapses are exempt from being reported as AE/SAE unless, in the judgment of the Investigator, it is unusually severe or medically unexpected. MS relapses are collected on the eCRF and analyzed as part of the efficacy analyses.

Observation periods

In general, there should be no pretreatment AEs in the LTS16004 study since participants were to roll directly into LTS16004 after completing the DRI15928 study. However, in case there is a gap, the pre-treatment period for the LTS16004 study is defined as the time from signing the ICF until first IMP intake in the LTS16004 study.

The on-treatment period is from first administration of tolebrutinib in the LTS16004 study to the last administration +10 days, including both Part A and Part B treatment periods.

The post-treatment period, if applicable, is from the end of the on-treatment period to the end of the follow-up in LTS16004.

The on-study period is from signing the ICF to the end of follow-up in the LTS16004 study.

2.1.4.1 Adverse events variables

Adverse event observation period

Pre-treatment adverse events are AEs that developed, worsened, or became serious during the pre-treatment period.

TEAEs are AEs that developed, worsened, or became serious during the on-treatment period.

AEs for Part A are AEs that developed, worsened, or became serious during Part A of the study.

Post-treatment AEs are events that developed, worsened, or became serious during the post-treatment period.

All adverse events including SAEs and AESIs will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the version of MedDRA currently in effect at Sanofi at the time of database lock.

Selection criterion for each AESI category is listed as below. The AESI categories are described in the protocol Section 8.3.1.

Table 1 - Selection criterion for each AESI category

AESIs	Selection
Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP	'Pregnancy' or 'Partner Pregnancy' ticked on the Pregnancy eCRF.
Symptomatic overdose (serious or nonserious) with IMP/ NIMP	AECAT="OVERDOSE DATA"; must be symptomatic
Increase in ALT - increase of ALT > 3 x ULN	AECAT="ALT INCREASE DATA" and AESI check box marked.
ECG observation of atrial fibrillation or atrial flutter	CMQ30003 for selection and AESI check box marked.
Severe infection that may or may not meet seriousness criteria (eg, a severe opportunistic infection)	SOC of Infections and Infestations, intensity being severe and AESI check box marked.
Moderate or severe hemorrhagic events, including but not limited to symptomatic bleeding, bleeding in a critical area or organ such as the CNS, or intraocular bleeding.	SMQNAME='Haemorrhage terms (excl laboratory terms)" for selection, intensity being moderate or severe, and AESI check box marked.
Thrombocytopenia, platelet count <75 x 10^9/L	PT="Thrombocytopenia" and AESI check box marked.

2.1.4.2 Deaths

The death observation periods are per the observation periods defined above.

- Death pre-treatment: death occurring during the pre-treatment observation period
- Death on-study: death occurring during the on-study observation period
- Death on-treatment: death occurring during the on-treatment observation period

Death poststudy is death occurring after the last protocol planned visit and before database lock for LTS16004.

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology and clinical chemistry, and urinalysis. Clinical laboratory values after conversion will be analyzed in standard international units and international units will be used in all listings and tables. Baseline for laboratory variables is baseline from DRI15928.

Blood samples for clinical laboratories will be obtained according to the SoA, protocol Section 1.3, unless otherwise specified. The laboratory parameters are detailed in the protocol Section 10.2.

2.1.4.4 Vital signs variables

Vital signs include body temperature (degrees Celsius), heart rate (beats/minute), respiratory rate (breaths/minute), and systolic and diastolic blood pressure (mmHg). Blood pressure and heart rate measurements will be assessed consistently in sitting or supine position. The baseline for vital signs is the baseline from DRI15928.

2.1.4.5 Electrocardiogram variables

Single 12-lead ECGs will be obtained using an ECG machine that automatically calculates ECG parameters: heart rate, PR, QRS, QT, and QTc. Due to differences in ECG between DRI15928 and LTS16004, the LTS16004 Day 1 ECG will be used as baseline.

2.1.4.6 Columbia suicide severity rating scale

The C-SSRS is a tool used to assess the lifetime suicidality of a participant and to track suicidal events throughout the study. The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality.

The scale is administered by the Investigator or a qualified designee at the time points indicated in the protocol SoA (protocol Section 1.3).

The C-SSRS categories have binary responses (yes, no):

Category 1 - Wish to be dead

Category 2 - Non-specific active suicidal thoughts

Category 3 - Active suicidal ideation with any methods (not plan) without intent to act

Category 4 - Active suicidal ideation with some intent to act, without specific plan

Category 5 - Active suicidal ideation with specific plan and intent

Category 6 - Preparatory acts or behavior

Category 7 - Aborted attempt

Category 8 - Interrupted attempt

Category 9 - Actual attempt (non-fatal)

Category 10 - Suicidal behavior

Composite endpoints are defined as:

Suicidal ideation - a “yes” answer at any time during treatment to any 1 of the 5 suicidal ideation questions (Categories 1-5)

Suicidal behavior - a “yes” answer at any time during treatment to any 1 of the 5 suicidal behavior questions (Categories 6-10)

Suicidal ideation or behavior - a “yes” answer at any time during treatment to any 1 of the 10 suicidal and behavior questions (Categories 1-10)

2.1.5 PD endpoints

The following exploratory endpoints will be assessed in LTS16004.

- [redacted] in case of index AEs (cytopenia and arrhythmias).
- [redacted]

2.2 DISPOSITION OF PARTICIPANTS

Screened participants in LTS16004 are people who signed the informed consent form. Screen failures are defined as participants who consent to participate in the LTS16004 study but cannot continue due to eligibility criteria.

For participant study status, the total number of participants for each one of the following categories will be presented in the clinical study report using a summary table and/or flow chart diagram:

- Screened/Randomized participants in DRI15928
- Participants who completed the planned study treatment period as per protocol in DRI15928

LTS16004:

- Screened participants
- Screen failure participants according to reason, if available
- Enrolled participants
- Treated participants
- For Part A, participants who completed treatment and those who permanently discontinued by main reason
- For Part A, participants who completed the study period, and those who ended the study period prematurely by main reason

- For Part B, participants who completed treatment and those who permanently discontinued treatment by main reason
- For Part B, participants who completed the study period and those who ended the study period prematurely by main reason

For interim assessment of disposition, those ongoing on treatment and/or study will also be included.

For all categories of participants (except for screened/randomized in DRI15928, completed treatment in DRI15928 and screened categories in LTS16004) percentages will be calculated using the number of enrolled participants in the LTS16004 study as the denominator. A listing of participants who discontinued treatment will include the treatment the participant was receiving at the time of discontinuation. A separate listing of reasons for study discontinuation will be provided.

A participant is considered lost to follow-up at the end of the study if he/she is not assessed at the last protocol planned visit and is unable to be contacted by the study site.

Additionally, the analysis populations for safety and efficacy (Section 2.3) will be summarized in a table by number of participants on the enrolled population.

Data will be presented for the following tolebrutinib dose groups: 5/60, 15/60, 30/60, and 60/60 mg, and all.

2.2.1 Protocol deviations

The number and percentage of participants with a critical or major protocol deviation will be summarized by deviation and overall, within dose group. A by participant listing of all critical and major deviations will be provided.

2.3 ANALYSIS POPULATIONS

2.3.1 Efficacy population

mITT population: defined as all participants enrolled in LTS16004 who have at least 1 day of IMP exposure during the study. All participants will be summarized in the dose group to which they were randomized in DRI15928 and overall.

2.3.2 Safety population

Safety population: all participants enrolled in LTS16004 and exposed to IMP during LTS16004, regardless of the amount of exposure.

2.4 STATISTICAL METHODS

Continuous data will be summarized using the number of available data, mean, SD, median, minimum, Q1, Q3, and maximum for each dose group. Categorical and ordinal data will be summarized using the number and percentage of participants in each dose group.

P-values will not be calculated.

2.4.1 Demographics and baseline characteristics

Only participants enrolled in LTS16004 will be summarized on demographic and baseline characteristic data. Parameters described in Section 2.1.1 will be summarized by the tolebrutinib dose group and overall using descriptive statistics.

Medical and surgical history data will be summarized by SOC and PT. Events are sorted by SOC internationally agreed order and by decreasing frequency of PT based on incidence in the overall tolebrutinib group.

2.4.2 Prior and Concomitant medications

Prior and concomitant medication will be summarized by dose group and overall, only for the participants enrolled into LTS16004. Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, participants may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of anatomic category followed by all other therapeutic classes based on the overall incidence across dose groups. In case of equal frequency regarding anatomic categories (respectively therapeutic categories), alphabetical order will be used.

The tables for concomitant medications will be sorted by decreasing frequency of anatomic category followed by all other therapeutic classes based on the incidence in the overall group. In case of equal frequency regarding anatomic categories (respectively therapeutic categories), alphabetical order will be used.

In addition, the systemic corticosteroid treatment for MS relapse will be analyzed by number and percentage of confirmed relapse requiring steroid treatment. These medications will be summarized by ATC code and standardized medication name.

2.4.3 Extent of investigational medicinal product exposure and compliance

2.4.3.1 Extent of investigational medicinal product exposure for tolebrutinib

The extent of IMP exposure will be assessed by the duration of IMP exposure in LTS16004.

Duration of IMP exposure is defined as last dose date in LTS16004 - first dose date in LTS16004 + 1 day, regardless of unplanned intermittent discontinuations. Exposure will be summarized for the study as a whole and separately for Parts A and B. Part A exposure will be summarized according to tolebrutinib dose group (5, 15, 30, and 60 mg).

Overall duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of IMP exposure will be summarized categorically by counts and percentages for each of the following categories and cumulatively according to these categories:

- 0 < Duration ≤24 weeks
- 24 < Duration ≤48 weeks
- 48 < Duration ≤72 weeks
- 72 < Duration ≤96 weeks
- 96 < Duration ≤120 weeks
- 120 < Duration ≤144 weeks
- 144 < Duration ≤168 weeks
- 168 < Duration ≤192 weeks
- 192 < Duration ≤216 weeks
- 216 < Duration ≤240 weeks
- Duration ≥240 weeks.

For Part A exposure, 12-week intervals will be used.

Additionally for each exposure summary, the cumulative duration of treatment exposure will be provided, defined as the sum of the duration of treatment exposure for all participants, and will be expressed in participant years.

2.4.3.2 Compliance

Compliance data will be summarized by tolebrutinib dose group and overall, only for the LTS16004 participants in the safety population. A given administration will be considered noncompliant if the participant did not take the planned dose of treatment as required by the protocol. No imputation will be made for participants with missing or incomplete data.

Percentage of compliance for a participant will be defined as the number of administrations that the participant was compliant divided by the total number of administrations that the participant was planned to take from the first to the last administration.

Treatment compliance percentages will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). The percentage of participants who have a compliance of <80% will also be summarized.

Cases of symptomatic overdose, as mentioned in protocol Section 8.3.1, will be listed as AESIs. Dosing irregularities categorized as critical or major protocol deviations will be listed (Section 2.2.1).

2.4.4 Analysis of efficacy endpoints

The primary objective of this LTS16004 study is to evaluate safety. Efficacy data will be summarized with appropriate measures of variability.

For by visit summaries including data from DRI15928, visits during the DRI15928 period correspond to weeks on tolebrutinib treatment.

MRI variables

Number and volume of lesions will be summarized by visit using descriptive statistics in the mITT population including data from both DRI15928 and LTS16004. For parameters with a baseline value, change and/or percent change from baseline will be included. For new/enlarging T2 lesions, the values will be standardized to per month values by dividing by the number of months (4-week intervals) from the previous MRI to the current MRI. In addition, average number of lesions per scan (new Gd-enhancing T1 hyperintense and new T1 non-enhancing hypointense) or annualized rate of lesions (new/enlarging T2) will be summarized descriptively. Graphical presentations may be used to illustrate trends over time.

Values for Gd-enhancing T1 lesions will be excluded if the participant had a suspected MS relapse and was receiving systemic corticosteroids within the 30 days prior to the MRI assessment date given the short-term effects of systemic corticosteroids on Gd-enhancing lesions.

Listings of MTR recovery and number of phase rim lesions will be provided.

For each dose group and overall, the percentage of participants with no new MRI disease activity will be provided by visit.

Time course of intensity related parameters and MTR recovery will be modeled using generalized linear mixed modeling. Annualized brain volume loss will be modeled as well.

Annualized MS relapse rate

A gross estimate of ARR is the total number of relapses for participants by dose group divided by the sum of the standardized study duration for participants in the dose group.

Total number of confirmed relapses and standardized study duration will be calculated for each participant as:

- Total number of confirmed relapses is defined as number of confirmed relapses with onset between first IMP date and treatment discontinuation/completion date (same as last dose intake date) in LTS16004.
- Standardized study duration (in years) will be calculated by (last dose intake date - first IMP date + 1) / 365.25 in LTS16004.

ARR will be analyzed using a negative binomial regression model in the mITT population. The model will include the total number of confirmed relapses with onset between first and last IMP doses in LTS16004 as response variable and dose group (5/60, 15/60, 30/60, and 60/60 mg) as covariate. Log transformed standardized treatment duration will be included in the model as an "offset" variable. The estimated ARR for each dose group and corresponding 95% 2-sided CI will be derived from the negative binomial model. The relative reductions in ARR (60/60 mg versus each other dose group) along with 95% CIs will be estimated from the model.

Number of participants with 0, 1, 2, 3, 4, or ≥5 relapses will be presented by dose group, namely, 5/60, 15/60, 30/60, and 60/60 mg.

The ARR for the tolebrutinib 60 mg treatment period will be analyzed using a negative binomial regression model, as well. Only relapses with onset during the tolebrutinib 60 mg treatment period will be counted, which means Part B only for participants originally assigned to 5, 15 and 30 mg dose groups and Parts A and B for participants originally assigned to the 60 mg dose group. Excluded are patient years and relapses during the first 8 weeks of tolebrutinib treatment after the switch to Part B for participants in the 5/15/30 to 60 mg groups and the same for participants in the 60/60 mg dose group, if the sum of the placebo run-out period (if applicable) and any gap period is >4 weeks. The negative binomial regression model will use total number of relapses as the response variable and log transformed standardized treatment duration as an "offset" variable. The estimated ARR and the 95% CI will be provided.

The number of participants with 0, 1, 2, 3, 4, or ≥5 relapses during the tolebrutinib 60 mg treatment period will also be presented.

Proportion of participants relapse free

Time to first confirmed relapse in LTS16004 is defined as "the date of first relapse - first IMP date (in LTS16004) + 1". If the participant has no relapse before treatment discontinuation/completion, then the participant will be considered as free of relapse until the date of treatment discontinuation/completion. His/her data will be censored after this date. The proportion of participants without confirmed relapse in LTS16004 will be estimated based on the Kaplan-Meier curve at yearly time points (1, 2, 3, 4 and 5 years since first IMP in LTS16004).

Change from baseline in EDSS scores

Change from baseline in EDSS scores will be summarized by tolebrutinib dose group and overall using descriptive statistics. Only EDSS scores on scheduled visits will be used for the analysis to exclude the temporary fluctuations in the clinical status that may occur with a relapse.

[redacted]

[redacted]

2.4.5 Analyses of safety data

The safety of long-term tolebrutinib treatment will be presented by SAR dose group (5/60, 15/60, 30/60, and 60/60 mg) and overall. in the safety population. Selected summaries will be included for Part A only to assess for any dose related trends in adverse events. If average exposure across the dose groups is very different, exposure adjusted summaries will be considered.

General common rules

All safety analyses will be performed on the LTS16004 safety population, unless otherwise specified, using the following common rules:

- The baseline value of planned parameters for each participant is defined as the last available value before the first study drug intake in DRI15928 whether it was a planned or an unscheduled evaluation, unless otherwise specified.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG.
- PCSA criteria will determine which participants had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed, including nonscheduled or repeated evaluations. The number of all such participants will be the numerator for the PCSA percentage.
- The on-treatment PCSA denominator by dose group for a given parameter will be based on the number of participants assessed for that given parameter in the on-treatment period by dose group on the safety population.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and dose group.
- All values including unscheduled measurements will be assigned to the appropriate safety analysis visit window. In the presence of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summaries.
- The analysis of the safety variables will be descriptive; no systematic testing is planned.

2.4.5.1 Analyses of adverse events

Generalities

If an AE date/time of onset (occurrence or worsening) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, TEAE or posttreatment. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment emergent unless there is definitive information to determine it is pre- or post-treatment.

Adverse event incidence tables will present by primary SOC and PT, the number (n) and percentage (%) of participants experiencing an adverse event by tolebrutinib dose group, and overall. Multiple occurrences of the same event in the same participant will be counted only once in the tables. The denominator for computation of percentages is the safety population within each dose group/overall.

Summaries by primary SOC and PT will be presented by internationally agreed order of SOC and decreasing frequency of PT in the 60/60 mg tolebrutinib dose group within each SOC. Summaries by PT will be sorted by decreasing frequency of PT in the 60/60 mg tolebrutinib dose group.

Selected summaries (noted with an * below) will also be provided for Part A only. These tables will summarize incidence of adverse events by tolebrutinib dose group, namely, 5, 15, 30, and 60 mg, sorted by decreasing frequency in the tolebrutinib 60 mg dose group.

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated for the safety population:

- Overview* of treatment-emergent adverse events, summarizing number (%) of participants with any.
  - TEAE.
  - Treatment emergent SAE.
  - Severe TEAE.
  - AE leading to death.
  - TEAE leading to permanent treatment discontinuation.
  - TEAE considered by the investigator as related to IMP.
- All TEAEs by primary SOC and PT*.
- All TEAEs by PT.
- All TEAEs considered related to IMP (by the investigator) by primary SOC and PT.
- All TEAEs (for which intensity is collected) by maximal intensity (mild, moderate, severe), presented by primary SOC and PT.

Analysis of all treatment emergent serious adverse event(s)

- All treatment emergent SAEs by primary SOC and PT*.
- All treatment emergent SAEs by PT.
- All treatment emergent SAEs considered related to IMP (by the investigator) by primary SOC and PT.
- Listing of all SAEs including treatment emergent status.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All TEAEs leading to permanent IMP discontinuation by primary SOC and PT.
- All TEAEs leading to permanent IMP discontinuation by PT.
- Listing of all TEAEs leading to permanent IMP discontinuation.

Analysis of AESIs

- All treatment emergent AESIs by AESI category and PT* sorted by decreasing frequency of PT in the 60 or 60/60 mg dose group within each AESI category.
- Listing of all AESIs by AESI category including treatment emergent status.

Analysis of COVID-19 related AEs

- All treatment emergent COVID-19 related AEs by primary SOC and PT sorted by decreasing frequency of PT in the 60/60 mg dose group within each SOC.
- Listing of all COVID-19 related AEs.

Analysis of pre-treatment/post-treatment adverse events

- Pre-treatment and post-treatment adverse events, if any, including serious, will be summarized separately.
- Listing of all pre-and post-treatment adverse events.

Safety findings on MRI are collected as AEs on the eCRF and will be analyzed in together with other AEs.

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population.

- The number of participants who died by study period (Section 2.1.4.2).
- Listing of all deaths including treatment emergent status and the tolebrutinib dose at the time of death.

2.4.5.3 Other Safety

2.4.5.3.1 Analyses of laboratory, vital signs and ECG variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all laboratory values (central laboratory values and changes from baseline), vital signs, and ECG variables will be calculated for each visit or study assessment (baseline, each post-baseline time point) by tolebrutinib dose group and overall. Mean changes from baseline with the corresponding standard error may be plotted over time on treatment by tolebrutinib dose group for selected parameters.

The incidence of PCSAs at any time during the TEAE period will be summarized by (biological function for laboratory data) dose group and overall, whatever the baseline level and/or according to the following baseline status categories:

- Normal/missing.
- Abnormal according to PCSA criterion or criteria.

For laboratory parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

Centralized data will be used preferentially to local measures when several measurements are performed on the same date and at the same time for a given laboratory test.

Potential drug-induced liver injury

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin will be used to assess possible drug-induced liver toxicity.

In addition to the PCSA summaries, a graph of the distribution of peak values of ALT versus peak values of total bilirubin will be presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

A listing of all liver function values will be provided for any participant with a treatment emergent ALT >3 x ULN and/or AST >3 x ULN with bilirubin >2 x ULN including the timing in terms of days on IMP.

2.4.5.3.2 Analyses of suicidality assessment

Summaries of participants for the C-SSRS categories of suicidal ideation or suicidal behavior, and shift tables for baseline and during treatment responses will be provided.

2.4.6 Analyses of PD data

[redacted] in case of index AEs will be reported using descriptive statistics.

[redacted] data will be summarized for each visit by dose group and overall using the following descriptive statistics: mean, geometric mean, median, SD, coefficient of variation, minimum, and maximum.

2.5 DATA HANDLING CONVENTIONS

2.5.1 Contingency measures for a regional or national emergency that is declared by a governmental agency

For participants in Ukraine and Russia who are impacted by the national emergency and are lost to follow-up, their data will be handled as follows:

- For the efficacy endpoint annualized adjudicated relapse rate, all observed events, if any, up to the last contact date for the participant will be included in the analysis and the observation duration will be from the first IMP in LTS16004 to the last contact date. No imputation will be performed for the unobserved events that may happen after the last contact date.
- Similarly, for the efficacy endpoint proportion of relapse-free participants, if the participant has no relapse by the last contact date, then the participant will be considered as free of relapse until that date. His/her data will be censored after the last contact date.
- For other efficacy endpoints including MRI parameters, EDSS, [redacted] and safety endpoints including laboratory parameters, vital signs and ECG, all observed data up to the last contact date will be included for assessment. Summary statistics will be computed based on the observed data. No imputation will be performed for data missing due to lost to follow-up.

2.5.2 Missing data

For categorical variables, participants with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of participants with missing data is presented.

Handling of computation of treatment duration if IMP end-of-treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment CRF page. If this date is missing, the exposure duration should be left as missing.

The last dose intake should be clearly identified in the CRF and should not be approximated by the last returned package date.

Handling of concomitant medication missing/partial dates

No imputation of medication start/end dates or times will be performed.

Handling of AEs with missing or partial date/time of onset

Missing or partial AE onset dates and times will be imputed so that if the partial AE onset date/time information does not indicate that the AE started prior to treatment or after the TEAE period, the adverse event will be classified as treatment emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing intensity/severity of adverse events

If the intensity is missing for one of the treatment-emergent occurrences of an AE, the maximal intensity on the remaining occurrences will be considered. If the intensity is missing for all the occurrences, a "missing" category will be added in the summary table. This does not apply for events for which intensity is not collected in the eCRF, ie, overdose and pregnancy.

Handling of potentially clinically significant abnormalities

If a participant has a missing baseline he will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing, eg, for eosinophils the PCSA is >0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

2.5.3 Windows for time points

For LTS16004, data will be assigned to an appropriate analysis visit by using the windowing scheme in Table 2 below and following the Sanofi standards.

For safety assessments, the reference date for the derivation of relative days of events or findings will be the date of first drug intake in LTS16004.

Table 2 - Analysis visit windows

Analysis Windows						
AVISITC	**AVISITN**	**Target**	**Intervals**			
			VS, ECG, Urinalysis, Suicidality assessment (C-SSRS), Hematology, Biochemistry	**β-HCG test Body weight**	**EDSS**	**MRI**
Screening - LTS	**200**	**-1**	<1	<1		
Day 1 - LTS	**300**	**1**	[1,1]	[1,1]	<2	<32
Month 1 - LTS	**501**	**28**	[2,56]	[2,56]		
Month 3 - LTS	**503**	**84**	[57,126]	[57,126]	[2,126]	[32,126]
Month 6 - LTS	**506**	**168**	[127,210]	[127,210]	[127,210]	[127, 252]
Month 9 - LTS	**509**	**252**	[211,294]	[211,294]	[211,294]	
Month 12 - LTS	**512**	**336**	[295,378]	[295,504]	[295,378]	[253,420]
Month 15 - LTS	**515**	**420**	[379,462]		[379,462]	
Month 18 - LTS	**518**	**504**	[463,546]		[463,546]	[421,588]
Month 21 - LTS	**512**	**588**	[547,630]		[547,630]	
Month 24 - LTS	**524**	**672**	[631,714]	[505,840]	[631,714]	[589,840]
Month 27 - LTS	**527**	**756**	[715,798]		[715,798]	
Month 30 - LTS	**530**	**840**	[799,882]		[799,882]	
Month 33 - LTS	**533**	**924**	[883,966]		[883,966]	
Month 36 - LTS	**536**	**1008**	[967,1092]	[841,1176]	[967,1092]	[841,1176]
Month 42 - LTS	**542**	**1176**	[1093,1260]		[1093,1260]	
Month 48 - LTS	**548**	**1344**	[1261,1428]	[1177,1512]	[1261,1428]	[1177,1512]
Month 54 - LTS	**541**	**1512**	[1429,1596]		[1429,1596]	
Month 60 - LTS	**560**	**1680**	[1597,1708]	[1513,1708]	[1597,1708]	[1513,1708]

1 month = 28 days.

2.5.4 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will not be included in the by-visit summaries but will be used for computation of baseline and PCSAs.

2.5.5 Pooling of centers for statistical analyses

No pooling of centers, eg, regional pooling, is planned.

2.5.6 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

No formal interim analysis is planned. An interim database lock may be performed as needed for strategic decision making or regulatory submission, but the study will continue as planned. Since this extension study is supportive, there is no impact for the final CSR.

4 DATABASE LOCK

The final database is planned to be locked 4 weeks after the last participant last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.0 or higher.

6 REFERENCES

Not applicable.

Signature Page for VV-CLIN-0556147 v2.0
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Approve & eSign	[redacted]
Approve & eSign	[redacted]