NCT03889639

STATISTICAL ANALYSIS PLAN

A Phase 2b dose-finding study for SAR442168, a Bruton's tyrosine kinase inhibitor, in participants with relapsing multiple sclerosis

SAR442168-DRI15928

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AEs:	adverse events
AESI:	adverse event of special interest
BTK:	Bruton's tyrosine kinase
DMT:	disease modifying therapy
ECG:	electrocardiogram
EDSS:	Expanded Disability Status Scale
E_{max}:	nonlinear model frequently used in dose response analyses
Gd:	gadolinium
HAD:	highly active disease
IMP:	investigational medicinal product
IVRS:	interactive voice response system
IVRS/IWRS:	Interactive Voice/Web Response System
IWRS:	interactive web response system
LXRS:	*IVRS or IWRS*
LTS:	long term safety
MCP-Mod:	Multiple Comparison Procedure-Modelling
MedDRA:	Medical Dictionary for Regulatory Activities
MRI:	magnetic resonance imaging
MTR:	magnetization transfer ratio
NA:	Not Applicable
NIMP:	noninvestigational medicinal product
PBMC:	peripheral blood mononuclear cell
PCSAs:	potentially clinically significant abnormalities
[redacted]	
PK:	pharmacokinetic
PT:	preferred term
RMS:	relapsing multiple sclerosis
SAEs:	serious adverse events
SD:	standard deviation
SoA:	Schedule of Activities
SOC:	primary system organ class
SWI:	susceptibility-weighted imaging
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a Phase 2b, randomized, double-blind, placebo-controlled, cross-over, dose-ranging study in people with relapsing multiple sclerosis (RMS).

All participants will be centrally assigned to 1 of 8 arms (4 dose groups in each of 2 cohorts at equal ratio to start with SAR442168 (in Cohort 1) or placebo (in Cohort 2) period before cross-over, using an Interactive Voice/Web Response System (IVRS/IWRS).

- Within each cohort, participants will be randomly assigned equally to 1 of 4 SAR442168 doses, 5, 15, 30, or 60 mg once daily, in a blinded manner
- Cohort 1: Participants will receive 1 of the SAR442168 doses for the first 12 weeks, then cross-over to placebo for 4 weeks
- Cohort 2: Participants will receive placebo for the first 4 weeks, then cross over to 1 of the SAR442168 doses for 12 weeks

The study will be rater-blinded for brain magnetic resonance imaging (MRI). All brain scans will be reviewed and interpreted by 1 or more MRI experts at an independent, central facility with no access (ie, blinded) to treatment, thereby avoiding bias and assuring standardized endpoint evaluation.

Approximately 160 people will be screened to randomize approximately 120 participants (based on a 25% screening failure rate) to the study intervention such that approximately 105 evaluable participants (based on an approximately 15% dropout rate, providing at least 26 participants for each dose level of SAR442168) complete 12 weeks of SAR442168 treatment. Participants from Cohort 2 (n = 60) will receive 4 weeks of placebo before crossing over to SAR442168.
The 4-week placebo data can be utilized in estimating a dose-response curve based on the assumption of a theoretical constant rate of new Gd-enhancing T1-hyperintense lesions over 12 weeks under placebo. The approach will minimize placebo exposure to study participants.

Individuals who do not meet the criteria for participation in the study (screen failure) may be rescreened up to 2 times. Rescreened individuals are assigned the same participant number as the initial screening.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to determine the dose-response relationship for SAR442168 to reduce the number of new active brain lesions.

1.2.2 Secondary objectives

The secondary objectives are to evaluate efficacy of SAR442168 on disease activity, assessed by imaging measures and to evaluate the safety and tolerability of SAR442168.

1.3 DETERMINATION OF SAMPLE SIZE

The study will have 120 participants equally randomly assigned to 1 of 4 SAR442168 doses in 2 cohorts (60 participants in each of Cohorts 1 and 2). Cohorts 1 and 2 represent different treatment sequences, and participants in each will cross-over to SAR442168 or placebo in a blinded manner.

The 60 participants in Cohort 2 will start with a 4-week placebo run-in that will be utilized as the placebo data in analyses for the primary endpoint based on the assumption of the constant monthly mean number of new Gd-enhancing T1-hyperintense lesions over 12 weeks of placebo treatment. Assuming 15% of participants without the primary endpoint at the end of 12 weeks of SAR442168, 105 participants (approximately 26 per SAR442168 dose) has at least 83% power to detect the maximum reduction of 85% using a 2-step Multiple Comparison Procedure-Modelling (MCP-Mod) with 6 pre-defined dose response curves (2 E_{max} models, a quadratic model, a linear model, a logistic model, and an exponential model). This calculation assumes the dispersion parameter of 2 (estimated from Week 12 placebo data from the vatelizumab [SAR339658] DRI13839 study), within-subject correlation ranging from -0.9 to 0.9 in measurements between 4-week placebo and 12-week SAR442168 in Cohort 2, and placebo mean number of $\geq$1 for new Gd-enhancing T1-hyperintense lesions at 4 weeks.

This power was calculated using the package DoseFinding from the Comprehensive R Archive Network (CRAN)(1), using the 6 candidate curves considered for dose-response modelling in a negative binomial regression framework.

1.4 STUDY PLAN

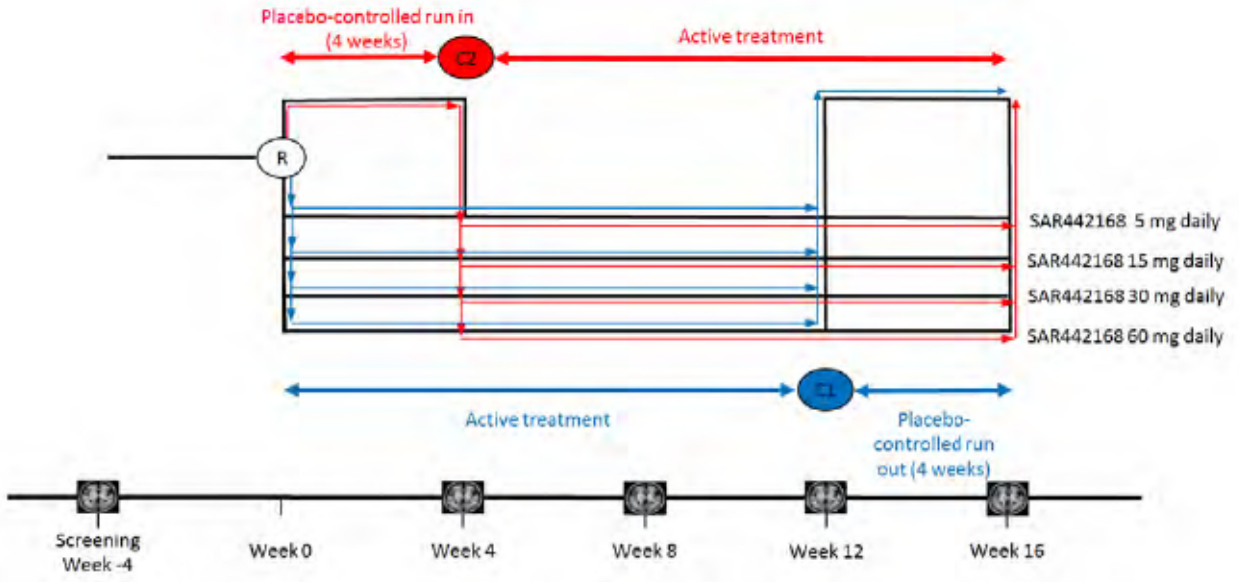
This study is blinded for dose and for administration sequence. It is focused on dose finding but also takes into account the need to minimize participant exposure to placebo.

The dose range is evaluated using 4 doses: 5, 15, 30, and 60 mg once daily, for 12 weeks. To minimize exposure to placebo while maintaining the blinding of Investigators and participants, each participant will be assigned to a 4-week placebo period that will occur during either the first (Cohort 2) or the last 4 weeks of the study (Cohort 1). A graphical representation of the study design is provided below.

For the detailed Schedule of Activities (SoA), see Section 1.3 (Table 1) of the study protocol.

Upon completing the double-blinded treatment period, participants will be given the option to enroll in a long-term safety (LTS) follow-up study to assess safety and tolerability of SAR442168. The LTS follow-up study is described in a separate protocol, LTS16004.

Figure 1 – Graphical study design



C1: Cohort 1; C2: Cohort 2; R: randomization

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The protocol section 9.5 described a potential interim analysis, to be performed in the case of slower than anticipated recruitment. Recruitment was not slower than anticipated and an interim analysis was not performed.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is generally defined as the last measurement collected on or before the randomization visit (Day 1) prior to initiation of the first dose of study intervention.

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 (Sections 2.4.4 and 2.4.5).

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, and ethnicity (Hispanic, non-Hispanic).

Age categories (<=40 years, >40 years) will also be included.

Medical or surgical history

Medical or surgical history includes all the relevant medical or surgical history within the previous 3 months.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Substance use – alcohol habit

The frequency of alcohol use in the last 12 months is reported.

Multiple sclerosis history and disease characteristics at baseline

Multiple sclerosis history includes the date of first symptoms of RMS, date of RMS diagnosis, date of most recent relapse, multiple sclerosis type, number of relapse(s) within the past year and within past 2 years, date of most recent brain MRI and number of active Gd-enhancing brain lesion(s) on the MRI. Time (in months) will be calculated from date of first symptoms/diagnosis/most recent relapse to randomization visit. (The study inclusion criteria included: 'The participant must have at least 1 documented relapse within the previous year OR ≥2 documented relapses within the previous 2 years OR ≥1 active Gd-enhancing brain lesion on an MRI scan in the past 6 months and prior to screening.')

Highly active disease (HAD) category (yes, no) is also included, and HAD is defined as the participant having:

- 1 relapse in the previous year **and** 1 of the following:

- at least 1 Gd-enhancing lesion **or**
- 9 or more T2 lesions at baseline – for participants who were already treated with disease modifying therapy (DMT) (any treatment with DMTs would be considered if documented in 1 year period*) **or**
- 2 or more relapses in the previous year, whether treated with DMT or not.

*Note, for this study, prior medications received during the 4 weeks prior to enrollment and all prior MS treatments and treatments considered clinically important to assess MS or concomitant disease are collected.

The following disease characteristics will be summarized at baseline:

- Expanded Disability Status Scale (EDSS) [assessed at both screening visit and baseline]
- Brain imaging characteristics (eg, T1-Hyperintense Lesion Volumes and T2-Hyperintense Lesion Volumes) [assessed at screening visit]

Any technical details related to computation, dates, and imputation for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications

All medications are coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

Medications are categorized as:

- Prior medications are those the participant used prior to first investigational medicinal product (IMP) intake. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the participant concomitantly to the IMP, from randomization to the last study visit. A given medication can be classified as both a prior and as a concomitant medication.

A locally approved noninvestigational medicinal product (NIMP) was used for T1 contrast-enhanced MRI sequences.

Any technical details related to computation, dates, imputation for missing dates for the prior or concomitant medications are described in Section 2.5.

2.1.3 Efficacy endpoints

Baseline for efficacy endpoints assessed by change from baseline is defined as the last non-missing value prior to the first administration of randomized study intervention, unless otherwise specified.

MRI data

The efficacy analyses will be based on the MRI data from the blinded central reader. Central review will be used to identify new Gd-enhancing T1-hyperintense lesions not present at the previous visit MRI, the total count of Gd-enhancing T1-hyperintense lesions and the number of new and enlarging T2 lesions (compared to previous visit MRI). The total volume of T2 lesions and the number of T1-hypointense lesions will also be assessed as supportive data with respect to efficacy. The complete list of MRI parameters from the blinded central readings is in Appendix B.

For all efficacy analyses, the MRI assessment (all MRI parameters for the assessment) was excluded from the analyses if the participant had a suspected MS relapse and was receiving systemic corticosteroids within the 30 days prior to the MRI assessment date. Treating these assessments as missing data is to avoid confounding to the efficacy analyses, given the short-term effects of systemic corticosteroids on Gd-enhancing lesions.

Magnetization transfer ratio (MTR) and susceptibility-weighted imaging (SWI) MRI parameters are also shown in Appendix B.

No new MRI disease activity

No new MRI disease activity is defined as the patient has 0 new Gd-enhancing T1-hyperintense lesions and 0 new and enlarging T2 lesions at the MRI assessment at the end of 12 weeks of SAR442168 treatment (Week 12 for Cohort 1 and Week 16 for Cohort 2).

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.

MS relapse

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

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy endpoint of the study is the number of new Gd-enhancing T1-hyperintense lesions (lesions not present at the previous visit MRI) as detected by brain MRI at the end of 12 weeks of SAR442168 treatment (Week 12 for Cohort 1 and Week 16 for Cohort 2).

The 4-week post-randomization placebo data from Cohort 2 (ie, Week 4 data from Cohort 2) will be utilized as the placebo data in the MCP-Mod analysis, under the assumption of a constant rate of Gd-enhancing T1-hyperintense lesion formation if participants would be receiving placebo over 12 weeks.

2.1.3.2 Secondary efficacy endpoints

The secondary efficacy endpoints are the number of new or enlarging T2 lesions (compared to previous visit MRI) at the end of 12 weeks of SAR442168 treatment and the total number of Gd-enhancing T1-hyperintense lesions at the end of 12 weeks of SAR442168 treatment (Week 12 for Cohort 1 and Week 16 for Cohort 2).

The 4-week post-randomization placebo data from Cohort 2 (ie, Week 4 data from Cohort 2) will be utilized as the placebo data in the MCP-Mod analysis.

[redacted]

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (AEs), serious adverse events (SAEs), potentially clinically significant abnormalities (PCSAs) in laboratory tests, vital signs (body temperature, heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate), physical examination, electrocardiogram [ECG] (heart rate and PR, QRS, QT, and QTc intervals) and the Columbia Suicide Severity Rating Scale (C-SSRS).

Multiple sclerosis relapses are exempt from being reported as AEs except when they meet the definition of an SAE. MS relapses are collected on the eCRF and analyzed as part of the efficacy analyses.

Observation periods

- For safety variables, the following observation periods are defined and used for classification of AEs and determination of on-treatment PCSA values:
- The pretreatment period is defined as the time from the signed ICF to the first administration of randomized study intervention
- For the purpose of defining 'treatment-emergent', the on-treatment period is defined as the time from the first administration of randomized study intervention until the last study visit. The treatment periods are further defined as:
  - The "Weeks 1 to 4 period" is defined as the time from first administration of randomized study treatment to the administration of the Week 4 study treatment. For Cohort 1 this is SAR442168 treatment for 4 weeks and for Cohort 2 is placebo treatment for 4 weeks
  - The "SAR442168 treatment period" is defined as Weeks 1 to 12 for Cohort 1 and Weeks 4 to 16 for Cohort 2

Note: participants from the Cohort 1 Weeks 1 to 4 period are also included in the 12 weeks of the SAR442168 period.

  - The "placebo/post-SAR442168 dose period" is defined as Week 12 to Week 16 for Cohort 1. This is the 4 weeks of placebo treatment following 12 weeks of SAR442168 treatment

2.1.4.1 Adverse events variables

Adverse event observation period

- Pretreatment AEs are defined as AEs that developed, or worsened, or become serious during the pretreatment period
- Treatment-emergent AEs are defined as AEs that develop, worsen, or become serious during the on-treatment period

All adverse events (including serious adverse events) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

2.1.4.2 Adverse events of special interest (AESIs)

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. AESIs are described in Protocol [Section 8.3.1].

AESIs are indicated by a checkbox (yes/no) on the adverse event eCRF.

Increase in ALT is recorded as the adverse event category on the adverse event eCRF.

Overdose and pregnancy are recorded on separate eCRFs.

2.1.4.3 Deaths

The deaths observation periods are defined as:

- Death on-study: death occurring after the start of the TEAE period up to the last protocol planned visit of the participant
- Death on-treatment: death occurring during the TEAE period
- Death poststudy: death occurring after the last protocol planned visit of the participant and before database lock

2.1.4.4 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, 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.

Blood samples for clinical laboratories will be taken as detailed in the SoA (Protocol [Section 1.3]) unless otherwise specified. The laboratory parameters are detailed in the Protocol (Section 10.2).

2.1.4.5 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 pulse measurements will be assessed consistently in sitting or supine position.

2.1.4.6 Electrocardiogram (ECG) variables

Twelve-lead ECGs were recorded automatically by the device at the Investigator site, with central ECG review to ensure consistency of ECG evaluation (normal, abnormal, unable to evaluate).

ECG parameters include heart rate, PR, QRS, QT, and corrected QTc (according to Bazett/Fridericia).

2.1.4.7 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a tool used to assess the lifetime suicidality of a participant and to track suicidal events through 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 screening and 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)

2.1.4.8 Physical examination

The physical examination is performed at all visits and described in Protocol (Section 8.2.1).

2.1.5 Pharmacokinetic (PK) variables

The SAR442168 concentrations at selected time points after IMP intake will be summarized for the CSR using descriptive statistics and the PK analyses will be reported separately.

[redacted]

[redacted]

2.2 DISPOSITION OF PARTICIPANTS

This section describes participant disposition for both participant study status and the participant analysis populations.

Screened participants are defined as any participants who signed the informed consent form. Screen failures are defined as participants who consented to participate in the clinical study but were not subsequently randomly assigned to the study intervention. Individuals who did not meet the criteria for participation in this study (screen failure) could be rescreened up to 2 times. Rescreened individuals were assigned the same participant number as the initial screening.

Randomized participants consist of all participants with a signed informed consent form who have had a treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used.

Treated (exposed) participants are all participants who took any of the IMP.

For participant study status, the total number of participants in each of the following categories will be presented in the clinical study report using a summary table:

- Screened participants
- Screen failure participants and reasons for screen failure
- Randomized participants
- Randomized but not treated participants
- Randomized and treated participants
- Participants who did not complete the study treatment period as per protocol

- Participants who discontinued study treatment by main reason for permanent treatment discontinuation

For all categories of participants (except for the screened and nonrandomized categories) percentages will be calculated using the number of randomized participants as the denominator divided by the number of participants. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by the randomized treatment arm, and for the total participants. A listing of participants who discontinued will include treatment arm and the treatment the participant was receiving at the time of discontinuation.

A summary table of disposition of screened participants by country/site will be provided, sorted by alphabetical order.

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.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group.

Additionally, the analysis populations for safety, efficacy, and pharmacokinetics will be summarized in a table by number of participants in the randomized population.

- Efficacy population: modified intent-to-treat (mITT) population
- Safety population
- Pharmacokinetics population

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible participant is randomized or b) a participant is randomized twice

   OR

2. A participant is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a participant at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized participant is treated with IMP reserved for randomized participants.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized participants (number and percentages). Nonrandomized, treated participants will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
Kit dispensation without IXRS call at randomization
Kit dispensation without IXRS call at resupply visit(s)
Erroneous kit dispensation at randomization visit
Erroneous kit dispensation at any visit(s)
Treatment arm not available at site level
Randomization of a nonexistent participant
Non-eligible participant randomized by error
Participant randomized twice
Participant switched to another site

2.3 ANALYSIS POPULATIONS

Participants treated without being randomized will not be considered randomized and will not be included in any efficacy population.

The randomized population includes any participant who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

For any participant randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of participants treated and not randomized will be reported separately, and these participants will not be in the safety population.

2.3.1 Efficacy populations

2.3.1.1 Modified intent-to-treat population

The modified intent-to-treat population is defined as all randomly assigned participants analyzed in the treatment group to which they are randomized (ie, ITT) and who were exposed to study intervention.

2.3.2 Safety population

The safety population is defined as the randomized population who actually received at least 1 dose or part of a dose of the IMP, analyzed according to the treatment actually received.

In addition:

- Nonrandomized but treated participants will not be part of the safety population; however, their safety data will be presented separately
- Randomized participants for whom it is unclear whether they took the IMP will be included in the safety population as randomized

2.3.3 Pharmacokinetic population

The pharmacokinetic population is the same as the safety population.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

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

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized.

Parameters described in Section 2.1.1 will be summarized by treatment group and overall SAR442168 treatment group using descriptive statistics. The 4-week post-randomization placebo data from Cohort 2 (ie, Week 4 data from Cohort 2) will be utilized as the placebo data in summaries by visit week and treatment group. For the SAR44268 treatment groups (5 mg, 15 mg, 30 mg, 60 mg), data will be summarized by the weeks on SAR442168 treatment, eg, Week 8 for Cohort 1 with Week 12 for Cohort 2.

Medical or surgical history data will be summarized by primary system organ class (SOC) and preferred term (PT). Events are sorted by SOC internationally agreed order and by decreasing frequency of PT based on incidence in the overall treatment group.

P-values on demographic and baseline characteristic data will not be calculated.

No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

No specific description of the efficacy parameters will be provided at baseline. If relevant, the baseline values will be described along with each efficacy analysis.

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for the randomized population.

Medications will be summarized by treatment group 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 ATC followed by all other therapeutic classes based on the overall treatment group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

The tables for concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the SAR442168 60 mg treatment group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual treatment within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product (IMP) exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure, and actual dose information.

Duration of IMP exposure is defined as last dose date – first dose date + 1 day, regardless of unplanned intermittent discontinuations.

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories: 1 to 28 days [Week 4], 29 to 56 days [Week 8], 57 to 84 days [Week 12], 85 to 112 days [Week 16], and >112 days.

Additionally, 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 months.

2.4.3.2 Compliance

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 quantitative variables (number, mean, SD, median, minimum, and maximum).

Cases of overdose (Protocol [Section 8.3.1]) will constitute serious adverse events and will be listed as such. More generally, dosing irregularities will be listed in Section 2.2.1.

2.4.4 Analyses of efficacy endpoints

2.4.4.1 Analysis of primary efficacy endpoint

The primary efficacy analysis will be based on the mITT population.

The primary analysis will be based on pooled data of Cohorts 1 and 2 for each of the SAR442168 doses (ie, data at Week 12 for Cohort 1 and at Week 16 for Cohort 2 for the number of new Gd-enhancing T1-hyperintense lesions at the end of 12 weeks of SAR442168 treatment). Data from Cohorts 1 and 2 may also be separately explored, as necessary.

For each cohort, descriptive statistics will be summarized over time (Weeks 4, 8, 12, and 16) when appropriate. The summary from Cohort 1 will include descriptive statistics for the 4-week placebo period after 12 weeks of SAR442168 treatment (ie, 4-week placebo run-out period).

Dose-response relationship

For the mITT population, the dose-response relationship will be evaluated by a 2-step MCP-Mod procedure. The first step of this procedure tests for an efficacy signal (compared to the null hypothesis of a flat, no dose-response curve) in a procedure that controls the type 1 error. To account for the uncertainty of the dose-response shape, 6 candidate models have been considered to cover diverse and potential dose-response profiles: 2 Emax models (ED50 = 10 mg, ED50 = 30 mg), a linear model, a quadratic model, a logistic model, and an exponential model. The second step is the estimation of the dose-response curve, provided that an efficacy signal is established in the first step.

A negative binomial regression model with covariates for baseline Gd-enhancing T1-hyperintense lesion count, treatment, and cohort (Cohort 1 or Cohort 2) will be used to assess the mean count of new Gd-enhancing T1-hyperintense lesions in each of the 4 dose groups at the end of 12 weeks of SAR442168 treatment and at the end of 4 weeks of placebo. The 4-week post-randomization placebo data from Cohort 2 (ie, Week 4 data from Cohort 2) will be utilized as the placebo data in analysis, under the assumption of a constant rate of Gd-enhancing T1-hyperintense lesion formation if participants would be receiving placebo over 12 weeks. Participants in Cohort 2 contribute to the placebo data (at Week 4) as well as the data of 4 SAR442168 doses (at Week 16). In order to account for the potential correlation between the measurements in the 4-week placebo period and the subsequent 12-week SAR442168 treatment period in Cohort 2, a GEE

approach is used to fit the negative binomial model accounting for the within-participant correlation via the repeated statement in SAS PROC GENMOD, and the mean lesion counts are estimated for the treatment groups (see SAS code in Appendix C).

A minus log transformation of the mean lesion count will be entered into the MCP-Mod procedure (see R code example in Appendix C). The null hypothesis of a flat dose-response curve (ie, no dose–response relationship) at the end of 12 weeks of SAR442168 treatment for the primary endpoint will be jointly evaluated for each of the 6 candidate dose response models with a contrast test that controls the family wise error rate at 2-sided alpha = 0.05. If step 1 yields significant results, the best fitting model (smallest AIC) from the 6 predefined candidate models will be chosen using the generalized AIC. The dose for the Phase 3 program will then be estimated from the final selected model.

Data from Cohorts 1 and 2 will be combined for the primary analysis (ie, data at Week 12 for Cohort 1 and at Week 16 for Cohort 2 for the number of new Gd-enhancing T1-hyperintese lesions). Data from each cohort may be separately explored.

The mean new Gd-enhancing T1 hyperintense lesion counts, obtained from the negative binomial regression model, for the 4 SAR442168 dose groups and placebo, and the relative reduction to placebo, will be provided for each of the 4 SAR442168 dose groups. The means and 95% confidence intervals will be shown graphically for the placebo and SAR442168 dose groups in a bar chart.

The multiple contrasts and adjusted p-values for the candidate models, the estimated dose response curves and target doses, will be provided.

Descriptive statistics will also be provided for the 4 SAR442168 doses for observed number of new Gd-enhancing T1-hyperintense lesions over time (ie, Week 4/Week 8, Week 8/Week 12, and Week 12/Week 16 for Cohort 1/Cohort 2) and placebo (Week 4 Cohort 2). The means plus standard deviation will be displayed graphically over time.

Missing data handling

All available MRI data for endpoint, after applying the corticosteroid use exclusion, will be used in the analyses.

- ***Subgroup and sensitivity analyses***

A sensitivity analysis, similar to the primary analysis for the primary endpoint, will be performed with all Week 12 data, ie, including any observations that had been excluded from the analysis if the participant had a suspected MS relapse and was receiving systemic corticosteroids within the 30 days prior to the MRI assessment date.

To assess the consistency in treatment effects in each dose group across different subgroup levels, subgroup analyses using descriptive statistics may be conducted for the primary and secondary endpoints with respect to age (<=40 years, >40 years), sex, baseline EDSS score (<4.0, >= 4.0),

HAD (yes, no), and baseline MRI (< median T1 count, >= median T1 count). These will be provided in tables.

Subgroup analyses using descriptive statistics, based on type of imaging scanner, ie, 1.5 tesla vs 3 tesla may be performed.

If the number of new Gd-enhancing T1 lesions for the 4-week placebo group is small, eg, zero, then the MCP-Mod procedure may be applied to the 4 SAR442168 dose groups, to evaluate dose-response over the 4 doses of SAR442168.

2.4.4.2 Analyses of secondary efficacy endpoints

Total number of Gd-enhancing T1-hyperintense lesions and Number of new or enlarging T2 lesions

For the secondary endpoints, a similar negative binomial model and MCP-Mod procedure will be used. As it is reasonable to assume a constant rate of lesion formation over 12 weeks under placebo for the endpoints, the same approach as that utilized for the primary endpoint will be used, ie, by using the Week 4 data in Cohort 2 as the Week 12 placebo data while accounting for the within-participant correlation.

Similar tables and figures as for the primary analysis will be provided.

Sensitivity analyses using all Week 12 data, will be performed similarly to the primary endpoint analyses. Similar subgroup analyses may be performed.

2.4.4.3 Multiplicity issues

For each of the primary and secondary analyses, the family-wise error rate for each of the null hypotheses associated with dose group comparisons will be controlled by the MCP-Mod procedure.

[redacted]

[redacted]

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group. Results will be presented separately for the 'Weeks 1-4 period', for the 'SAR442168 treatment period', and for the 'placebo/post-SAR442168 dose period'.

The 'Weeks 1-4 period' will include the data through Week 4 from both the Cohort 2 placebo participants and the Cohort 1 SAR442168 participants and will be displayed by treatment group.

The 'SAR442168 treatment period' includes the Cohort 1 participants through Week 12 and Cohort 2 participants from Weeks 4 through Week 16, and will be displayed by the SAR442168 dose group and overall.

The results from the 'placebo/post-SAR442168 dose period', ie, Week 12 to Week 16 for Cohort 1, will be presented separately, and displayed by the SAR442168 treatment group and overall.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- Safety data in participants who do not belong to the safety population (eg, exposed but not randomized) will be listed separately
- The baseline value is defined as the last measurement collected on or before the randomization visit (Day 1) prior to initiation of the first dose of study intervention.
- 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 version dated January 2014 [Appendix A])
- PCSA criteria will determine which participants had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations. The number of all such participants will be the numerator for the on-treatment PCSA percentage

- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of participants assessed for that given parameter in the treatment-emergent adverse event period by treatment 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 treatment group; for the SAR44268 treatment groups, data will be summarized by the weeks on SAR442168 treatment, eg, Week 8 for Cohort 1 with Week 12 for Cohort 2.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pretreatment and posttreatment adverse events will be provided separately, in listings.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment or treatment-emergent. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

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

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pretreatment, treatment-emergent). For that purpose, the table of all treatment-emergent adverse events presented by primary SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on results for the experimental arm given with the highest dose, ie, SAR442168 60 mg.

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
  - Treatment-emergent adverse event

  - Serious treatment-emergent adverse event
  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent treatment discontinuation
  - Treatment-emergent adverse event leading to study discontinuation
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of participants with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing frequency of PTs for the SAR442168 60 mg group. This sorting order will be applied to all other tables, unless otherwise specified
- All treatment-emergent adverse events regardless of relationship and related by primary SOC, and PT, showing the number (%) of participants with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order, with PTs sorted by decreasing frequency according to the all TEAEs summary
- All treatment-emergent adverse events by maximal intensity, presented by primary SOC and PT, showing the number (%) of participants with at least 1 treatment-emergent adverse event by intensity (ie, mild, moderate, or severe), sorted by the sorting order defined above

Analysis of all treatment emergent serious adverse events

- All treatment-emergent serious adverse events by primary SOC and PT, showing the number (%) of participants with at least 1 serious treatment-emergent adverse event, sorted by the sorting order defined above
- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC and PT, showing the number (%) of participants with at least 1 treatment-emergent serious adverse event, sorted by the sorting order defined above

Analysis of all treatment-emergent adverse events leading to treatment discontinuation

- All treatment-emergent adverse events leading to treatment discontinuation, by primary SOC and PT, showing the number (%) of participants sorted by the sorting order defined above

Analysis of adverse events with prespecified monitoring (AESI)

- All treatment emergent adverse events with prespecified monitoring (AESI), by PT, showing the number (%) of participants, sorted by the sorting order defined above

Analysis of pretreatment adverse events

- Pretreatment adverse events, including serious pretreatment adverse events, will be provided in a listing

2.4.5.2 Deaths

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

- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC and PT showing number (%) of participants sorted by the sorting order defined above
- The number of participants who died by study period (in TEAE period: from first IMP to participant's last protocol planned visit, in post-study period: occurring after participant's last protocol planned visit and reported in the clinical database)

Deaths for nonrandomized or randomized and not treated participants will be presented separately.

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point) by treatment group. For parameters CPK and platelets, mean changes from baseline with the corresponding standard error will be plotted over time on treatment in each SAR442168 treatment group (ie, Week 4 from Cohort 1 with Week 8 from Cohort 2).

The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period will be summarized by biological function and treatment group whatever the baseline level and/or according to the following baseline status categories:

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

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all vital signs variables, and changes from baseline, will be calculated for each visit or study assessment (baseline, each postbaseline time point, by treatment group. For parameters systolic blood pressure, diastolic blood pressure, and respiratory rate, the mean changes from baseline with the corresponding standard error will be plotted over time in each treatment group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of the baseline level and according to the following baseline status categories:

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

2.4.5.5 Analyses of electrocardiogram (ECG) variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all ECG variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point [based on weeks on SAR442168 treatment, eg, Week 8 for Cohort 1 with Week 12 for Cohort 2]) by treatment group. For parameters heart rate, PR, QRS, QT and QTc, mean changes from baseline with the corresponding standard errors will be plotted over time in each treatment group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

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

2.4.5.6 Analyses of suicidality assessment

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

2.4.5.7 Analyses of other safety endpoints

Physical examination assessments (normal, abnormal but not clinically significant, abnormal and clinically significant) will be summarized by treatment group and visit.

2.4.5.8 Analyses of pharmacokinetic [redacted]

The pharmacokinetic [redacted] will be based on the PK population.

SAR442168 concentrations at selected time points after IMP intake will be reported using descriptive statistics. Additional PK parameters such as C_{max}, t_{max}, and AUC at steady state will be estimated using a population PK approach. These parameters will be presented in a separate, stand-alone report.

The reported percentage of BTK occupancy at the time points predose for first IMP and 1 hour (± 0.5 hr) postdose, Week 12 at 1 hour (± 0.5 hr) postdose, and Week 16 at 1 hour (± 0.5 hr) postdose will be summarized using descriptive statistics. Similar summaries will be provided for Nfl, CHI3L1 and Ig levels.

Lymphocyte phenotypes parameters (CD3, CD4, CD8, CD19, CD16+ CD56 counts and percentages of lymphocytes) at the time points predose for first IMP and 1 hour (± 0.5 hr) postdose, Week 12 at 1 hour (± 0.5 hr) postdose, and Week 16 at 1 hour (± 0.5 hr) postdose will be summarized using descriptive statistics, and the medians ± IQR displayed over time.

2.4.6 Analyses of quality of life/health economics variables

Not applicable

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

Prior and concomitant medications are derived using the Sanofi standards.

2.5.2 Data handling conventions for secondary efficacy variables

Not applicable

2.5.3 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 investigational medicinal product 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 case report form page. If this date is missing, the exposure duration should be left as missing.

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

Handling of medication missing/partial dates

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

If the recorded medication end date is prior to the study enrollment date for a participant, the medication is categorized as a prior medication discontinued before study enrollment.

If a medication end date has only the year part and it is prior to the year of the enrollment date, or if the medication end date has only month and year and both are prior to the month and year of the enrollment date, then the medication is categorized as a prior medication discontinued before study enrollment.

Otherwise, the medication is categorized as a concomitant medication.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

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 grades of adverse events

If the intensity/severity grade is missing for an adverse event, the adverse event will be counted as 'severe'.

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.

Handling of missing/partial dates for first MS symptoms or MS diagnosis

If a participant has a complete date, then that date will be used for the calculation. For a partial date, the last day of the month will be imputed for a missing day, and 'December' will be imputed for a missing month.

2.5.4 Windows for time points

A scheduled visit will be assigned to the same analysis visit equivalent to it. Data from early withdrawal and unscheduled visits will be assigned to an appropriate analysis visit by using the windowing scheme in the table below, and following the Sanofi standards.

If only 1 record is within an analysis visit window, the data from that record will be used in the summary statistics and by visit week analyses. If more than 1 record is within the same analysis visit window, the record from the regularly scheduled visit will be used in the summary statistics and by visit analyses. If more than 1 record is from a regularly scheduled visit, or more than 1 record is from unscheduled visits within the same analysis visit window, the record from the visit nearest to the target day will be used in the summary statistics and by visit analyses. If 2 visits have the same distance from the target day, the later record will be used in the summary statistics and by visit analyses. If the scheduled visit does not have any record but the windowed unscheduled visit is in an analysis visit window, data from the unscheduled visit will be used for the summary statistics and by visit analyses.

Table 1 – Analysis Visit Windows

Analysis Visit (AVISITC)	Analysis Visit Number (AVISITN)	Target Day	Parameters and Intervals				
			VS, PE, ECG, Urinalysis, Suicidality assessment (C-SSRS)	β-HCG test	Hematology, biochemistry	EDSS	MRI
Screening	-99	-1	[-28, -1]	[-28, -1]	[-28, -1]	[-28, -1]	[-28, -1]
Baseline/Day1	0	1	[1,1]	[1,1]	[1,1]	[1,1]	
Week 1	1	7					
Week 2	2	14			[2,21]		
Week 3	3	21					
Week 4	4	28	[2, 42]	[2, 42]	[22, 35]		[1, 42]
Week 5	5	35					
Week 6	6	42			[36, 49]		
Week 7	7	49					
Week 8	8	56	[43,70]	[43,70]	[50,70]		[43,70]
Week 9	9	63					
Week 10	10	70					
Week 11	11	77					
Week 12	12	84	[71, 98]	[71, 98]	[71, 98]	[2, 99999]	[71, 98]
Week 13	13	91					
Week 14	14	98					
Week 15	15	105					
Week 16	16	112	[99, 119]	[99, 999999]	[99, 119]		[99, 999999]
Week 17	17	119					
Week 18-20	18	126	[120, 999999]		[120, 999999]		

2.5.5 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.

2.5.6 Pooling of centers for statistical analyses

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

2.5.7 Statistical technical issues

Not applicable.

[redacted]

4 DATABASE LOCK

The database is planned to be locked in January 2020.

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

1. Bornkamp B, Pinheiro J, Bretz F. Package 'DoseFinding', January 4, 2018.

7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix B: MRI parameters

Appendix C: Analysis programming code notes

APPENDIX A POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES (PCSA) CRITERIA (SANOFI VERSION 2014)

Parameter	PCSA
Clinical Chemistry	
ALT (Alanine Aminotransferase)	>3 ULN
AST (Aspartate Aminotransferase)	>3 ULN
Alkaline Phosphatase	>1.5 ULN
TBILI (Total Bilirubin)	>1.5 ULN
Direct Bilirubin and Total Bilirubin	Direct bilirubin >35% Total Bilirubin and Total Bilirubin >1.5 ULN
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN
CK (Creatine kinase)	>3 ULN
CPK	>3 ULN >10 ULN
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline
BUN (Blood Urea Nitrogen)	≥17 mmol/L
Sodium	≤129 mmol/L ≥160 mmol/L
Potassium	<3 mmol/L ≥5.5 mmol/L
Lipase Lipasemia	≥3 ULN
Amylase Amylasemia	≥3 ULN
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)
CRP	>2 ULN or >10 mg/L (if ULN not provided)

Parameter	PCSA
Hematology	
Leukocyte count (WBC)	<3.0 * 10^9/L (Non-Black); <2.0 * 10^9/L (Black) ≥16.0 * 10^9/L
Lymphocytes	>4.0 * 10^9/L
Neutrophils	<1.5 * 10^9/L (Non-Black);<1.0 * 10^9/L (Black)
Monocytes	>0.7 * 10^9/L
Basophils	>0.1 * 10^9/L
Eosinophils	>0.5 * 10^9/L or >ULN (if ULN≥0.5 * 10^9/L)
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)
Erythrocyte count (RBC)	≥6 * 10^12/L
Platelet count	<100 * 10^9/L ≥700 * 10^9/L
Urinalysis	
pH	≤4.6 ≥8
Vital signs	
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg
Weight	≥5% increase from baseline ≥5% decrease from baseline

ECG	
HR	<50 bpm
	<50 bpm and decrease from baseline ≥20 bpm
	<40 bpm
	<40 bpm and decrease from baseline ≥20 bpm
	<30 bpm
	<30 bpm and decrease from baseline ≥20 bpm
	>90 bpm
	>90 bpm and increase from baseline ≥20bpm
	>100 bpm
	>100 bpm and increase from baseline ≥20bpm
	>120 bpm
	>120 bpm and increase from baseline ≥20 bpm
PR	>200 ms
	>200 ms and increase from baseline ≥25%
	> 220 ms
	>220 ms and increase from baseline ≥25%
	> 240 ms
	> 240 ms and increase from baseline ≥25%
QRS	>110 ms
	>110 msec and increase from baseline ≥25%
	>120 ms
	>120 ms and increase from baseline ≥25%
QT	>500 ms
QTc Bazett	>450 msec
QTc Fridericia	>480 msec
	>500 msec
	Increase from baseline [30-60] msec
	Increase from bseline >60 msec

APPENDIX B MRI PARAMETERS

Table 2 – MRI parameters

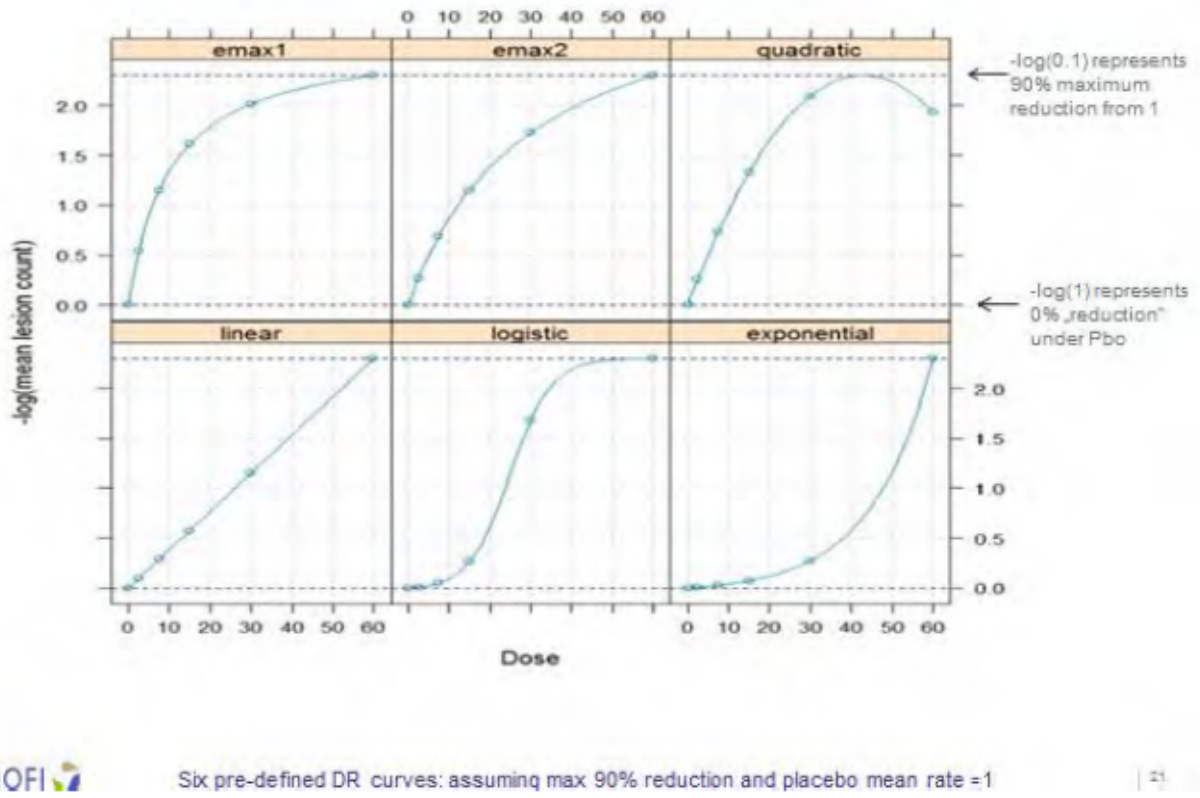
MRI measurement	Test name	Test code	Screening	Week 4	Week 8	Week 12	Week 16	Week ET
secondary endpoint – number of Gd-enhancing T1-hyperintense lesions at the end of 12 weeks of SAR442168 treatment	Gadolinium enhancing lesion count	GDCOUNT	X	X	X	X	X	X
primary endpoint – number of new Gd-enhancing T1-hyperintense lesions at the end of 12 weeks of SAR442168 treatment	New Gad enhancing lesion count	NEWGDCNT		X (previous)	X (previous)	X (previous)	X (previous)	X (previous)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
secondary endpoint – number of new or enlarging T2 lesions at the end of 12 weeks of SAR442168 treatment	New/enlarging T2 lesion count	NEWT2CNT		X (previous)	X (previous)	X (previous)	X (previous)	X (previous)

[redacted]

APPENDIX C ANALYSIS PROGRAMMING CODE NOTES

BTK SAP: primary analysis using MCP-mod

The primary endpoint, the dose-response relation of the five doses, will be assessed using the multiple comparison procedure with modelling techniques (MCP-mod). This approach consists of two key steps. Step 1 is the inferential part of the model that tests for an efficacy signal (a non-flat dose-response curve) in a procedure controlling for type 1 error. The procedure requires a set of dose-response curves to be pre-defined; the chosen profiles are selected to cover both plausible and diverse dose-response profiles, reflecting the range of candidate models believed to be capable of describing the dose-response relation. Step 2 is the estimation part of the model that will be done only if Step 1 shows an efficacy signal. In this step, the best-fitting dose-response curve is estimated. In this study, a negative binomial regression model will be used to assess the mean T1 lesion count in each dose group and the run-in placebo. Then a minus log transformation of the mean lesion count will be entered into the MCP-mod process. In the first step, 6 dose response curves will be considered, which cover the plausible shapes of interest (see plot 1). When data are available, the null hypothesis of a flat dose-response relation (i.e., no dose response) at 3 months for the primary endpoint (the mean T1 lesions count in different dose groups vs the run-in control) will be jointly tested for each of the candidate dose-response models with a contrast test that controlled for the familywise at two-sided alpha=0.05. If such test results in significance, the best-fitted model will be selected. From the selected model, the doses of interest can be estimated.



Six pre-defined dose response curves:

- Two Emax models (ED50=10mg, ED50=30mg)
- Linear model
- Quadratic model (max effect at 40-45mg)
- Logistic model (flat to 10mg and max at 50mg)
- Exponential model (slow effect to 30mg)

To account for the potential correlation for cohort 2 between the measurements in the run-in period and the treatment period, a generalized estimating equation approach (GEE) is used to fit the model accounting for the with-subject correlation. We will prepare data according to the following structure :

	id	y	cohort	trt	bline	age
1	104	5	1	1	11	31
2	106	3	1	2	11	30
3	107	2	1	1	6	21
4	108	2	1	2	6	27
5	109	2	1	1	6	29
6	110	2	1	2	6	25
7	114	4	2	0	8	36
8	114	3	2	1	8	36
9	115	1	2	0	8	23
10	115	2	2	2	8	23
11	116	3	2	0	8	30
12	116	2	2	2	8	30
13	117	4	2	0	8	28
14	117	2	2	1	8	28

Here "Y" denotes the new T1 lesion counts, "cohort=1" means the cohort without placebo run-in and cohort=2" means the cohort with placebo run-in, "trt" is the dose variable with 0 denoting the run-in placebo, 1 to 5 denote the actual dose groups. Bline is some baseline variables (i.e. lesion count at baseline) that we may need to adjust for.

The following is the sample SAS code for fitting the GEE model is

```
ods output GEEEmpPEst=test GEERCorr=corr;

proc genmod data=thall0;

class id trt(param=ref ref=first);

model y=trt bline   COHORT   /dist=negbin;

repeated subject=id /type=ind corrb;

run;
```

Suppose $\mu_A = (a_0, a_1, \ldots, a_5)$ be the coefficients of the intercept and "trt" with variance V. The dose-specific log-risk will be $\mu_B = (b_0, b_1, \ldots, b_5)$, where $b_0 = a_0, b_j = a_0 + a_j, j = 1, \ldots, 5$. Using the matrix expression, $\mu_B = G\mu_A$. The variance of μ_B will be $W = GVG^{\mathrm{T}}$.

The parameter $\mu_B = (b_0, b_1, \ldots, b_5)$ and W will be entered into the MCP-mod analysis in R using the package "DoseFinding", the sample codes are

```
### Install and load the package in R

install.packages("DoseFinding")

library(DoseFinding)


###Enter (input) μ_B and W

muB=muBSAS

W=WSAS


### Enter the 5 doses

doses <- c(0,2.5,7.5,15,30,60)


### Enter the parameters for the six dose response curves

fmodels<-Mods(emax=c(10,30),quadratic=-0.7/60,linear=NULL,

        logistic = c(25,5),exponential=c(15), doses = doses, placEff =-log(1.0), maxEff = -
log(0.1))

plot(fmodels,ylab="-log(mean lesion count)",xlab="Dose") # This will re-produce Figure 1.


### Calculate the optimal contrast matrix

contMat <- optContr(fmodels, S=W)


### Doing MCPMod modeling and use AIC criteria to find the best model, from which the dose
level with ### the risk reduction at least 90% from control is calculated.

MCPMod(doses, muB, S=W, models=fmodels, type="general", critV=TRUE, selModel="AIC",
alpha=0.05, alternative="two.sided", doseType="TD",Delta=-log(0.1)).
```

Signature Page for VV-CLIN-0540311 v1.0
dri15928-16-1-9-sap

Approve & eSign	[redacted]	

Approve & eSign	[redacted]	