AMENDED CLINICAL TRIAL PROTOCOL 04

Protocol title:	**A Phase 2 double-blind, randomized, placebo-controlled study evaluating the effect of SAR443820 on serum neurofilament levels in participants with multiple sclerosis, followed by an open-label long-term extension period**
Protocol number:	**ACT16753**
Amendment number:	**04**
Compound number (INN/Trademark):	**SAR443820** **Not applicable**
Brief title:	**Phase 2 study of SAR443820 in participants with multiple sclerosis (MS)**
Acronym:	**Not Applicable**
Study phase:	**Phase 2**
Sponsor name: **Legal registered address:**	**Sanofi-Aventis Recherche & Developpement** **1 avenue Pierre Brossolette** **91380 Chilly-Mazarin, France**
Monitoring team's representative name and contact information	**Click here to type**

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Date: 13-Dec-2023 Total number of pages: 115

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 04	All	13 Dec 2023, version 1 (electronic 7.0)
Amended Clinical Trial Protocol 03	All	06 July 2023, version 1 (electronic 6.0)
Amended Clinical Trial Protocol 02	All	19 May 2023, version 2 (electronic 5.0)
Amended Clinical Trial Protocol 01	All	21 September 2022, version 1 (electronic 2.0)
Original Protocol		18 March 2022, version 1 (electronic 2.0)

Amended protocol 04 (13 December 2023)

This amended protocol (amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

An identified risk of drug induced liver injury (DILI) for SAR443820 is added based on internal data review of another Phase 2 study (ACT16970) testing 20 mg BID SAR443820 in patients with amyotrophic lateral sclerosis (ALS).

The main purpose of protocol amendment 04 is to add 23 visits (Weeks 8, 10, 14, 18, 20, 22, 28, 32, 40, and 44 in Part A, and Weeks 50, 54, 58, 62, 64, 66, 68, 70, 76, 80, 84, 88, and 92 in Part B) for liver chemistry monitoring at each added visit. Also, two diagnostic tests in case of events of ALT increase are made mandatory.

Protocol amendment summary of changes table

Section # and Name	Description of change	Brief rationale
1.2 SCHEMA 1.3.1 Part A 1.3.2 Part B 4.1 OVERALL DESIGN	Added visits for liver chemistry test on Weeks 8, 10, 14, 18, 20, 22, 28, 32, 40, and 44 in Part A and Weeks 50, 54, 58, 62, 64, 66, 68, 70, 76, 80, 84, 88, and 92 visit in Part B. Added instructions on sample collecting, testing and results reporting at the visits added. Updated the Part A to include biweekly liver chemistry monitoring for D1 through Week 24, then monthly from Week 24 through 48. Updated Part B to include biweekly liver chemistry monitoring from Week 48 through Week 72, then monthly Week 72 through the end of the study.	To enable earlier detection and management of liver abnormalities to protect participants' safety and get additional liver enzyme data in participants with MS treated with 20 mg OD.
2.3.1 Risk Assessment 2.3.3 Overall benefit/risk conclusion	Added an identified risk of DILI for SAR443820. Added clinical data and mitigation strategy supporting the potential risk of ALT increase.	To update the risk of SAR443820 based on current data from the ongoing clinical trial and minimize the risk for participants.

Section # and Name	Description of change	Brief rationale
10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW UP ASSESSMENTS AND STUDY INTERVENTION RECHALLENGE GUIDELINES	Updated to include mandatory hepatobiliary ultrasonography as part of the steps to investigate cases of ALT>5xULN; Hepatitis B surface antigen testing added to safety follow up	Update of mandatory procedures for etiology investigation
10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY	Summary of changes table for amendment 03 is moved to appendix 10.12.	To describe the protocol amendment history.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A Phase 2 double-blind, randomized, placebo-controlled study evaluating the effect of SAR443820 on serum neurofilament levels in participants with multiple sclerosis, followed by an open-label long-term extension period

Brief title:

Phase 2 study of SAR443820 in participants with multiple sclerosis (MS)

Rationale:

Multiple sclerosis (MS) is a chronic autoimmune disease characterized by neuroinflammation, demyelination, and axonal degeneration (1). Despite the availability of several disease-modifying therapy (DMT) that reduce relapses, there is still a significant unmet need for therapies that target disease progression in relapsing and progressive forms of MS (2). Clinically, most relapsing signs are effectively controlled with a broad arsenal of DMTs that target the peripheral adaptive immune system. Even when the relapses are well-controlled, ongoing inflammatory activity in the central nervous system (CNS) inflicts insidious chronic damage and progressive physical disability predominates in absence of relapse activity (3, 4). This is particularly true for people with progressive forms of MS including primary progressive multiple sclerosis (PPMS) and secondary progressive multiple sclerosis (SPMS) leading to relentless accumulation of nervous system disability. This is in part due to a complex cellular and biochemical milieu that perpetuates mediators of inflammation, leading to neuroaxonal damage and demyelination (3, 4).

Receptor interacting serine/threonine-protein kinase (RIPK1) is a critical signaling protein in the tumor necrosis factor receptor 1 (TNFR1) pathway that regulates inflammation and cell death in tissues throughout the body. RIPK1 is activated in response to several inflammatory stimuli, with subsequent initiation of a complex signaling cascade that triggers intracellular responses, including cytokine release, microglial activation, and necroptosis, a regulated form of cell death. There is evidence for RIPK1, receptor interacting serine/threonine-protein kinase 3 (RIPK3), and mixed lineage kinase domain-like protein (MLKL) activation in MS postmortem tissue, playing a role in both microglial and astrocyte inflammatory signaling and necroptosis of oligodendrocytes, which can be subject to RIPK1-dependent cell death. Inhibition of RIPK1 activity has been shown to protect against necroptotic cell death in vitro across a range of cell death models (5, 6, 7). Genetic and pharmacological inhibition of RIPK1 kinase ameliorated disease pathology and disease scores, improved animal behavior, attenuated the production of proinflammatory cytokines, reduced plasma neurofilament heavy chain levels, and decreased recruitment of immune cells in 2 animal models of MS, the experimental autoimmune encephalomyelitis (EAE), and cuprizone models (5 ,7), recapitulating certain aspects of immunological and degenerative components of MS (3, 4). These nonclinical findings coupled with observations of increased RIPK1 activity in human disease suggest a CNS-penetrant RIPK1 inhibitor may be beneficial in treating neurological diseases such as MS (5, 6, 7).

SAR443820 is a selective, orally bioavailable, CNS-penetrant, reversible kinase inhibitor of RIPK1. SAR443820 has demonstrated strong RIPK1 inhibition with high potency in vitro in various cell types. Dose ranging from 10 mg to 40 mg daily and 15 mg to 20 mg BID were safe and well tolerated. The first-in-human (FIH) single ascending dose (SAD; Study TDU16519) and multiple ascending dose (MAD; Study TDR16520) showed a good tolerability and pharmacokinetic (PK) profile ($t_{1/2}$ 7 to 9 hours and t_{max} 1 to 2 hours), a strong target engagement relative to the RIPK1 inhibition evidenced at peripheral level and good penetration of SAR443820 in cerebrospinal fluid (CSF).

Neuronal loss is a hallmark pathological feature of MS that is associated with brain atrophy, disease progression, and long-term disability (8, 9). Neurofilaments (heavy and light chain) are structural elements of axons and markers of neuronal damage. Neurofilaments are increased in the CSF, plasma, and serum in a range of neurological diseases including MS (10). Neurofilament light chain (NfL) levels have been demonstrated in numerous studies to be predictive of disease course and are responsive to DMTs in MS (11). Most approved and clinically effective MS treatments also reduce serum neurofilament light chain (sNfL) levels serving as a surrogate biomarker of treatment efficacy in numerous relapsing remitting multiple sclerosis (RRMS), PPMS, and SPMS randomized clinical trials (12, 13, 14). Therapeutic administration of a CNS-penetrant RIPK1 inhibitor has been demonstrated to cause dose-dependent reduction in disease score and plasma heavy chain neurofilament levels in the EAE animal model, substantiating neurofilament's suitability for objectively measuring SAR443820's effect on this marker in MS patients while evaluating the clinical and radiological signs that may respond to this intervention, especially the degenerative aspects that axonal injury manifests in the form of neurofilament elevation across the spectrum of neurological disease (7, 10, 11).

The aim of the ACT16753 Phase 2 proof-of-concept study is to demonstrate SAR443820's effect on sNfL levels when compared to placebo in participants with RRMS, SPMS, and PPMS. This study will also evaluate the effect of SAR443820 on clinical and imaging markers of disease progression and activity. Participants will be permitted to continue specified standard of care (SOC) background therapies (see Section 5) throughout the double-blinded treatment (Part A) and open-label long-term extension period (Part B). Safety and tolerability of SAR443820 will be monitored throughout the trial.

Objectives and endpoints:

Part A

Objectives	Endpoints
Primary	
• To assess the effect of SAR443820 compared to placebo on sNfL	• Week 48 sNfL levels relative to baseline
Secondary	
• To evaluate efficacy of SAR443820 compared to placebo on imaging and clinical endpoints	• Cumulative number of new gadolinium (Gd)-enhancing T1 hyperintense lesions as detected by MRI at Week 48, defined as the sum of the individual number of new Gd-enhancing T1 hyperintense lesions at all scheduled visits starting after baseline up to and including the Week 48 visit • Cumulative number of new and/or enlarging T2 hyperintense lesions as detected by MRI, at Week 48, defined as the sum of the individual number of new and/or enlarging T2 lesions at all scheduled visits starting after baseline up to and including the Week 48 visit • Time to onset of 12 weeks confirmed disability progression (CDP) from baseline as assessed by the Expanded Disability Status Scale (EDSS) score • Time to onset of sustained 20% increase in 9-Hole Peg Test (9-HPT) confirmed over at least 12 weeks • Time to onset of sustained 20% increase in timed 25-foot walk test (T25-FW) confirmed over at least 12 weeks • Change from baseline in EDSS-Plus at Week 48 • Annualized relapse rate (ARR) of RMS population (relapsing SPMS and RRMS) up to Week 48
• To explore effect of SAR443820 compared to placebo on brain volume and chronic lesions	• Percent change from baseline in brain volume loss (BVL) as detected by brain MRI at 48 weeks • Change from baseline in the volume, number, and intensity (T1) of slowly expanding lesions (SELs), and normalized T1 intensity in lesions at Weeks 12, 24, 36, and 48 • Change from baseline in the total number and volume of non-enhancing lesions volume at Weeks 12, 24, 36, and 48 • Change from baseline in the number of phase rim lesions (PRL) at Weeks 12, 24, 36, and 48; among participants at sites with 3T capability
• To assess the safety and tolerability of SAR443820	• Incidence of AE, SAE, TEAE, PCSA in laboratory tests
• To assess pharmacokinetic (PK) of SAR443820	• Plasma concentration of SAR443820

Part B

Objectives	Endpoints
Primary	
• To assess long-term trends in durability of sNfL	• Week 96 sNfL levels relative to baseline
Secondary	
• To explore the effect of SAR443820 on brain volume and chronic lesions	• Percent change from baseline in BVL as detected by brain MRI at Week 96 • Change from baseline in volume, number and intensity (T1) in SEL and normalized T1 intensity in lesions to Week 96 • Change from baseline in the total number and volume of non-enhancing lesions Week 96 • Change from baseline in the number of PRLs (same participants/centers from Part A) at Week 96
• To assess the long-term safety and tolerability of SAR443820	• Incidence of AE, SAE, TEAE, PCSA in laboratory tests, ECG, and vital signs during through Week 96
• To evaluate long-term effect of SAR443820 on disease progression and activity assessed by other clinical and imaging measures on physical function and patient-reported outcomes (PROs)	• Cumulative number of new Gd-enhancing lesions as detected by T1-weighted MRI between 48 and 96 weeks; number of new or enlarging T2-hyperintense lesions on MRI at Week 96 relative to Week 48 • Annualized relapse rate (ARR) of RMS population (relapsing SPMS and RRMS) up to Week 96 • Time to onset of composite CDP (CCDP), confirmed over at least 12 weeks (3-month CCDP), by the EDSS-Plus composite (EDSS score increase, OR 20% increase in the T25-FW test, OR 20% increase in the 9-HPT) • Time to onset of 12 weeks CDP as assessed by the EDSS score • Time to onset of sustained 20% increase in 9-HPT confirmed over at least 12 weeks • Time to onset of sustained 20% increase T25-FW test confirmed over at least 12 weeks • Change from baseline in EDSS-Plus at Week 96 • Change in MSIS-29v2 physical and psychological domains scoring from baseline through Week 96 • Change in MSWS-12 from baseline through Week 96

For China, please see Section 10.8.1 for details.

Overall design:

Study ACT16753 is a Phase 2, randomized, double-blind, placebo-controlled study (Part A) followed by an open-label, long-term extension period (Part B).

Brief summary:

This is a Phase 2, randomized, double-blind, placebo-controlled 2 parallel-arm study to assess the effect on sNfL, safety and tolerability of 20 mg once daily (QD) oral SAR443820 compared to placebo in male and female participants aged 18 to 60 years with RRMS, SPMS (relapsing or non-relapsing), or PPMS followed by an open-label long-term extension period.

The total study duration is approximately 100 weeks and includes the following:

- 4-week screening period
- 48-week double-blind treatment period (Part A)
- 48-week open-label long-term extension period (Part B)

Number of participants:

Approximately 280 participants will be screened to achieve 168 participants randomly assigned at a 1:1 ratio to SAR443820 or placebo (based on a 40% screen failure rate). A minimum of 50% of study participants are required to have progressive multiple sclerosis (PMS) (PPMS and SPMS).

Intervention groups and duration:

Study intervention(s)

SAR443820 OR matching placebo

Investigational medicinal product(s)

- Formulation: Both SAR443820 20 mg and matching placebo will be formulated in tablets
- Route(s) of administration: Tablets will be taken orally. The suggested method for IMP administration is detailed in Section 6.
- Dose regimen:
  - Part A:
    - Treatment arm: SAR443820, 20 mg QD
    - Placebo arm: Placebo QD
  - Part B:
    - Treatment arm: SAR443820, 20 mg QD

Noninvestigational medicinal products(s) (NIMP)

- Formulation: MRI contrast enhancing preparations
- Route(s) of administration: intravenous (IV)
- Dose regimen: as per respective country-specific labelling

Devices

Not applicable.

Poststudy access to study medication

Part B is an open-label long-term extension period up to Week 96 in which all eligible participants from Part A may rollover to Part B and receive open-label IMP. In addition to this open-label extension, poststudy access to study medication could be provided based on local/country regulations.

Duration of study intervention

Treatment duration is up to 48 weeks each in Part A and Part B.

Statistical considerations:

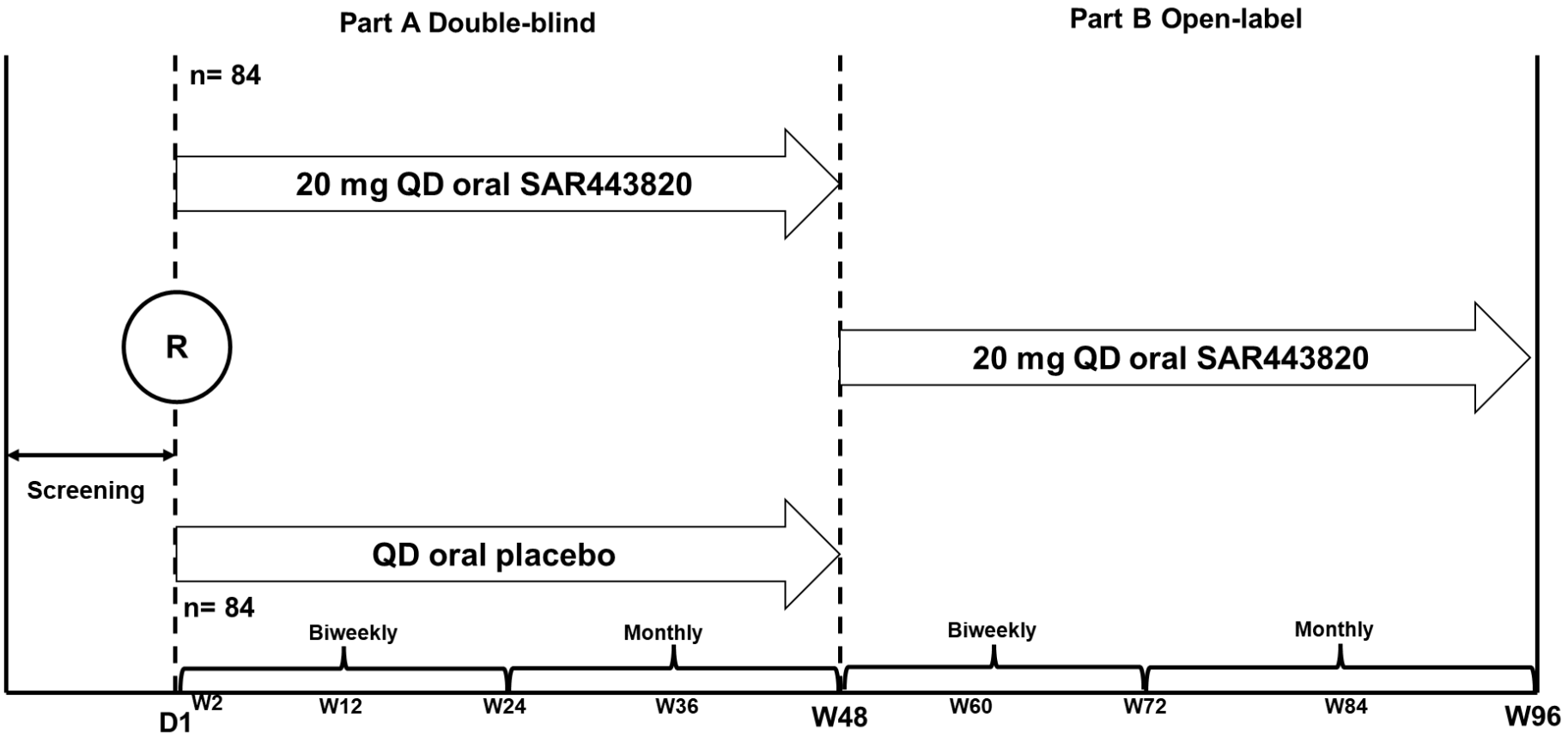
- **Primary endpoint:** Week 48 sNfL levels relative to baseline
- **Main secondary endpoints:**
  - Cumulative number of new Gd-enhancing T1 hyperintense lesions as detected by MRI at Week 48, defined as the sum of the individual number of new Gd-enhancing T1 hyperintense lesions at all scheduled visits starting after baseline up to and including the Week 48 visit
  - Cumulative number of new and/or enlarging T2 hyperintense lesions as detected by MRI, at Week 48, defined as the sum of the individual number of new and/or enlarging T2 lesions at all scheduled visits starting after baseline up to and including the Week 48 visit
  - Time to onset of 12 weeks confirmed disability progression (CDP) from baseline as assessed by the Expanded Disability Status Scale (EDSS) score

The reduction in sNfL levels (primary endpoint) or correlation to other covariates (main secondary endpoints) for participants treated with SAR443820 relative to participants receiving placebo will be estimated in the modified intent-to-treat (mITT) population.

Data Monitoring/Other committee: Yes

1.2 SCHEMA

Figure 1 - Graphical study design



Abbreviations: D = Day; n = number; QD = once daily; R = randomization; W = Week; Biweekly and monthly refers to liver chemistry monitoring visits

1.3 SCHEDULE OF ACTIVITIES (SOA)

1.3.1 Part A

Procedure	Screening (up to 4 weeks before Day 1)[a]	Interventional period																				Early discontinuation visit
		Day 1		Week 2	Week 4	Week 6	Week 8	Week 9	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48[b]	
		Predose (baseline)	Post dose	Day 14±3	Day 28±3	Day 42 ±3	Day 44±3	Day 56 ±3	Day 70 ±3	Day 84 ±3	Day 98 ±3	Day 112 ±3	Day 126 ±3	Day 140 ±3	Day 154 ±3	Day 168 ±3	Day 196 ±3	Day 224 ±3	Day 252 ±3	Day 280 ±3	Day 308 ±3	Day 336 ±3	
Visit	1[c]	2		3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Informed consent	X																						
Demography	X																						
Eligibility check (inclusion and exclusion criteria)	X	X																					
Medical/ surgical history (includes substance usage)[d]	X																						
Current/new medical conditions (includes substance usage)[d]	X	X		X		X				X						X			X			X	X
Concomitant therapy and procedures recording	←==========																					→==========	X
Randomization		X																					

Procedure	Screening (up to 4 weeks before Day 1)[a]	Interventional period																				Early discontinuation visit
		Day 1		Week 2	Week 4	Week 6	Week 8	Week 9	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48[b]	
		Predose (baseline)	Post dose	Day 14±3	Day 28±3	Day 42 ±3	Day 44±3	Day 56 ±3	Day 70 ±3	Day 84 ±3	Day 98 ±3	Day 112 ±3	Day 126 ±3	Day 140 ±3	Day 154 ±3	Day 168 ±3	Day 196 ±3	Day 224 ±3	Day 252 ±3	Day 280 ±3	Day 308 ±3	Day 336 ±3	
Visit	1[c]	2		3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
IRT contact	X	X								X						X			X			X	X
IMP dispensation/ reconciliation		X								X						X			X			X[e]	X[f]
Safety																							
Physical examination[g]	X	X		X		X				X						X			X			X	X
Neurological examination[h]	X	X		X		X				X						X			X			X	X
Height	X																						
Weight	X	X		X		X				X						X			X			X	X
HIV and hepatitis B and C screening	X																						
Vital signs[i]	X	X	X	X		X				X						X			X			X	X
12-lead ECG	X		X	X		X				X												X	X
Laboratory tests for hematology and chemistry	X	X		X	X[i]	X	X[i]	X[i]	X[i]	X	X[i]	X[i]	X[i]	X[i]	X[i]	X	X[i]	X[i]	X	X[i]	X[i]	X	X
Urine sample for urinalysis	X	X		X		X				X						X			X			X	X

Procedure	Screening (up to 4 weeks before Day 1)[a]	Interventional period																				Early discontinuation visit
		Day 1		Week 2	Week 4	Week 6	Week 8	Week 9	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48[b]	
		Predose (baseline)	Post dose	Day 14±3	Day 28±3	Day 42 ±3	Day 44±3	Day 56 ±3	Day 70 ±3	Day 84 ±3	Day 98 ±3	Day 112 ±3	Day 126 ±3	Day 140 ±3	Day 154 ±3	Day 168 ±3	Day 196 ±3	Day 224 ±3	Day 252 ±3	Day 280 ±3	Day 308 ±3	Day 336 ±3	
Visit	1[c]	2		3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Urine pregnancy test (WOCBP only)[k]	←==========																				==========→	X
Serum β-HCG test (WOCBP only)	X																					
Serum FSH[l] and estradiol	X																					
C-SSRS questionnaire[m]	X	X[m]		X[m]		X[m]				X[m]						X[m]			X[m]			X[m]	X[m]
AE review	←==========																				==========→	X
SAE review	←==========																				==========→	X
Efficacy																						
EDSS	X	X								X						X			X			X	X
Timed 25-foot walk test (T25-FW)[n]		X								X						X			X			X	X
9-hole peg test (9-HPT)[n]		X								X						X			X			X	X
Brain MRI with and without Gd		X[o]								X						X			X			X	X[p]

Procedure	Screening (up to 4 weeks before Day 1)[a]	Interventional period																				Early discontinuation visit
		Day 1		Week 2	Week 4	Week 6	Week 8	Week 9	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48[b]	
		Predose (baseline)	Post dose	Day 14±3	Day 28±3	Day 42 ±3	Day 44±3	Day 56 ±3	Day 70 ±3	Day 84 ±3	Day 98 ±3	Day 112 ±3	Day 126 ±3	Day 140 ±3	Day 154 ±3	Day 168 ±3	Day 196 ±3	Day 224 ±3	Day 252 ±3	Day 280 ±3	Day 308 ±3	Day 336 ±3	
Visit	1[c]	2		3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Clinical outcome assessment																						
MSIS-29v2[q]	X	X								X						X			X			X	X
MSWS-12[q]	X	X								X						X			X			X	X
Pharmacokinetics																						
Blood samples for plasma PK			X[r]	X[s]		X[t]				X[t]									X[t]				
Pharmacodynamics/biomarkers																						
Blood samples for sNfL	X	X								X						X			X			X	X
Blood samples for neuro-degeneration/ neuro-inflammation markers[u]	X	X								X						X			X			X	X

Abbreviations: 9-HPT = 9-Hole Peg Test; AE = adverse event; β-HCG = beta human chorionic gonadotropin; CCL3 = Chemokine (C-C motif) ligands 3; CCL4 = Chemokine (C-C motif) ligands 4; CHI3L1 = Chitinase 3-like protein 1; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; EOT = end of treatment; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; IL1β = Interleukin 1 beta; IL6 = Interleukin 6; IL8 = Interleukin 8; IMP = investigational medicinal product; IRT = interactive response technology; MIP1a = Macrophage Inflammatory Protein-1 alpha; MIP1b = Macrophage Inflammatory Protein-1 beta; MRI = magnetic resonance imaging; MSIS-29v2 = Multiple Sclerosis Impact Scale-29 items version 2; MSWS-12 = Multiple Sclerosis Walking Scale-12 items; PK = pharmacokinetic(s); SAE = serious adverse event; SEL= slowly expanding lesions; sGFAP = serum glial fibrillary acidic protein; sNfL = serum neurofilament light chain; T25-FW = Timed 25 foot walk test; TNFα = tumor necrosis factor alpha; WOCBP = woman of childbearing potential

a A maximum of 11 days is required to get IMP on site. The Randomization Visit date of the participants must take into consideration this constraint.

b The Week 48 visit can be considered as both the last visit for Part A and the first visit for Part B. For all participants last dose of double-blind IMP should be taken the prior day. Week 48 visit will consist of 1st open-label (Part B) IMP. All assessments for end of Part A should be completed prior to first dose of open-label IMP.

c The Screening Visit can be performed over up to 2 days if needed (the days need not to be consecutive days) to minimize the burden on participants.

d Substances include drugs of abuse, alcohol, tobacco, and caffeine.

e Reconciliation of IMP dispensed in Part A and dispensation of open-label IMP in Part B will be performed at this visit (Week 48). The IMP may be dispensed in the clinic or provided for home administration via direct-to-patient services, except if prohibited by local regulatory authorities.

f Only IMP reconciliation will be performed at this visit.

g A full physical examination will be performed at the Screening Visit, and a brief physical examination will be performed at all other visits.

h A full neurological examination will be performed at the Screening Visit, and a brief neurological examination including cranial nerves, coordination/cerebellar function, reflexes, motor function, and stance/gait will be performed at other visits.

i Laboratory tests for liver chemistry will be conducted every two weeks (biweekly) from W2 through Week 24, every month from Week 24 through Week 48. Hence the only hematology and chemistry laboratory tests performed at the visits denoted with footnote "i" are liver chemistry assessments. These visits can be conducted remotely. On-site, local laboratory or home health nurse, are permitted based on availability. In case of remote visits, the blood sample must be collected at a local clinic or at home by a nurse, and the sample must be tested at a local lab or the central lab. In case of testing at a local lab, the study site staff must contact participants, within 2 working days after the results are expected to be available, to collect results of blood test. The following parameters will be investigated: alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and bilirubin.

j Vital signs include blood pressure, heart rate, respiratory rate, and temperature. Refer to Section 8.2.3 for further details.

k A urine pregnancy test will be provided direct-to-patient on a monthly basis except for the months coinciding with scheduled clinic visits (ie, Day 1 and Weeks 2, 6, 12, 24, 36, and 48), which should be conducted on-site, should not be older than 24 hours upon first IMP intake on Day 1.

l Only for female participants, if needed, to establish menopausal status.

m The “Since Last Visit” version of the C-SSRS will be used.

n 9-HPT: All individuals will complete a practice test and an actual test for both hands (1 task [right and left hand]). T25FW: the amount of time will vary for each participant.

o Baseline scan can be carried out within 5 to 7 days prior to Day 1 randomization but after all other screening assessments have been completed and none have excluded the patient.

p To be performed only if the previous MRI was done more than 4 weeks ago.

q MSIS-29v2 and MSWS-12 will be completed by participants prior to discussion of health status or other tests, and prior to administration of IMP. MSIS-29v2 will be self-administered, with a recall/observation period of 2 weeks. The time to complete MSIS-29v2 is 2 to 4 minutes. MSWS-12 will be self-administered with a recall/observation period of 2 weeks. The time to complete MSWS-12 is less than 5 minutes.

r Two samples will be taken within 15 minutes to-1 hour postdose and within 1-to-3 hours postdose (at least 45 minutes apart).

s One sample will be taken predose (within 1-hour predose), and 1 sample will be taken within 0.5-to-3 hours postdose.

t One sample will be taken predose (within 1-hour predose).

u Disease biomarkers will include the followings: CHI3L1 and sGFAP (not collected in China); Cytokines and Chemokines including IL1β, IL6, IL8, TNFα, CCL3 (MIP1a), and CCL4 (MIP1b).

1.3.2 Part B

Procedure	Intervention period (Part B)																		Safety Follow-up[b]	Early discontinuation visit
	Week 50	Week 52	Week 54	Week 56	Week 58	Week 60	Week 62	Week 64	Week 66	Week 68	Week 70	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96 / EOT		
	Day 350 ±7	Day 364 ±7[a]	Day 378 ±7	Day 392 ±7	Day 406 ±7	Day 420 ±7	Day 434 ±7	Day 448 ±7	Day 462 ±7	Day 476 ±7	Day 490 ±7	Day 504 ±7	Day 532 ±7	Day 560 ±7	Day 588 ±7	Day 616 ±7	Day 644 ±7	Day 672 ±7/ EOT		
Visit	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	
Concomitant therapy and procedures recording	←==========																		==========→	X
IRT contact												X						X		X
IMP dispensation/ reconciliation[c]												X						X[d]		X[d]
Safety																				
Physical examination[e]		X										X						X	X	X
Neurological examination[f]		X										X						X	X	X
Weight		X										X						X	X	X
Vital signs[g]		X										X						X	X	X
12-lead ECG		X																X	X	X
Laboratory tests for hematology and chemistry	X[h]	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X	X[h]	X[h]	X[h]	X[h]	X[h]	X	X	X
Urine sample for urinalysis		X										X						X	X	X

Procedure	Intervention period (Part B)																		Safety Follow-up[b]	Early discontinuation visit
	Week 50	Week 52	Week 54	Week 56	Week 58	Week 60	Week 62	Week 64	Week 66	Week 68	Week 70	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96 / EOT		
	Day 350 ±7	Day 364 ±7[a]	Day 378 ±7	Day 392 ±7	Day 406 ±7	Day 420 ±7	Day 434 ±7	Day 448 ±7	Day 462 ±7	Day 476 ±7	Day 490 ±7	Day 504 ±7	Day 532 ±7	Day 560 ±7	Day 588 ±7	Day 616 ±7	Day 644 ±7	Day 672 ±7/ EOT		
Visit	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	
Urine pregnancy test (WOCBP only)[i]	←==========																			==========→
C-SSRS questionnaire[j]		X				←==========														X
AE review	←==========																			X
SAE review	←==========																			X
Efficacy																				
EDSS												X						X		X
Timed 25-foot walk test (T25-FW)[k]												X						X		X
9-hole peg test (9-HPT)[k]												X						X		X
Brain MRI with and without Gd																		X		X
Clinical outcome assessment																				
MSIS-29v2[l]																		X		X
MSWS-1[l]																		X		X

Procedure	Intervention period (Part B)																		Safety Follow-up[b]	Early discontinuation visit
	Week 50	Week 52	Week 54	Week 56	Week 58	Week 60	Week 62	Week 64	Week 66	Week 68	Week 70	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96 / EOT		
	Day 350 ±7	Day 364 ±7[a]	Day 378 ±7	Day 392 ±7	Day 406 ±7	Day 420 ±7	Day 434 ±7	Day 448 ±7	Day 462 ±7	Day 476 ±7	Day 490 ±7	Day 504 ±7	Day 532 ±7	Day 560 ±7	Day 588 ±7	Day 616 ±7	Day 644 ±7	Day 672 ±7/ EOT		
Visit	**21**	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	
Pharmacodynamics/biomarkers																				
Blood samples for sNfL												X						X		X

Abbreviations: 9-HPT = 9-Hole Peg Test; AE = adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; EOT = end of treatment; Gd = gadolinium; IMP = investigational medicinal product; IRT = interactive response technology; MRI = magnetic resonance imaging; MSIS-29v2 = Multiple Sclerosis Impact Scale-29 items version 2; MSWS-12 = multiple sclerosis walking scale 12 items; SAE = serious adverse event; sNfL = serum neurofilament light chain; T25-FW = Timed 25 foot walk test; WOCBP = woman of childbearing potential

a The first visit for Part B is the Week 48 Visit in Part A. First dose of open-label (Part B) IMP will be taken at that visit, upon completion of all Week 48 assessments.

b The participants will attend a safety follow-up visit within 2 weeks following discontinuation of IMP, if they no longer wish to remain in the study

c In addition to the IMP being dispensed in the clinic, the IMP may be dispensed for home administration via direct-to-patient services, except if prohibited by local regulatory authorities during the intervening 3 months between site visits.

d Only IMP reconciliation will be performed at this visit if participants are still on study intervention.

e A brief physical examination will be performed at each visit.

f A brief neurological examination including to cranial nerves, coordination/cerebellar function, reflexes, motor function, stance/gait will be performed at all visits.

g Vital signs include blood pressure, heart rate, respiratory rate, and temperature. Refer to Section 8.2.3 for further details.

h Only laboratory tests for liver chemistry will be conducted: every two weeks (biweekly) from Week 50 through Week 72, every month from Week 72 through Week 96. Hence the only hematology and chemistry laboratory tests performed at the visits denoted with the footnote "h" are liver chemistry assessments. On-site, local laboratory or home health nurse, are permitted based on availability. These can be conducted remotely. In such cases, the blood sample must be collected at a local clinic or at home by a nurse, and the sample must be tested at a local lab or the central lab. In case of testing at a local lab, the study site staff must contact participants, within 2 working days after the results are expected to be available, to collect results of blood test. The following parameters will be investigated: alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and bilirubin.

i A urine pregnancy test will be provided direct-to-patient on a monthly basis except for the months coinciding with scheduled clinic visits (Weeks 52, 72, and 96).

j The "Since Last Visit" version of the C-SSRS will be used.

k 9-HPT: All individuals will complete a practice test and an actual test for both hands (1 task [right and left hand]). T25FW: the amount of time will vary for each participant.

l MSIS-29v2 and MSWS-12 will be completed by participants prior to discussion of health status or other tests, and prior to administration of IMP. MSIS-29v2 will be self-administered, with a recall/observation period of 2 weeks. The time to complete MSIS-29v2 is 2 to 4 minutes. MSWS-12 will be self-administered with a recall/observation period of 2 weeks. The time to complete MSWS-12 is less than 5 minutes.

2 INTRODUCTION

SAR443820 is a novel, potent, selective, CNS-penetrant RIPK1 inhibitor that is being developed for neurodegenerative diseases, including MS.

2.1 STUDY RATIONALE

Multiple sclerosis is a chronic autoimmune disease characterized by neuroinflammation, demyelination, and axonal degeneration (1). Despite the availability of several DMTs that reduce relapses, there is still a significant unmet need for therapies that target disease progression in relapsing and progressive forms of MS (2). Clinically, most relapsing signs are effectively controlled with a broad arsenal of DMTs that target the peripheral adaptive immune system. Even when the relapses are well-controlled, ongoing inflammatory activity in the CNS inflicts insidious chronic damage and progressive physical disability predominates in absence of relapse activity (3, 4). This is particularly true for people with progressive forms of MS including PPMS and SPMS leading to relentless accumulation of nervous system disability. This is in part due to a complex cellular and biochemical milieu that perpetuates mediators of inflammation, leading to neuroaxonal damage and demyelination (3, 4).

Receptor interacting serine/threonine-protein kinase is a critical signaling protein in the TNFR1 pathway that regulates inflammation and cell death in tissues throughout the body. RIPK1 is activated in response to several inflammatory stimuli, with subsequent initiation of a complex signaling cascade that triggers intracellular responses, including cytokine release, microglial activation, and necroptosis, a regulated form of cell death. There is evidence for RIPK1, RIPK3, and MLKL activation in MS postmortem tissue, playing a role in both microglial and astrocyte inflammatory signaling and necroptosis of oligodendrocytes, which can be subject to RIPK1-dependent cell death. Inhibition of RIPK1 activity has been shown to protect against necroptotic cell death in vitro across a range of cell death models (5, 6, 7). Genetic and pharmacological inhibition of RIPK1 kinase ameliorated disease pathology and disease scores, improved animal behavior, attenuated the production of proinflammatory cytokines, reduced plasma neurofilament heavy chain levels, and decreased recruitment of immune cells in 2 animal models of MS, the EAE, and cuprizone models (5, 7), recapitulating certain aspects of immunological and degenerative components of MS (3, 4). These nonclinical findings coupled with observations of increased RIPK1 activity in human disease suggest a CNS-penetrant RIPK1 inhibitor may be beneficial in treating neurological diseases such as MS (5, 6, 7).

SAR443820 is a selective, orally bioavailable, CNS-penetrant, reversible kinase inhibitor of RIPK1. SAR443820 has demonstrated strong RIPK1 inhibition with high potency in vitro in various cell types. Dose ranging from 10 mg to 40 mg daily and 15 mg to 20 mg BID were safe and well tolerated. The FIH SAD (Study TDU16519) and MAD (Study TDR16520) showed a good tolerability and PK profile ($t_{1/2}$ 7 to 9 hours and t_{max} 1 to 2 hours), a strong target engagement relative to the RIPK1 inhibition evidenced at peripheral level and good penetration of SAR443820 in CSF.

Neuronal loss is a hallmark pathological feature of MS that is associated with brain atrophy, disease progression, and long-term disability (7, 8, 9). Neurofilaments (heavy and light chains) are structural elements of axons and markers of neuronal damage. Neurofilaments are increased in the CSF, plasma, and serum in a range of neurological diseases including MS (10). Neurofilament light chain levels have been demonstrated in numerous studies to be predictive of disease course and are responsive to DMTs in MS (11). Most approved and clinically effective MS treatments also reduce sNfL levels serving as a surrogate biomarker of treatment efficacy in numerous RRMS, PPMS, and SPMS randomized clinical trials (12, 13, 14). Therapeutic administration of a CNS-penetrant RIPK1 inhibitor has been demonstrated to cause dose-dependent reduction in disease score and plasma heavy chain neurofilament in the EAE animal model, substantiating neurofilament's suitability for objectively measuring SAR443820's effect on this marker in MS patients while evaluating the clinical and radiological signs that may respond to this intervention, especially the degenerative aspects that axonal injury manifests in the form of neurofilament elevation across the spectrum of neurological disease (7, 10, 11).

The aim of the ACT16753 Phase 2 proof-of-concept is to demonstrate SAR443820's effects on sNfL levels when compared to placebo in RRMS, SPMS, and PPMS participants. This study will also evaluate the effect of SAR443820 on clinical and imaging markers of disease progression and activity. Participants will be permitted to continue specified SOC background therapies (see Section 5) throughout the double-blinded treatment (Part A) and open-label long-term extension period (Part B). Safety and tolerability of SAR443820 will be monitored throughout the trial.

2.2 BACKGROUND

Immunomodulatory drugs have been the mainstay of MS therapy, most of which target the peripheral immune response, and have conferred significant benefit to patients suffering from MS with clinical relapses and MRI activity.

There is still a significant unmet need for therapies that target neuroinflammation in the CNS with the goal of halting long-term disability and neurodegeneration in all diagnostic categories of MS (ie, progressive forms of the disease such as PPMS and SPMS, as well as progression in RRMS) (15). Even the most recent high efficacy DMTs act mainly on adaptive immunity in the periphery with only modest or temporary ability to slow neuroinflammatory and neurodegenerative processes and stop disease progression (10, 11). Therefore, development of MS treatments with new modes of action is of interest.

Beyond the existing strategy to modulate cellular elements of adaptive immunity, there is mounting evidence that innate immunity, mediated by cells of a myeloid lineage (eg, bone marrow-derived monocytes, macrophages, and CNS resident microglial cells), is responsible for many of the neurodegenerative aspects of MS that persist in spite of the effectiveness of approved DMTs in preventing acute relapses (11, 15). Modulation of innate immunity has the potential to curtail such neuroinflammation and other manifestations of disease progression that remain unaddressed by current, approved therapies.

SAR443820 has demonstrated strong RIPK1 inhibition with high potency in vitro in various cell types and has been investigated in 4 clinical trials. Overall, in 100 healthy participants, doses

ranging from 10 mg to 40 mg daily and 15 to 20 mg BID were safe and well tolerated. The FIH SAD (Study TDU16519) and MAD (Study TDR16520) studies showed a good tolerability and PK profile ($t_{1/2}$ of 7 to 9 hours and t_{max} of 1 to 2 hours), strong target engagement relative to the RIPK1 inhibition evidenced at the peripheral level, and good penetration of SAR443820 in CSF. A preliminary PK-PD model has been developed using PD data [redacted] from the SAD and MAD. Typical I_{max} and IC_{50} values were [redacted]% and [redacted] ng/mL, respectively, confirming the[redacted] efficacy and potency of SAR443820 on pRIPK1 inhibition. Study BDR16957 evaluated the relative bioavailability between tablet and capsule formulations in Part 1 and showed [redacted] of the SAR443820 formulation, and in Part 2,[redacted] of SAR443820 administered in fasted or fed (high-fat meal) conditions were observed. Study PKM17247 assessed safety and PK in East Asian healthy participants (Chinese and Japanese cohorts). [redacted]. Refer to the SAR443820 Investigator's Brochure (IB) for detailed descriptions of the chemistry, pharmacology, efficacy, and safety of SAR443820.

2.3 BENEFIT/RISK ASSESSMENT

2.3.1 Risk assessment

Table 1 - Risk assessment (identified risk of clinical significance)

Identified risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Drug induced liver injury (DILI)	During clinical trials with SAR443820, mild-severe ALT increases have been reported, including 2 SUSARs with total bilirubin increase >2 ULN (DILI) reported in the ALS patients. These events often involved patients who were also taking concomitant medications that are known to induce liver function abnormalities, or who had concomitant diseases that could also affect ALT level. A lower percentage of ALT increases greater than 3xULN have been reported in the ongoing phase 2 MS study (ACT16753)	Hepatic impairment will be considered by excluding participants with moderate to severe hepatic impairment (see item 5 of Section 2.3.3). All participants are requested to undergo biweekly liver chemistry monitoring from D1 through Week 24, then monthly liver chemistry monitoring from Week 28 through Week 48. In Part B all participants are requested to undergo biweekly liver chemistry monitoring from Week 50 through Week 72, and then monthly liver chemistry monitoring through Week 96. Participants will be discontinued from the study based on ALT levels. Detailed instructions to be followed in case of the occurrence of an AESI of ALT increase >3 ULN are described in Appendix 6 in this protocol, and cover ALT monitoring, IMP administration, etiology assessment and IMP rechallenge

Abbreviations: ALT = alanine transaminase; DILI = drug induced liver injury; IMP = investigational medicinal product.

Table 2 - Risk assessment (potential risk of clinical significance)

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s)		
Convulsion/seizures	Convulsions are considered a potential risk based on nonclinical findings in single-dose, 10 and 28-day nonhuman primate toxicity studies and in a 6-month rat study. In nonhuman primate studies, convulsions/tremors were observed at 75 mg/kg in the single-dose study, at 100 mg/kg/day in the 10-day study, and at 60 mg/kg/day in the 28-day study. No convulsions were observed in the 3 or 9-month monkey studies at dose levels up to [redacted] mg/kg/day (the highest dose tested in these studies). In an in vivo genetic toxicity study in rats, convulsions were observed after a single dose of 500 mg/kg and above/. In the 6- and 9-month studies in rats, convulsions were noted at 400 mg/kg/day (males) and 200 mg/kg/day (females). Convulsions and other findings that necessitated euthanasia were also observed in a single female rat receiving 50 mg/kg/day.	Based on the uncertainty in the interspecies translatability of convulsive risk, a conservative safety approach to limit human exposure (ie, C_{max} and AUC) was taken regarding the selected dose of 20 mg QD, which maintained a minimum of a [redacted] to the NOAEL exposure (C_{max} and AUC) in the 6-month toxicology study in rat and 9-month toxicology study in nonhuman primate. Excluding participants in whom exposure may be increased (participants weighing <45 kg, or participant with moderate or severe hepatic impairment). Moreover, to mitigate risk, participants with a history of noninfantile seizure will not be eligible to participate in this study. Additionally, concomitant medications that may increase the risk of seizure or increase exposure (moderate or strong cytochrome P450 [CYP]3A4 inhibitors or strong inducers of CYP3A4) are not allowed in the study. Convulsion will be considered an AESI.
Immunomodulatory effects	Findings consistent with immune system modulation were observed with SAR443820 in the 3- and 9-month nonhuman primate studies. These pathological findings included mononuclear cell infiltrates in various tissues and changes in lymphoid tissues (increased/decreased cellularity and/or increased germinal centers). None of these microscopic findings for SAR443820 were considered adverse based on incidence, severity, and/or recoverability, as well as the lack of clinical pathology correlates or relevant clinical observations.	Frequent monitoring via hematology tests, physical examinations (eg, skin, lymph nodes), and occurrence of infection TEAEs is planned. Serious infection will be considered an AESI.
Off target potential risks		
Thrombocytopenia Anemia	Related to other similar compounds, and to a potential bone marrow effect	Regular CBC assessments will be performed.
Skin reaction		Clinical examination will be performed.
Study procedures		
Blood drawing	Pain or other discomfort from collection of blood samples	Minimize the frequency and amount of blood drawing.

Abbreviations: AESI = adverse event of special interest; ALT = alanine aminotransferase; AUC = area under the curve; CBC = complete blood count; C_{max} = maximum plasma concentration; NOAEL = no-observable-adverse-effect level; Pop PK = population pharmacokinetic; QD: once daily; TEAEs = treatment-emergent adverse events

2.3.2 Benefit assessment

SAR443820 is anticipated to demonstrate efficacy across multiple parameters of MS (disability progression in particular). Based on the mechanism and CNS penetrance of SAR443820, its potential to interfere with early and ongoing central inflammation that leads to activation of microglia, which is responsible in part for neurodegeneration, may confer protection from clinical sequelae and physical improvement. These benefits may further translate into cognitive stabilization and overall amelioration of quality of life.

2.3.3 Overall benefit/risk conclusion

In the completed FIH studies, SAR443820 was safe and well-tolerated up to the highest doses administered, ie, a single dose of [redacted] mg and 14-day dose of 20 mg BID in healthy volunteers who received SAR443820 as of November 2021. Neither convulsions, immunomodulatory effects, thrombocytopenia, anemia, skin reactions, nor infections were observed. In addition, a preliminary physiologically based pharmacokinetic (PBPK) model indicates that at the dose of 20 mg QD, [redacted](RIPK1 auto-phosphorylation inhibition test [pSer166-RIPK1] in peripheral blood mononuclear cell [PBMC] lysates) during the dosing interval. Convulsions believed to be SAR443820 related have been observed in [redacted] at similar SAR443820 levels in plasma. The risk of convulsion will be mitigated through the following:

1. limiting the dose chosen in this study with maximum plasma concentration (C_{max}) and area under the curve (AUC) that are [redacted] at the no-observed–adverse-effect level (NOAEL) in the [redacted] studies;
2. excluding participants with a history of seizures;
3. excluding concomitant medications that may increase the risk of seizures;
4. excluding concomitant medications that may increase exposure (moderate or strong CYP3A4 inhibitors);
5. excluding participants with moderate or severe hepatic impairment and with body weight <45 kg.

In the ongoing study ACT16970, a limited number of cases meeting criteria for severe DILI have been reported. ALT and bilirubin levels fully recovered in these cases after stopping the IMP and riluzole. These blinded data suggest that DILI is an identified risk of SAR443820, in particular when used in combination with hepatotoxic concomitant medications. The exact mechanism is not known. In nonclinical studies in rats and monkeys, non-adverse microscopic changes were noted in the liver without ALT increases. In Phase 1 studies, there were three mild (<3 ULN) asymptomatic cases of ALT increase (all recovered). Risk minimization measures during the study include limitation of alcohol consumption, although a relationship with alcohol use has not been established.

In addition, frequent monitoring of safety through hematology and liver chemistry tests, physical examination (eg, skin, lymph nodes), and occurrence of infections, will be implemented in both Parts A and B.

Participants in this study will be permitted to continue their current stable dose of DMT (see Section 5), except for those explicitly prohibited in the exclusion criteria. SAR443820 is a centrally acting RIPK1 inhibitor that is poised to reduce MS disease processes in the central nervous system and to complement the relapse-reducing effects of peripherally acting DMT's. The primary endpoint of neurofilament levels measures the impact of SAR443820 on reducing neuronal damage, which is expected to occur over the 12-month treatment duration. It is critical that the trial does not deprive MS patients from taking stable dosages of selected safe and effective DMT's that are expected to control relapses during the trial duration.

Combining a centrally acting RIPK1 inhibitor such as SAR443820, with well-established MS therapies believed to act through separate, peripheral, immune mechanisms argues for potential added beneficial effects on disease processes in the central nervous system while limiting the risk of relapses. When considering risks associated with addition of SAR443820 on top of the allowed background DMTs, several safeguards were put in place to avoid risks related to overlap in mechanism of action, potential additive adverse effects between SAR443820 with MS concomitant medications, and PK drug-drug interactions. Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with SAR443820 are justified by the anticipated benefits that may be afforded to participants with MS.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 2 - Objectives and endpoints

Part A

Objectives	Endpoints
Primary	
• To assess the effect of SAR443820 compared to placebo on sNfL	• Week 48 sNfL levels relative to baseline
Secondary	
• To evaluate efficacy of SAR443820 compared to placebo on imaging and clinical endpoints	• Cumulative number of new gadolinium (Gd)-enhancing T1 hyperintense lesions as detected by MRI at Week 48, defined as the sum of the individual number of new Gd-enhancing T1 hyperintense lesions at all scheduled visits starting after baseline up to and including the Week 48 visit • Cumulative number of new and/or enlarging T2 hyperintense lesions as detected by MRI, at Week 48, defined as the sum of the individual number of new and/or enlarging T2 lesions at all scheduled visits starting after baseline up to and including the Week 48 visit • Time to onset of 12 weeks confirmed disability progression (CDP) from baseline as assessed by the Expanded Disability Status Scale (EDSS) score • Time to onset of sustained 20% increase in 9-Hole Peg Test (9-HPT) confirmed over at least 12 weeks • Time to onset of sustained 20% increase in timed 25-foot walk test (T25-FW) confirmed over at least 12 weeks • Change from baseline in EDSS-Plus at Week 48 • Annualized relapse rate (ARR) of RMS population (relapsing SPMS and RRMS) up to Week 48
• To explore effect of SAR443820 compared to placebo on brain volume and chronic lesions	• Percent change from baseline in brain volume loss (BVL) as detected by brain MRI at 48 weeks • Change from baseline in the volume, number, and intensity (T1) of slowly expanding lesions (SELs), and normalized T1 intensity in lesions at Weeks 12, 24, 36, and 48 • Change from baseline in the total number and volume of non-enhancing lesions volume at Weeks 12, 24, 36, and 48 • Change from baseline in the number of phase rim lesions (PRL) at Weeks 12, 24, 36, and 48; will be conducted at 3T capable sites
• To assess the safety and tolerability of SAR443820	• Incidence of AE, SAE, TEAE, PCSA in laboratory tests
• To assess pharmacokinetic (PK) of SAR443820	• Plasma concentration of SAR443820

Objectives	Endpoints
Tertiary	
• To assess the effect of SAR443820 compared to placebo on sNfL in subpopulations of multiple sclerosis (MS)	• Change from baseline in sNfL level in MS subpopulations (RRMS, SPMS, PPMS) over 48 weeks
• To assess the effect of SAR443820 compared to placebo on biomarkers of neurodegeneration, inflammation, and disease progression	• Change from baseline compared to Week 48 in: plasma chitinase-3-like protein 1 (CHI3L1), serum glial fibrillary acidic protein (sGFAP), interleukin-1B (IL1B), IL6, IL8, Chemokine (C-C motif) ligands 3 (CCL3), and Chemokine (C-C motif) ligands 4 (CCL4)
• To assess efficacy of SAR443820 compared to placebo on patient-reported outcomes (PROs) assessing the physical and psychological impact of MS from the patient's perspective (MSIS-29v2) and the impact of MS on the individual's walking ability (MSWS-12)	• Change from baseline in MSIS-29v2 physical and psychological domains scoring at Week 12, 24, 36, and 48 • Change from baseline in MSWS-12 at Week 12, 24, 36, and 48

Part B

Objectives	Endpoints
Primary	
• To assess long-term trends in durability of sNfL	• Week 96 sNfL levels relative to baseline
Secondary	
• To explore the effect of SAR443820 on brain volume and chronic lesions	• Percent change from baseline in BVL as detected by brain MRI at Week 96 • Change from baseline in volume, number and intensity (T1) in SEL and normalized T1 intensity in lesions to Week 96 • Change from baseline in the total number and volume of non-enhancing lesions Week 96 • Change from baseline in the number of PRLs (same participants/centers from Part A with 3T capability) at Week 96
• To assess the long-term safety and tolerability of SAR443820	• Incidence of AE, SAE, TEAE, PCSA in laboratory tests, ECG, and vital signs during through Week 96
• To evaluate long-term effect of SAR443820 on disease progression and activity assessed by other clinical and imaging measures on physical function and patient-reported outcomes (PROs)	• Cumulative number of new Gd-enhancing lesions as detected by T1-weighted MRI between 48 and 96 weeks; number of new or enlarging T2-hyperintense lesions on MRI at Week 96 relative to Week 48 • Annualized relapse rate (ARR) of RMS population (relapsing SPMS and RRMS) up to Week 96 • Time to onset of composite CDP (CCDP), confirmed over at least 12 weeks (3-month CCDP), by the EDSS Plus composite (EDSS score increase, OR 20% increase in the T25-FW test, OR 20% increase in the 9-HPT) • Time to onset of 12 weeks CDP as assessed by the EDSS score

Objectives	Endpoints
	• Time to onset of sustained 20% increase in 9-HPT confirmed over at least 12 weeks • Time to onset of sustained 20% increase T25-FW test confirmed over at least 12 weeks • Change from baseline in EDSS Plus at Week 96 • Change in MSIS-29v2 physical and psychological domains scoring from baseline through Week 96 • Change in MSWS-12 from baseline through Week 96

For China, please see Section 10.8.1 for details.

The primary estimand defined for the primary efficacy endpoint is summarized in Table 3 below. The comparison of interest will be the comparison of SAR443820 versus placebo. More details are provided in Section 9.2.

Table 3 - Summary of primary estimand

Endpoint	Estimands			
Category	**Endpoint**	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (analysis and missing data handling)**
Primary objective: to assess the effect of SAR443820 compared to placebo on serum neurofilaments				
Primary endpoint	sNfL levels at Week 48 relative to baseline	mITT	Had IMP not been discontinued (hypothetical strategy), had baseline DMT not been permanently modified (hypothetical strategy)	Geometric means ratio (GMR) between interventions from the mixed effect model with repeated measures (MMRM) on log-transformed data. Missing data will be handled by MMRM under the missing at random (MAR) assumption

Abbreviations: ANCOVA = analysis of covariance; DMT = disease modifying therapy; IMP = investigational medicinal product; mITT = modified intent-to-treat; sNfL = serum neurofilament light chain

3.1 APPROPRIATENESS OF MEASUREMENTS

3.1.1 Measurements for efficacy assessment

A hallmark feature of MS that correlates highly with disability is axonal damage and loss, which has been associated with brain atrophy, the ultimate diagnostic evidence of disease progression and plays a key role in long-term disability (8, 9). This axonal damage manifests in CSF, plasma and serum in the form of neurofilaments (heavy and light chain) that are lost as part of the neurodegenerative process in a range of neurological diseases (10). In some cases of progressive MS, elevated neurofilament has been reported as the only evidence of disease (16). Neurofilament light chain levels have been demonstrated in studies to be predictive of disease course and are responsive to DMTs in MS (11); therefore, serum neurofilament is chosen as the primary endpoint in this trial.

Measurement of delay of disability progression is an important clinical endpoint and is endorsed by regulatory guidance (17). The EDSS is widely used to measure neurological disability in clinical trials and routine settings (18). Due to the known fluctuation in EDSS scores, CDP confirmed after 12 and 24 weeks is used as an endpoint in clinical trials of progressive MS (19, 20).

Due to the limited sensitivity of the EDSS to changes in upper limb function and early gait symptoms, the timed 25-foot walk test (T25-FW) test and the 9-hole peg test (9-HPT were added to the EDSS, making a composite endpoint, the EDSS-Plus (13). The EDSS-Plus is used as a secondary endpoint to attempt a more sensitive measurement for efficacy evaluation.

MRI markers of inflammatory activity in the brain observed in previous clinical trials of progressive MS (19, 20) and RMS will be measured. The number of new Gd-enhancing T1 hyperintense lesions will be used as a secondary endpoint, as accumulation of Gd contrast agent in brain tissue is related to inflammatory activity in MS patients. Also, the number of new T2-hyperintense lesions and change in their volume are included as secondary endpoints, as they reliably reflect accumulating MS lesion load over time. Additional MRI measurements include change in brain volume, slowly expanding/evolving lesions, and phase rim lesions, which are considered to be markers of the CNS degenerative process and are therefore assessed to inform on SAR443820's effect on disease progression.

Clinical relapse is the main clinical expression of RMS that constitutes up to 50% of this study population and will therefore be assessed due to its clinical importance and in an attempt to collect additional efficacy data. Although all enrolled RMS participants will be expected to be stable on their DMTs, MS relapses may occur. Thus, relapse data will be carefully collected and their impact on the primary endpoint will be assessed.

Clinical outcome assessments are considered important for understanding the impact of treatment on function and wellbeing (21). In both progressive and relapsing MS, the increasing limitation and loss of physical function are prevalent and among the most debilitating signs and symptoms of the disease (22). Physical function limitations are associated with decrements in quality of life due to diminishing productivity and ability to perform daily activities, maintain employment, and maintain social roles and emotional wellbeing. Reduction of disease impact on patient-reported physical function is therefore important to assess in addition to the clinician assessment and constitutes a direct measure of treatment effectiveness, ie, whether a treatment influences how a participant feels or functions (23).

3.1.2 Pharmacokinetic assessments

Whole blood samples will be collected for measurement of the plasma concentration of SAR443820 as specified in the SoA.

3.1.3 Pharmacodynamic assessments

Blood samples will also be collected to measure changes in markers of neuroinflammation, plasma CHI3L1, and cytokines and chemokines including IL1β, IL6, IL8, TNFα, CCL3, and CCL4. Additionally, serum glial fibrillary acidic protein (GFAP) will be collected from serum as

a potential marker of risk of relapse, treatment response and risk of disability progression (Note: serum GFAP will not be collected from participants in China).

3.1.4 Safety and tolerability assessment

Adverse events, SAEs, treatment emergent adverse events (TEAEs), adverse events of special interest (AESI), electrocardiogram (ECG) measurements, vital signs, C-SSRS scores, and laboratory test analyses will be reported.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Study ACT16753 is a Phase 2, randomized, double-blind placebo-controlled 2 parallel-arm study followed by an open-label, long-term extension period.

The study consists of 2 parts (A and B) as follows:

Part A is a 48-week, double-blind, placebo-controlled part, preceded by a screening period of up to 4 weeks before Day 1.

- The screening period will be up to 4 weeks and is designed to evaluate suitability for participation in the study in terms of MS diagnosis, clinical status based on EDSS, and safety screening evaluations. No IMP will be administered in this period.
- The double-blind treatment period will have a total duration of 48 weeks for each participant and will include the following:
  - Participants will be randomized at 1:1 ratio to receive SAR443820 20 mg QD (n = 84) or matching placebo QD (n = 84).
  - Randomization will be stratified by MS clinical subtypes (ie, RRMS, SPMS, or PPMS) in order to ensure a balance between the treatment and placebo arms within each MS clinical subtype. Participants will attend in-clinic study assessments at baseline (Day 1) and Weeks 2, 4, 6, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 28, 32, 40, 44 and 48 (Weeks 4, 8, 9, 10, 14, 16, 18, 20, 22, 28, 32, 40, and 44 visits for liver chemistry only may be conducted at local labs and via home health nursing where available).

All participants who successfully completed Part A will rollover to Part B. Participants who discontinue the treatment or choose not to enter Part B will have their early discontinuation or safety follow-up visit, respectively, up to 2 weeks after the last dose of IMP.

Part B is an open-label, long-term extension of Part A. Part B starts from the end of Part A (Week 48) and continues up to Week 96.

- The assignment of participants to study intervention in Part A will remain double-blinded during Part B unless there is medical need to unblind the study intervention assignment.
- All participants will receive 20 mg QD SAR443820 in Part B.
- Participants will attend in-clinic study assessments at Weeks 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 76, 80, 84, 88, 92 and 96 (and Week 48 which is the last visit of Part A and first visit of Part B; Weeks 50, 54, 56, 58, 60, 62, 64, 66, 68, 70, 76, 80, 84, 88, and 92 visits for liver chemistry only may be conducted at local labs and via home health nursing where available).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a Phase 2 proof-of-concept study for which a double-blind, randomized, placebo-controlled design has been selected to minimize possible biases in the study outcome.

Male and female participants with a diagnosis of RRMS, SPMS or PPMS between 18 and 60 years inclusive will be selected for this study. The age range is limited to participants ≤60 years to increase the probability of response to treatment and reduce potential confounding from age-related neurofilament elevations. Participants enrolled in this study will be under stable conditions (absence of clinical relapse in the 8 weeks prior to screening) to capture the effect of treatment on chronic neuroaxonal damage reflected in sNfL levels, particularly because the mechanism of SAR443820 modifies disease pathology, rather than symptomology.

Part A of this study is a randomized double-blind, placebo-controlled design, while Part B is an open-label long-term extension during which neurofilament, imaging, clinical and safety data will be collected to characterize the long-term treatment effects of SAR443820.

4.3 JUSTIFICATION FOR DOSE

The dose of 20 mg QD SAR443820 is selected for this Phase 2 study to achieve the best potential treatment effectiveness in participants with MS and has previously demonstrated strong target engagement and was well tolerated in healthy participants.

Overall, in the FIH study, SAR443820 up to a highest single dose of [redacted] mg and 14-day dose of SAR443820 20 mg BID, was found to be safe and well tolerated. In the Phase 1a SAD study, there were no SAEs. All the TEAEs were of mild to moderate intensity except 1 severe TEAE (blood creatine phosphokinase [CPK] increase of Grade 3) reported in the placebo group. [redacted] In the MAD study, no SAEs were reported. All the AEs reported in the MAD study were of mild to moderate intensity. At 20 mg QD, the mean observed C_{max} and AUC_{0-24} at steady state are [redacted] µM and [redacted] µM*hour, respectively based on MAD study that are [redacted]-fold lower, respectively, than the exposure at NOAEL in the 6-month rat toxicology study.

The dose of 20 mg QD SAR443820 is estimated to provide a high level of target engagement required for obtaining a clinical effect. Internal preclinical data in animal models suggest that SAR443820 [redacted] (concentration enabling a [redacted]% decrease of the pS166-RIPK measurement compared to that at baseline) [redacted] activity. A preliminary PK-PD model has been developed using PD data (pS166-RIPK measurement in human PBMCs) from SAD and MAD studies and indicates high efficacy [redacted] and potency [redacted]) of SAR443820 on pRIPK1 inhibition. Good penetration of SAR443820 in CSF has been observed in human with mean values of the CSF/unbound plasma ratio close to 1.0. A preliminary PBPK model indicates that at a dose of 20 mg QD, [redacted]

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled assessment and/or procedure shown in the schedule of activities (SoA) for the last participant in the study globally.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be 18 to 60 years (inclusive) of age, at the time of signing the informed consent.

Type of participant and disease characteristics

I 01. Participants with a diagnosis of RRMS, SPMS (relapsing or non-relapsing), or primary progressive subtype according to the 2017 revision of the McDonald diagnostic criteria (SPMS diagnostic criteria according to [13] include an initial relapsing remitting disease course followed by progression with or without occasional relapses, minor remissions, and plateaus; progression denotes the continuous worsening of neurological impairment over at least 6 months).

I 02. Participants with an Expanded Disability Status Scale score of 2-6 inclusive at screening.

I 03. Participants who are either untreated or in the opinion of the Investigator are stable on an allowed DMT (interferons, glatiramer acetate, fumarates, or teriflunomide) for at least the past 3 months, AND not anticipated to require a change in MS treatment for the duration of Part A and Part B (through Week 96); in Part B changes in dose of allowed DMTs or transition to other allowed DMTs is permitted).

Weight

I 04. Participants with body weight ≥45 kg and body mass index (BMI) ≥18.0 kg/m^2.

Sex, contraceptive/barrier method, and pregnancy testing requirements

I 05. All

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants
   - Male participants are eligible to participate if they agree to the following during the study period and for at least 92 days following their last dose of IMP:
   - Refrain from donating or cryopreserving sperm

   Plus, either:
   - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier (male condom) as detailed below:

  A male condom and an additional highly contraceptive method as described in Section 10.4.2 when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant

b) Female participants

Female participants are eligible to participate if they are not pregnant or breastfeeding and 1 of the following conditions applies:

- Are a woman of nonchildbearing potential (WONCBP) as defined in Section 10.4.1.

  OR

- Are a WOCBP and agree to use a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Section 10.4.2 during the study intervention period (to be effective before starting the study intervention) and for at least 32 days after the last administration of the IMP, and agree not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.
- WOCBP must have a negative highly sensitive pregnancy test within 24 hours before the first administration of the study intervention, see Section 8.2.6.
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Informed consent

I 06. Participants are capable of giving signed informed consent as described in Appendix 1 (Section 10.1) of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Participants with immunodeficiency syndromes or other autoimmune diseases requiring immunosuppressive therapy.

E 02. Participants with a history of seizures or epilepsy (history of febrile seizure during childhood is allowed).

E 03. Participants with known clinical relapse (acute or subacute episodes of new or increasing neurological dysfunction followed by full or partial recovery, in absence of fever or infection) within 8 weeks of screening (1).

E 04. Participants with a neurological disease history other than MS, eg, head trauma within 3 months, cerebrovascular disease, and vascular dementia.

E 05. Participants with a history of recent serious infection (eg, pneumonia, septicemia) within 4 weeks of screening; an infection requiring hospitalization or intravenous antibiotics, antivirals, or antifungals within 4 weeks of screening; or chronic bacterial infections (such as tuberculosis) deemed unacceptable, as per Investigator's judgment.

E 06. Participants who have significant cognitive impairment, psychiatric disease, other neurodegenerative disorders (eg, Parkinson disease or Alzheimer disease), substance abuse (including a history of alcohol abuse), or any other conditions that would make the participants unsuitable for participating in the study or could interfere with assessment or completing the study in the opinion of the Investigator.

E 07. Participants with a documented history of attempted suicide over the 24 weeks prior to the Screening Visit, presents with suicidal ideation of category 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS), or if in the Investigator's judgment, the participant is at risk for a suicide attempt.

E 08. Participants with a history of unstable or severe cardiac, pulmonary, oncological, hepatic, or renal disease or another medically significant illness other than MS precluding their safe participation in this study.

E 09. Participants who received a live vaccine within 14 days before the Screening Visit.

E 10. Participants with a known history of allergy to any ingredients of SAR443820 (mannitol, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, and microcrystalline cellulose).

Prior/concomitant therapy

E 11. Participants with a current use of any medications that are moderate or strong inhibitors or strong inducers of CYP3A4 (see Appendix 10 [Section 10.10]).

E 12. Participants with a current use of any of the following medications/treatments: fampridine/dalfampridine, ofatumumab, fingolimod, cladribine, siponimod, ponesimod, ozanimod, alemtuzumab, mitoxantrone, ocrelizumab, natalizumab, or similar approved compounds but with different trade names and any unapproved treatments or therapies for MS; any DMTs newly approved after January 2023 that are marketed at any time during the course of the double-blind study period. These medications are not allowed within 5 half-lives before the Screening Visit and for the duration of Part A and Part B.

If the participant has received any of the prohibited medications/treatments, washout will be required according to the table below (no washout is required for permitted medications):

Medication	Exclusionary if used/used within required wash out period
Systemic corticosteroids, adrenocorticotropic hormone	4 weeks prior to the baseline MRI scan
Plasmapheresis, fingolimod, and natalizumab (participants who have discontinued natalizumab in the 24 weeks prior to randomization should be evaluated to rule out PML)	8 weeks prior to randomization
B cell depleting therapies such as ocrelizumab and rituximab	24 weeks prior to randomization or until the return of B cell counts to normal levels, whichever is longer
Alemtuzumab	4 years prior to randomization
Other prohibited MS DMT	5 half-lives or until the end of pharmacodynamics activity, whichever is longer

Abbreviations: DMT = disease-modifying therapy; MRI = magnetic resonance imaging; MS = multiple sclerosis; PML = progressive multifocal leukoencephalopathy

Prior/concurrent clinical study experience

E 13. Participants who have prior/concurrent clinical study enrollment, ie, the participant has taken other investigational drugs within 4 weeks or 5 half-lives, whichever is longer, before the first Screening Visit; concurrent or recent participation in non-interventional studies may be permitted.

Diagnostic assessments

E 14. Participants with a positive human immunodeficiency virus (HIV) antibody test.

E 15. Participants with abnormal laboratory test(s) at the Screening Visit:
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3.0 × upper limit of normal (ULN)
- Bilirubin >1.5 × ULN; unless the participant has documented Gilbert syndrome (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
- Serum albumin <3.5 g/dL
- Estimated glomerular filtration rate <60 mL/min/1.73 m^2 (Modification of Diet in Renal Disease [MDRD])
- Other abnormal laboratory values or electrocardiogram (ECG) changes that are deemed clinically significant as per Investigator's judgment

E 16. Participants with presence of hepatitis B surface antigen (HBsAg) or anti-hepatitis B core antibodies (HBcAb) at the Screening Visit or within 12 weeks prior to the first dose of study intervention. Serologies consistent with a resolved infection or vaccination, such as the presence of HBsAb, may not exclude potential participants from the trial.

E 17. Participants with positive hepatitis C antibody test result at screening or within 12 weeks prior to starting study intervention. NOTE: participants with a positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C ribonucleic acid (RNA) test is obtained.

E 18. Participants with a contraindication for MRI, ie, presence of a pacemaker, metallic implants in high-risk areas (ie, artificial heart valves, aneurysm/vessel clips), presence of metallic material (eg, shrapnel) in high-risk areas, known history of allergy to gadolinium, or history of claustrophobia that would prevent completion of all protocol-scheduled MRI.

Note: People with a contraindication to Gd can be enrolled into the study but cannot receive Gd contrast dyes during their MRI scan.

Other exclusions

E 19. Participants who are accommodated in an institution because of a regulatory or legal order; prisoners or participants who are legally institutionalized.

E 20. Participant who are not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 21. Participants who are employees of the clinical study site or other individuals directly involved in the conduct of the study or are immediate family members of such individuals (in conjunction with Section 1.61 of the International Council for Harmonisation of Good Clinical Practice (ICH-GCP) Ordinance E6).

E 22. Participants with any specific situation during study implementation/course that may raise ethics considerations.

E 23. Participants with sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

E 24. Participant is under tutorship or curatorship; participant under safeguard of justice or deprived of his/her liberty by a court decision.

E 25. Participant is unable to provide informed consent.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

SAR443820 can be administered without regards to meal. Participants should refrain from consuming grapefruit or grapefruit juice (including pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices) from 5 days before the start of the study intervention until 2 days after the final dose.

5.3.2 Caffeine, alcohol, and tobacco

The information of participant's regular use of alcohol and tobacco should be recorded in the electronic case report form (eCRF). During the entire study, participants should be warned not to

consume substantial quantities of alcohol, defined as >14 grams (1 standard drink) per day in female participants or >28 grams (2 standard drinks) per day in male participants on a regular basis.

5.3.3 Activity

No special restrictions.

5.4 SCREEN FAILURES

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreening is allowed for participants who fail the initial screening at the Investigator's medical judgment for any manageable reasons that caused the initial screening failure. Participants who fail the initial screening may be rescreened up to 2 times during the study recruitment period. Rescreened participants should be assigned a new identification number and sign a new consent form for every rescreening event.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol-mandated procedures, contingency measures are proposed in Appendix 9 (Section 10.9).

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 4 - Study intervention(s) administered

Intervention label	SAR443820	Placebo
Intervention name	SAR443820	Placebo
Intervention description	Tablet	Tablet
Type	Drug	Drug
Dose formulation	Tablet	Tablet
Unit dose strength(s)	20 mg tablet	0 mg tablet
Dosage level(s)	20 mg once daily	once daily
Route of administration	Oral	Oral
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Packaging and labeling	Study intervention will be provided in wallet blister packaging. Each wallet blister packaging will be labeled as required per country requirement.	Study intervention will be provided in wallet blister packaging. Each wallet blister packaging will be labeled as required per country requirement.
Current name	SAR443820	Not Applicable

Abbreviations: IMP = investigational medicinal product; NIMP = non-investigational product

SAR443820 or matching placebo tablets are to be taken once daily. The IMP tablet will be taken orally with water. The IMP should be taken around the same time each day under the same condition (with or without food) throughout the study unless adjustment is specifically requested due to PK sampling at the Day 1, Weeks 2, 6, 12, and 36 site visits.

SAR443820 or placebo may be supplied at the site or from the PI/site/Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9 (Section 10.9).

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and that any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

SAR443820 and placebo tablets require no preparation and will be supplied to the study participants in labeled child-resistant wallets.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.10).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for direct-to-patient [DTP] shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

- The study will be performed in a double-blind fashion for Part A. The placebo tablet will be identical to the SAR443820 tablet in appearance, quantity, taste, odor, and packaging.
- All participants will be centrally assigned to a randomized study intervention using an interactive response technology (IRT). Before the study is initiated, the login information and directions for the interactive web response system (IWRS) will be provided to each site. The study intervention will be dispensed at the study visits summarized in the SoA. Returned IMP should not be redispensed to participants.
- A randomized participant is defined as a participant from the screened population who has been allocated to a randomized intervention regardless of whether the intervention was received or not. A participant cannot be randomized more than once in the study.
- The randomization will be stratified by MS clinical subtypes (ie, RRMS, SPMS, or PPMS).

- Due to the open-label extension period, a participant assigned to a specific arm at randomization may be allocated, by the IRT, to several (varying) intervention numbers (and corresponding intervention kit numbers) for multiple visits despite having the same intervention arm assignment from randomization. That is, in these cases, the intervention/kit number varies but the arm assignment at randomization does not change.
- The Investigator, site staff, Sponsor monitoring team, and participants will remain blinded to the treatment assignment in Part A until the end of Part B. The Sponsor study team, except Sponsor monitors, will be unblinded after database lock of Part A.
- The bioanalyst and the pharmacokineticist responsible for sample analysis and PK evaluation will be unblinded. However, they will agree not to disclose the randomization schedule or the individual unblinded analytical results before the official opening of the randomization schedule. Preliminary PK data, if needed and available during the study, will refer to means with descriptive statistics, and individual data will not be associated with any individual randomization numbers or participant numbers.
- This is a double-blind study in which participants/care providers/ Investigators/ outcomes assessors, etc. are blinded to study intervention. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted (eg, in case of available antidote). Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, he/she may, at his/her discretion, contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.
- For regulatory reporting purposes, and if required by local health authorities, the Sponsor or designee will break the treatment code for all suspected unexpected serious adverse reactions (SUSAR) that are considered by the Investigator or Sponsor to be related to the study intervention.

Methods of blinding

Unless specified otherwise, the baseline brain MRI scan will be used as the reference to assess all MRI-derived endpoints. Standardized endpoint evaluation is assured by central review of brain MRI scans. A blinded MRI central review will be performed for all MRI-derived endpoints. All MRI reviewers will be blinded to treatment assignments and to other participant data. Details on MRI scanning and central review will be described in the central MRI Acquisition and Procedures manual. In addition, in accordance with standard clinical practice, during the blinded intervention period, the Treating Investigator can access MRI reports once a year starting at Month 12, or before if clinically required, through the local radiologist.

A data monitoring committee (DMC) will be used to periodically monitor the safety of this study. Unblinded data will be provided for DMC review by an unblinded independent statistician. Study team members, Investigators, and study participants will not have access to unblinded data.

6.4 STUDY INTERVENTION COMPLIANCE

IMP accountability will be as described below:

- Intervention units are returned by the participant at each visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract)
- The Investigator will count the number of tablets remaining in the returned packs and complete the Intervention Log Form
- The Investigator will record the dosing information on the appropriate page(s) of the case report form (CRF)
- The monitor in charge of the study will then check the CRF data by comparing them with the IMP that he/she has retrieved and intervention log forms

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned tablets during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of SAR443820 or matching placebo dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded.

6.5 DOSE MODIFICATION

Dose modification is not foreseen in this study. The IMP treatment may need to be interrupted or permanently discontinued if deemed necessary due to an AE.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Part B is an open-label long-term extension period up to Week 96 in which all eligible participants from Part A may rollover to Part B and receive open-label IMP. In addition to this open-label extension, poststudy access to study medication could be provided based on local/country regulations.

6.7 TREATMENT OF OVERDOSE

For this study, overdose is defined as at least at least [redacted] mg IMP within 24 hours.

The Sponsor does not recommend a specific treatment for an overdose, and treatment of an overdose will be based on the Investigator's clinical judgment in conjunction with the Sponsor's agreement.

In the event of an overdose, the Investigator should:

- Closely monitor the participant for any AE/SAE and laboratory abnormalities until the IMP can no longer be detected systemically (at least 2 days). Provide supportive and symptomatic treatment as needed.
- Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study intervention.
- Evaluate the participant to determine whether study intervention should be interrupted or whether the dose should be reduced.
- Document appropriately in the CRF.
- Contact the Sponsor immediately.

6.8 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with the following:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency
- The use of any live vaccine is prohibited within 14 days before the Screening Visit and during study duration.

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

The concomitant therapy should be reported to the Investigator and recorded on the Concomitant Medications electronic case report form (eCRF). The reported medications will be reviewed and evaluated by the Investigator or designee to determine whether they affect a participant's eligibility to participate or continue to participate in the study.

Medications for treatment of MS symptoms (eg, walking impairment, fatigue, spasticity, incontinence, pain) should be maintained at a stable dose prior to screening and for the duration of the treatment period (except those per exclusion criterion E 11), if clinically feasible. Allowed concomitant DMTs (ie, interferons, glatiramer acetate, fumarates, and teriflunomide) should be maintained at the pre-enrollment dose. Prohibited medications listed in exclusion criteria may not be exhaustive, and any exceptions (eg, newly marketed DMTs during the course of the study) should be discussed with the Medical Monitor.

Participants must abstain from starting prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Based on in vitro results, SAR443820 is mainly metabolized by CYP3A4. A [redacted] in [redacted] was observed in the presence of [redacted] in a drug-drug interaction study. Based on PBPK modeling, administration of potent CYP3A4 inhibitors are [redacted]. Administration of strong CYP3A4 inducer is predicted to decrease the SAR443820 AUC. Therefore, concomitant medications or substances that are strong or moderate inhibitors or strong inducers of CYP3A4 (Appendix 10, Section 10.10, Table 9) are not allowed within the specific wash out period before the Screening Visit and for the duration of Part A and Part B.

In Part A, any modifications of SOC therapy will result in participant discontinuation from the IMP. This includes stopping, changing the dose of allowed SOC DMTs, or switching to another allowed SOC DMT, or switching to a prohibited DMT (per exclusion criterion E 12). In Part B, changes to dose of allowed DMTs or switching to another allowed DMT will be permitted.

The use of any live vaccine is prohibited within 14 days before the Screening Visit and during study duration.

6.8.1 Rescue medicine

For all participants that experience relapse in the case of MS relapse, rescue treatments are allowed as per local routine practice (eg, high dose intravenous methylprednisolone for 3 to 5 days). Rescue treatments are defined as limited to this prescribed timeframe and medication and does not include transition to new permanent DMTs whether participants are switched to another allowed DMT or any prohibited DMT. Rescue medications must be reported in the eCRF, as for all other concomitant medications. The Investigator should document the discussion with the participant and the decision for rescue treatment in the source documentation.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1).

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

Compliance with and continuation of the study intervention is encouraged, while maintaining the safety of study participants and integrity of the study. In certain instances, it may be medically necessary for a participant to permanently discontinue study intervention.

In case of the events listed below, permanent discontinuation of the IMP is mandatory (this list is not intended to be exclusive):

- The Investigator or Sponsor determines it is in the best interest of the participant.
- Occurrence of AEs or any other medical condition that, in the opinion of the Investigator or Sponsor, may jeopardize the participant's safety or data integrity. These include, but are not limited to, abnormal livers tests and meeting the stopping criteria.
- Noncompliance with the protocol, dosing regimen and visits including switching DMT or taking a prohibited DMT in Part A or Part B.
- Pregnancy of a female participant.
- Occurrence of convulsions.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation after 24 hours before making a decision regarding permanent discontinuation of the IMP for the concerned participant.

Handling of participants after permanent intervention discontinuation

If a participant is withdrawn from study intervention permanently, the Sponsor will be notified within 2 business days and the date and reason(s) for the withdrawal will be documented by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

Participants will be followed up according to the study procedures specified in this protocol up to study completion, or up to recovery or stabilization of any AE to be followed up as specified in this protocol, whichever comes last.

If possible, and after the definitive discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last treatment day with the IMP including a PK sample. Details are provided in the SoA (Section 1.3). All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Liver function stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in Section 10.6 or in the presence of abnormal liver chemistry test results not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

7.1.3 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 9 [Section 10.9]). For all temporary intervention discontinuations, the duration should be recorded by the Investigator in the appropriate pages of the eCRF. Temporary discontinuation of study intervention is defined as stopping study intervention for a minimum of 1 day and a maximum of 2 weeks accumulative in Part A or 8 weeks accumulative in Part B.

7.1.4 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator has considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely, that there are no safety concerns, that the selection criteria for the study are still met (refer to Section 5.1 and Section 5.2), and the criteria for the permanent treatment discontinuation have not been met.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 [Section 10.9].

7.1.4.1 Study intervention restart or rechallenge after discontinuation of study intervention

Do not restart/rechallenge participant with study intervention unless:

- Ethics committee and/or IRB approval is obtained, if required, and based on local practice
- The participant is made aware of the potential risk, and separate consent for intervention restart/rechallenge is signed by the participant
- Sponsor should be notified.

NOTE: If study intervention was interrupted for suspected intervention-induced liver injury, the participant should be informed of the risk of death, liver transplantation, hospitalization, and jaundice and re-consented before resumption of dosing. In case of confirmed drug-induced liver injury caused by the IMP, the rechallenge with the IMP is not permitted and the participants must be permanently discontinued from IMP treatment.

Refer to Appendix 6 (Section 10.6) for details on the restart/rechallenge process.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

For Part A and Part B, if a participant no longer wishes to take the IMP, they will be encouraged to remain in the study or to attend a safety follow-up visit within 2 weeks following discontinuation of IMP.

NOTE: No IMP reconciliation is expected at the “Safety Follow-up” visit.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant’s medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be rerandomized/reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 STUDY LEVEL STOPPING CRITERIA

The study may be stopped if any of the following criteria are met:

- Cancellation of or change in the drug development program per the discretion of the Sponsor
- Emergence of AEs unknown to date or increased frequency and/or severity and/or a duration of known AEs that makes the benefit-risk for study continuation negative
- The results of the interim data review meet no-go criteria as detailed in the Statistical Analysis Plan (SAP)
- Participant enrollment (evaluated after a reasonable amount of time) is unsatisfactory

7.4 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count, urine tests) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- If onsite visits are not feasible (due to disease progression, increased monitoring for AE follow-up, etc.) for visits that require sample collection only (Week 4, Week 9, Week 16, Week 56 or Week 60 visits), remote visits (eg, with home nurses, a home health vendor, etc.) may be planned for sample collection, only if the service is put in place in the country in which the study is being conducted.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

8.1 EFFICACY ASSESSMENTS

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.1.1 Serum neurofilament response

Serum NfL will be collected as part of the blood specimen according to the SoA, with the mean of the screening and Day 1 predose sample levels serving as the baseline value for calculating NfL changes. sNfL samples will serve as the primary endpoint for the duration of the study in Parts A and B.

8.1.2 Expanded Disability Status Score

The Investigator will perform the EDSS assessment and will be trained and certified to perform the EDSS assessment in a consistent manner. Details regarding the interactive test and certification tool for a standardized, quantified neurological examination and assessment of Kurtzke's FS and EDSS in MS will be provided to Investigators. A Level B qualification will be required for this study. Details regarding the interactive test and certification tool for a

standardized, quantified neurological examination and assessment of Kurtzke's FS and EDSS in MS will be provided to Investigators. A Level B qualification will be required for this study.

The EDSS score will be captured using an electronic EDSS tool. Quality control measures will be put in place to ensure scoring error detection and thus minimize the impact of any scoring and calculation errors.

The Investigator will rate FS in the context of a standard neurological examination and will report these ratings as per the EDSS reporting instructions together with information on the participant's mobility, gait, and use of assistive devices. Standard EDSS assessments of 7 functional domains (visual, brainstem, pyramidal [motor], cerebellar [coordination], sensory, cerebral, and bowel/bladder) scoring will be performed by assessing neurological symptoms in each of these domains. Ambulation scoring will be done to conclude the evaluation. The fatigue evaluation may be optionally recorded, but it will not contribute to assignment of the EDSS score. The total EDSS score will be assigned according to the EDSS scoring rules.

A screening EDSS assessment must be completed to confirm eligibility, and the EDSS assessment must be repeated at the Randomization Visit.

The Investigator will be informed if 12 weeks CDP is observed based on the EDSS data reported in the electronic database. Participants will not be informed of their EDSS scores.

8.1.2.1 Confirmed disability progression

Twelve-week and 24-week (3 and 6-month, respectively) CDPs are defined as an increase in EDSS score (defined as an increase of ≥1.0 point from the baseline EDSS score when the baseline score is ≤5.5 or an increase of ≥0.5 points from the baseline EDSS score when the baseline score is >5.5) confirmed after a 12 or 24 week interval, respectively.

An EDSS score increase at CDP onset and confirmation at 12 weeks must be observed by the Investigator during routine quarterly visits. Results of all EDSS assessments obtained during routine or unscheduled visits over a minimum of a 12-week period will serve as the basis for conclusion for the endpoint.

8.1.3 Magnetic resonance imaging

A cranial (brain) MRI scan before and after administering the Gd contrast agent (according to local labeling requirements) will be performed.

- The basic MRI scan will be performed at all sites and will consist of the following sequences: T2- and T1-weighted sequences before and after administering a Gd contrast (if there is no contraindication).
- Basic MRI sequences will be used to evaluate following MRI-related endpoints (see Section 3):
  - change in T2-hyperintense lesion number and volume
  - new and enlarging T2-hyperintense lesion number and volume
  - Gd-enhancing T1-hypointense lesions number
  - brain volume

- SEL number, volume, and intensity (T1)
- Total PRL number

Additional details about the MRI assessments will be provided in the MRI acquisition and procedures manual.

Due to a potential safety risk related to deposition of certain IV Gd contrast agents in the brain, these agents should be used in accordance with local recommendations/regulations (24).

A study MRI acquisition and procedures manual, containing instructions for brain MRI standard image acquisition requirements, MRI acquisition validation, data transfer to the central review center, archiving and shipping, and image approval process, will be provided to all participating sites. Study site personnel will undergo training regarding MRI acquisition and data handling procedures. Training will be documented, and adherence to the manual will be monitored throughout the study with retraining performed as necessary.

Unless specified otherwise, the baseline brain MRI scan will be used as the reference to assess all MRI-derived endpoints. Baseline MRI scans may be conducted as early as 5 to 7 days prior to first dose but must be completed after all other screening activities have been completed, and none are deemed exclusionary. Standardized endpoint evaluation is assured by central review of brain MRI scans. A blinded MRI central review will be performed for all MRI-derived endpoints. All MRI reviewers will be blinded to treatment assignments and to other participant data. Details on MRI scanning and central review will be described in the MRI acquisition and procedures manual.

The MRI scans need to be reviewed by a local radiologist for any non-MS pathology to assure safety reporting as per Section 1. In the event of identification of MRI findings relevant to participant safety, the local radiologist will provide a report to the Investigator. Expected MS findings on MRI scans, not reflecting an acute safety concern for the participant, should not be disclosed to the Treating Investigator or to the site team if not relevant to any safety concern. Any safety concern noted on MRI, whether related to MS or not, shall be provided to the Investigator.

8.1.4 Multiple sclerosis relapse assessment

8.1.4.1 Definition of multiple sclerosis relapse

For the purposes of this study, MS relapse is defined as acute, new neurological symptoms or worsening of previous neurological symptoms with an objective change on neurological examination. Symptoms must be as follows:

1. Be attributable to MS,
2. Last for ≥24 hours,
3. Be present at normal body temperature (ie, no infection, excessive exercise, or excessively high ambient temperature), and
4. Be preceded by ≥30 days of clinical stability (including no previous MS relapse).

Note: An exacerbation or recurrence of symptoms and signs in a participant with MS that can be reasonably attributed to transient impairment of conduction in previously demyelinated pathways due to drugs (such as rarely occurs a few hours after injections of interferon beta), raised core body temperature (the Uhthoff phenomenon), or systemic cytokine release (such as occurs with the administration of alemtuzumab) will not be considered a relapse.

Refer to Section 8.3.7 for details regarding MS relapse reporting.

8.1.4.2 Unscheduled assessment visits

Participants must be instructed to immediately report new neurological symptoms and recurring or worsening of previous symptoms to the Investigator. Any reported symptoms will be collected. If a participant reports symptoms that may be consistent with relapse, an unscheduled assessment visit to the Investigator must be scheduled as soon as possible (whenever possible within 7 days of the onset of the symptoms). The assessment, management, and reporting of MS relapse is made by the Investigator. Diagnosing MS relapses during the study will occur as follows: the Investigator will assess whether the reported episode is consistent with the definition of MS relapse. If it is consistent with the definition of MS relapse or if there is any doubt and the possibility of relapse cannot be ruled out, the standard neurological examination (for the EDSS score) will be performed by the Investigator. If the participant is not referred for EDSS assessment, this will be documented with an explanation of the reason. Whenever possible, the Investigator should perform the EDSS assessment the same day the neurological examination is performed. Subsequent EDSS assessments can still be utilized for confirmation of MS relapses but should be avoided to reduce the risk of changes in participant status between the assessments.

All MS relapses must be reported on the MS relapse eCRF page. Multiple sclerosis relapse should not be reported as an AE unless, in the judgment of the Investigator, it is unusually severe or medically unexpected, or matches the definition of an SAE.

Safety laboratory tests are optional for the unscheduled assessment visit if no intercurrent disease is suspected. If any intercurrent disease is diagnosed, it will be reported as an AE as per the safety reporting rules.

The participant will be also asked to report possible relapse symptoms during scheduled quarterly visits. If relapse is suspected, the above decision-making and reporting rules apply.

8.1.5 Timed 25-foot walk test

As part of the Multiple Sclerosis Functional Composite (MSFC), the T25-FW test is currently the most widely implemented method to objectively quantify gait disability in clinical MS trials. The T25-FW test is developed to quantify changes in gait of MS patients; 1 task is completed, and the amount of time required depends on each patient.

The T25-FW test will be used to assess a participant's walking ability. The participant is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as safely possible with several repetitions (25, 26). The mean walk time will be used for assessment of the participant's walking ability. An increase of >20% from the baseline score in the T25-FW test is considered as meaningful worsening (27). The Examining Investigator/rater will perform this test.

8.1.6 9-Hole Peg Test

The 9-HPT will be used to assess a participant's manual dexterity and fine motor skills. This is a PerfRO tool (performance outcome). A participant will be asked to place pegs into holes and remove them with the dominant and non-dominant hand for several repetitions (26). The mean time to test completion will serve as an assessment of the participant's hand dexterity. An increase of >20% from the baseline score in the 9-HPT is considered meaningful worsening (27). The Examining Investigator/rater will perform this test.

8.1.7 Composite analysis

Data from the clinical assessments described above will be utilized in various composite analyses and endpoints to assess effects of SAR443820 on a range of clinical measures. The following sections provide additional details on these composite scales and related criteria for analyses.

8.1.7.1 EDSS-Plus

Time to onset of composite (CCDP), as assessed by composite endpoint EDSS-Plus (EDSS score, or T25-FW test, or 9-HPT), is to be confirmed over at least 12 and 24 weeks (28). Disability criteria for the individual components are defined as follows:

- Disability progression on the EDSS is defined as an increase of ≥1.0 point from the baseline EDSS score when the baseline score is ≤5.5 or an increase of ≥0.5 points from the baseline EDSS score when the baseline score is >5.5.
- Disability progression on the T25-FW test is defined as an increase (worsening) of ≥20% from the baseline score.
- Disability progression on the 9-HPT is defined as an increase (worsening) of ≥20% from the baseline score.

Refer to Section 8.1.5 and Section 8.1.6 for descriptions of T25-FW and 9-HPT, respectively.

8.1.8 MSIS-29v2

The Multiple Sclerosis Impact Scale with 29 items (MSIS-29v2) evaluates the specific physical and psychological impact of MS from a patient's perspective (29). This patient reported outcome (PRO) instrument has 2 subscales: 1) a physical impact score (20 items) and 2) a psychological impact score (9 items). The physical and psychological impact subscales of the MSIS-29v2 range from 0 to 100, with higher scores indicating greater physical or psychological impact.

8.1.9 MSWS-12

The multiple sclerosis walking scale (MSWS-12) measures the impact of walking impairment in patients with MS. This PRO instrument has 12 items with a global score ranging from 0 to 100. A higher score indicates better quality of life (30).

8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than AE which are presented in Section 1.

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the general appearance, head and neck, abdomen, lymph nodes, cardiovascular system, respiratory system, musculoskeletal system, and skin by the Investigator.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, abdomen (liver, spleen), and lymph nodes by the Investigator.
- The extent of the physical examination can be broadened at the discretion of the Investigator in order to evaluate AEs or abnormal clinical laboratory test values.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any clinically significant new finding or worsening of a previous finding should be reported as a new AE, per Investigator judgment.

8.2.2 Neurological examinations

- A neurological examination will be performed and the results recorded. A complete examination will include, at a minimum, assessments of mental status, cranial nerves, motor and sensory function, reflexes, coordination, and stance/gait.
- A brief neurological examination will include, at a minimum, assessments of cranial nerves, coordination/cerebellar function, reflexes, motor function, and stance/gait.
- Investigators should pay special attention to clinical signs related to previous neurological illnesses, including MS.

8.2.3 Vital signs

- Oral, tympanic, axillary, or skin temporal temperature, heart rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and heart rate measurements will be assessed with the participant in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded.

8.2.4 Electrocardiograms

- Single 12-lead ECG(s) will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates heart rate and measures PR, QRS, QT, and QTc intervals.
- In case the ECG machine does not automatically calculate QTcF, manual calculation using the following formula (QTcF = QT/RR1/3) or an automatic website calculator (eg, https://reference.medscape.com/calculator/48/ecg-corrected-qt) is acceptable.
- ECGs and (longer) rhythm strips will be obtained locally.
- If a clinically significant finding is identified in the ECG (including, but not limited to changes from baseline in QTcF after enrollment), the Investigator or delegate will determine if the participant can continue in the study and if any change in participant management is needed including but not limited to referral to cardiology and/or a Holter monitor. The Investigator or delegate should perform the following tasks:
  - Review the ECG in a timely manner.
  - Document the interpretation and sign and date it on the ECG printout.
  - Record your (or appropriate qualified physician) medical opinion ("normal" or "abnormal") on the study participant's records and in the eCRF.
  - Assess for any symptoms of cardiac issues.
  - Perform an additional ECG when it is medically needed for clinical management of the study participant and/or in case of any safety concerns and report the findings in the eCRF dedicated to additional ECG forms.
  - Check clinically significant findings with pre-existing medical history or/and, if appropriate, consider an AE.

8.2.5 Clinical safety laboratory tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for their timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the participant's condition.
- All abnormal laboratory values considered by the Investigators to be clinically significantly abnormal during participation in the study or within 2 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.2.6 Pregnancy testing

For female participants of childbearing potential, a pregnancy test will be performed at each visit during the whole study period. A serum pregnancy test will be conducted at the Screening Visit, and a urine pregnancy test will be performed for all other visits. For WOCBP, monthly urine pregnancy tests will be provided directly to participants for those not coinciding with a clinic visit. Results should not be older than 24 hours upon intake of first dose of IMP.

8.2.7 Suicidal ideation and behavior risk monitoring

SAR443820 crosses the blood-brain barrier. Assessment of suicidal ideation and behavior/treatment-emergent suicidal ideation and behavior will be monitored during ACT16753 using the C-SSRS. For safety reasons, the C-SSRS will be administered throughout the study by the Investigator or delegated to an individual who is certified to administer the scale.

Study intervention administration must be interrupted if a participant scores “yes” on item 4 or 5 of the Suicidal Ideation Section of the C-SSRS or “yes” on any item of the Suicidal Behavior Section. A mental health professional will be consulted and will decide whether the study intervention can be restarted and if any additional risk mitigation strategies are required (eg, increased monitoring, antidepressant administration).

Participants being treated with the study intervention should be monitored appropriately and observed closely for suicidal ideation and behavior (SIB) or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of SIB, should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.9.

The definitions of unsolicited and solicited AEs can be found in Appendix 3 (Section 10.3).

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant’s legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant’s legally authorized representative) that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or caused the participant to discontinue the study intervention (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the ICF until the follow-up visit at the timepoints specified in the SoA (Section 1.3).

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the prespecified study end-date, all SAEs and AESI (as defined in Section 8.3.9), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in the IB.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR, or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the time period for post-intervention contraception determined in Section 5.1.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy of a female participant or female partner of male participant after obtaining the necessary signed informed consent from the female partner.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant or female partner of male participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant or female partner of a male participant and the neonate, and the information will be forwarded to the Sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.6 Cardiovascular and death events

Since the risk of cardiovascular events is low based on preclinical and Phase 1 study results, cardiovascular events are not AESIs and will be reported per standard safety reporting and safety oversight practices (including a data review by the DMC).

Death events will be reported per standard SAE reporting rules. Every effort will be made to clarify the cause of death and to report the diagnosis of a fatal event as an SAE.

8.3.7 Multiple sclerosis relapse reporting

Multiple sclerosis relapses will be exempt from being reported as AEs except when they meet the definition of a SAE or are unusually severe or medically unexpected. Hospitalization for MS relapse, if done routinely at the site (eg, for high dose IV methylprednisolone administration), will not be considered as a seriousness criterion for this study.

Data for MS relapses will be collected on the eCRF and be analyzed as part of the efficacy analysis. Other worsening of neurological symptoms that do not meet the definition of MS relapse will be reported as AEs according to general safety reporting rules.

8.3.8 Magnetic resonance imaging

Magnetic resonance imaging scans need to be reviewed locally for any pathology. In case of clinically significant findings, relevant information needs to be provided to the Investigator for

appropriate safety reporting. When available, a diagnosis of the pathology at cause of such MRI findings or the findings themselves will be reported as an AE until the diagnosis is clear.

Multiple sclerosis findings from MRI scans do not need to be reported unless they are deemed unusual and thus a distinct safety finding.

8.3.9 Adverse events of special interest

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. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified, or removed during a study by protocol amendment.

For AESI, the Sponsor is to be informed immediately (ie, within 24 hours), as per the SAE notification guidelines described in Appendix 3 (Section 10.3), even if a seriousness criterion is not met, using the corresponding pages of the CRF or screens in the eCRF:

- 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;
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 4 [Section 10.4]).
- Symptomatic overdose (serious or nonserious) with IMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least at least [redacted] mg IMP within 20 hours.

    Note: an asymptomatic overdose has to be reported as a standard AE.
- Other project specific AESI(s)
  - Convulsions, seizures
  - Serious infections
  - Increase in ALT: see the "increase in ALT algorithm" in Appendix 6 (Section 10.6).

8.3.10 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 PHARMACOKINETICS

Whole blood samples will be collected for measurement of plasma concentrations of SAR443820 as specified in the SoA (Section 1.3), which is summarized in Table 5.

Table 5 - Schedule of PK sampling

	Part A				
	Day 1*	**Week 2**	**Week 6**	**Week 12**	**Week 36**
Before dose (within 1 hour predose)		X	X	X	X
After dose (15 minutes to 1 hour)	X				
After dose (1 hour to 3 hours)	X				
After dose (30 minutes to 3 hours)		X			

PK = Pharmacokinetics
* At least 45 minutes between the 2 PK samples at Day 1

Instructions for the collection and handling of biological samples will be provided by the Sponsor or Sponsor's designee in a separate document. The actual date and time of each sample will be recorded. Pharmacokinetic samples will be tested by the Sponsor or Sponsor's designee.

Samples collected for analyses of SAR443820 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Pharmacokinetic samples could be used for testing analytical method performance such as comparability and incurred sample reproducibility and for possible exploratory analysis of drug metabolites. The exploratory data will not be included in the study report but will be kept on file.

Population PK approaches will be used for SAR443820.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.5 GENETICS

Genetics is not evaluated in this study.

8.6 BIOMARKERS

Blood samples will be collected to evaluate peripheral markers of neuroinflammation and neurodegeneration in study subjects to evaluate the impact of treatment on these markers. Biomarkers will include sNfL, CHI3L1 (YKL40), sGFAP (excluding China), and specific serum cytokines and chemokines (IL1β, IL6, IL8, TNFα, CCL3 [MIP1a], and CCL4 [MIP1b]) known to be elevated in MS and could be modulated by RIPK1 inhibition. Samples will be collected according to the schedule described in the SoA (Section 1.3) and as detailed in the laboratory manual that is provided separately to sites.

For China, please see Section 10.8.1 for details.

8.7 IMMUNOGENICITY ASSESSMENTS

Not applicable.

8.8 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health economics OR medical resource utilization and health economics parameters are not evaluated in this study.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, mechanism of action, or possible toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF). For participants who consent to the storage and use of their data and remaining (leftover) and/or extra (additional) clinical samples, data and samples may be used for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

Remaining leftover samples will be used only after the study ends, ie, end of study as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at Randomization Visit) as defined in the study protocol.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects. Data and samples will be used in alignment with the information provided to participants in the ICF Part 2 (future research). For future research projects, all biological samples and relating data to be used will be coded such that no participant direct identifiers will be linked to them. These coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Relating data and biological samples for future research will be stored for up to 25 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed, and related coded data will be anonymized unless otherwise required by applicable laws.

Participant's coded datasets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

9 STATISTICAL CONSIDERATIONS

9.1 POPULATIONS FOR ANALYSES

The following populations for analyses are defined:

Table 6 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Randomized	All participants from screened population who have been allocated to a randomized intervention by IRT regardless of whether the intervention was received.
Exposed	All screened participants who take at least 1 dose of study intervention.
Intent-to-treat (ITT)	All randomized participants. Participants will be analyzed according to the intervention allocated by randomization.
Modified ITT (mITT)	All participants from the ITT population who takes at least 1 dose of study intervention and with an evaluable primary endpoint. The primary endpoint is evaluable when the following conditions are met: • The participant has a baseline and at least 1 post-baseline sNfL assessment before IMP discontinuation and before permanent modification of the background DMT. • Participants will be analyzed according to the intervention allocated by randomization.
Safety	All randomized participants who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic (PK)	All randomized and treated participants (safety population) with at least 1 post-baseline PK result with adequate documentation of dosing and sampling dates and times. Participants will be analyzed according to the intervention they actually received.
Open-Label Extension (OLE)	All participants who received at least 1 dose of intervention during the open-label extension phase.

Abbreviations: DMT = disease modifying therapy; ICF = informed consent form; IRT = interactive response technology; ITT = intent-to-treat; mITT = modified intent-to-treat; OLE = open-label extension; PK = pharmacokinetics; sNfL = serum neurofilament light chain

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

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 reported separately.

9.2 STATISTICAL ANALYSES

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and main secondary endpoints in Part A and primary endpoint in Part B.

9.2.1 General considerations

The baseline value is defined as the last available value before the first dose of double-blind IMP, except otherwise specified. For participants randomized but not treated, the baseline value is defined as the last available value before randomization/enrollment.

Unless otherwise specified, analyses will be performed by initial intervention group, ie, placebo or SAR443820 20 mg QD (and overall, for baseline and demographics characteristics).

The observation period will be divided into 4 segments:

- The **pre-treatment** period is defined as the period up to first IMP administration.
- The **treatment-emergent (TE) period** is defined as the period from the first IMP administration to the last IMP administration + 14 days. The TE period includes the following 2 periods:
  - The **on-treatment period** is defined as the period from the first IMP administration to the last administration of the IMP + 1 day.
  - The **residual treatment period** is defined as the period from the end of the on-treatment period to the end of the TE period.
- The **post-treatment period** is defined as the period from the end of the TE period.

9.2.2 Primary endpoint(s) analyses

9.2.2.1 Part A

The primary endpoint will be analyzed with the primary estimand defined according to the following attributes:

- Endpoint: sNfL levels at Week 48 relative to baseline
- Treatment condition: SAR443820 will be compared to placebo, on top of background therapy
- Analysis population: mITT population
- Intercurrent events (IE):
  - The IMP discontinuation IE will be handled with the hypothetical strategy. The primary endpoint will be assessed based on assessments performed before IMP discontinuation.
  - The modification in the background DMT (either dosage or medication) IE will be handled with the hypothetical strategy. The primary endpoint will be assessed based on assessments performed before the permanent modification of the background DMT (as distinguished from rescue therapy, which is intermittently limited to 2 to 5 days, after which the original background DMT will be restored at its prerescue dose).
- Population-level summary: geometric means ratio (GMR) between interventions.

The primary analytical approach will use a mixed effect model with repeated measures (MMRM) on natural (base 'e') log-transformed sNfL levels. The model will include the fixed categorical effects of the intervention group (SAR443820 or placebo), baseline MS type (RMS versus PMS), time point (Weeks 12, 24, 36, 48), treatment-by-time point interaction, MS type-by-time point interaction, as well as the continuous fixed covariates of log-transformed baseline sNfL levels and log-transformed baseline-by-time point interaction. An unstructured covariance structure will be used to model the within-subject errors. The Kenward-Roger (31) approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Missing data will be handled by MMRM under the missing at random (MAR) assumption. The geometric mean of sNfL levels at Week 48 relative to baseline in each intervention group, as well as the relative reduction under treatment with SAR443820 compared to placebo will be estimated (estimates and 2-sided 90% confidence intervals [CI], respectively) through exponentiated least squared means and exponentiated least squared means differences.

[redacted]

9.2.2.2 Part B

The primary endpoint of Part B, ie, sNfL levels at Week 96 relative to baseline, will be analyzed using the same statistical methods described for the primary endpoint of Part A (see Section 9.2.2.1) for descriptive purpose only. Efficacy analyses of Part B will present efficacy data by initial intervention group, ie, matching placebo or SAR443820 20 mg.

9.2.3 Secondary endpoint(s) analyses

The secondary endpoints in Part A detailed in this section are as follows:

- The cumulative number of new and/or enlarged T2 lesions as detected by MRI at Week 48, defined as the sum of the individual number of new and/or enlarging T2 lesions at all scheduled visits starting after baseline, up to and including the Week 48 visit will be analyzed through a negative binomial regression model. This model will include the baseline T2 lesion count as a covariate and treatment and baseline MS type (RMS versus PMS) as a factor. The number of scans will be also taken into account as an offset variable after natural logarithm transformation. The mean count/scan of new T2 lesions at Week 48 in each intervention group, as well as the relative reduction under treatment with SAR443820 compared to placebo will be estimated (estimates and 95% CIs, respectively). The cumulative number of new T2 lesions at Week 24 and Week 36 will be analyzed similarly.
- The cumulative number of new Gd-enhancing T1 hyperintense lesions as detected by MRI at Week 48, defined as the sum of the individual number of new Gd-enhancing T1 hyperintense lesions at all scheduled visits starting after baseline, up to and including the Week 48 visit will be analyzed similarly but using the number of Gd-enhancing T1 lesions at baseline as a covariate.

Other secondary endpoints analyses are defined in Section 9.2.6.1 (AE, SAE) and Section 9.2.6.2 (laboratory abnormalities).

9.2.4 Tertiary/exploratory endpoint(s) analyses

Tertiary/exploratory endpoint will be presented as descriptive data. Additional analyses may be done and will be detailed in the SAP.

9.2.5 Multiplicity adjustment

Not applicable.

9.2.6 Safety analyses

The analysis of safety variables will be essentially descriptive. No systematic analysis is planned. The summary of safety results will be presented by initial treatment group separately for Parts A and B.

9.2.6.1 Adverse events

General common rules for adverse events

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened, or became serious during the pre-treatment period
- TEAEs: AEs that developed, worsened, or became serious during the treatment-emergent period
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

Similarly, deaths will be analyzed in the pre-treatment, treatment-emergent, and post-treatment periods.

Analysis of all adverse events

An AE incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment-emergent AESI (defined with a preferred term [PT] or a prespecified grouping), all treatment-emergent SAEs, all TEAEs leading to permanent treatment discontinuation, and all TEAEs leading to death.

The AE summaries will be generated with the number (%) of participants experiencing at least 1 event.

Deaths will also be analyzed.

9.2.6.2 Laboratory variables, vital signs and electrocardiograms (ECGs)

Quantitative analyses

When relevant, for laboratory variables, vital signs and ECG variables, descriptive statistics for results and changes from baseline will be provided for each planned visit, the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using central measurements only (when available) for laboratory variables and ECG variables.

Analyses according to PCSA

- Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period using all measurements (either local or central, either scheduled, nonscheduled or repeated). For laboratory variables, vital signs, and ECG variables, the incidence of participants with at least 1 PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories: Normal/missing.
- Abnormal according to PCSA criterion or criteria

9.2.7 Other analyses

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

Plasma concentration over time will be summarized by time window using the number of available data, mean, geometric mean, standard deviation (SD), median, minimum, and maximum in the SAR443820 dose group.

The population PK analyses will be presented separately from the main clinical study report (CSR).

9.3 INTERIM ANALYSES

An interim analysis (IA) may be performed when 75% of participants have completed the Week 48 visit.

[redacted]

This IA will not have any impact on the conduct of the double-blind study period; therefore, no penalty is needed for the primary analysis.

The statistical analysis plan will describe the planned interim analyses in greater detail.

9.4 SAMPLE SIZE DETERMINATION

Sample size calculations were performed to ensure reasonable accuracy for the estimation of the ratio of the SAR443820 arm sNfL geometric mean relative to the placebo arm sNfL geometric mean. The width (when a GMR of [redacted] is observed, which corresponds to a [redacted]% reduction relative to placebo) of the 2-sided 90% CI, using a coverage correction to ensure coverage probability of 90%, is displayed for various sample sizes in Table 7:

Table 7 - Sample size determination

	Log-transformed data					Corresponding geometric mean ratio (GMR)			
N	**Difference in means**	**Standard deviation (SD)**	**90% confidence interval (CI) half width***	**Lower limit**	**Upper limit**	**GMR**	**Lower limit**	**Upper limit**	**Total width (asymmetric)**
[redacted]									

(*): with a coverage probability (probability that the observed interval will be no longer than the specified width) of 90%.

For an observed 30% reduction relative to placebo, a sample size of 168 participants (to account for an anticipated 17% dropout rate) will provide an upper limit below [redacted] ([redacted]% of reduction) for the 2-sided 90% CI, which is deemed sufficient.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
  - Applicable ICH-GCP guidelines.
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR]).
- The protocol, protocol amendments, ICF, Investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
  - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
  - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
  - The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the

finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.

- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participants and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the GDPR and of the French law, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s). Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc.).
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative, where applicable.

Participants who are rescreened are required to sign a new ICF.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy and Data Protection laws and regulations, including the GDPR. The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because they are expected to modify the drug response/because they are required by regulatory agencies (eg, on the African American population for the US Food and Drug Administration (FDA) or on the Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan). They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com). In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study.
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep

their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.

- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 46 avenue de la Grande Armée, 75017 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

10.1.5.1 Study Steering Committee

A study Steering Committee, composed of 4 experts in the field of MS, will advise the Sponsor on the study design and conduct. In collaboration with the Sponsor, the committee will provide scientific leadership to the study to ensure that the highest standards are maintained. Details describing the committee processes and procedures are outlined in the Steering Committee charter.

10.1.5.2 Independent Data Monitoring Committee (DMC)

A DMC, operating independently of the Sponsor and clinical Investigators, will be responsible for overseeing the safety of participants throughout the study. This committee is composed of externally based individuals with expertise in the disease under study, biostatistics, or clinical research. The primary responsibilities of the DMC are to review and evaluate the safety data during the trial and to make appropriate recommendations to the Sponsor regarding the conduct of the clinical trial.

Details describing the DMC processes and procedures are outlined in the DMC charter. To maintain continuous blinding and study integrity, the analysis will be conducted by an independent statistician who will directly transfer data to DMC members.

10.1.6 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU Clinical Trials Register (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

Professionals involved in the study or in the drug development program

Sanofi undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/ hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration (NMPA) in its guidance "Drug Clinical Trial Registration and Information Disclosure Management Practice (Trial Implementation)", requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "European Federation of Pharmaceutical Industries and Associations (EFPIA) Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organizations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on a printed or an eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio.
  - Discontinuation of further study intervention development.
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 8 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 8 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	RBC indices:
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	%Reticulocytes

Laboratory tests	Parameters
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	
	Blood urea nitrogen (BUN)
	Creatinine
	Glucose[b]
	Potassium
	Sodium
	Calcium
	Albumin
	Creatine phosphokinase
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase[c]
	Total and direct bilirubin
	Total protein
Routine urinalysis	Specific gravity
	pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
	Microscopic examination (if blood or protein is abnormal)
Pregnancy testing	Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[d]
Other screening tests	Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only)
	Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody or specify other tests)
	All study-required laboratory tests will be performed by a central laboratory except local urine pregnancy test and urinalysis (See Appendix 8 [Section 10.8])

Abbreviations: AESI = adverse events of special interest; ULN = upper limit of normal

NOTES:

a Details of the liver chemistry stopping criteria and required actions and follow-up are given in Appendix 6 (Section 10.6) (liver and other safety. Suggested actions and follow-up assessments [and study intervention rechallenge guidelines). All events of ALT >3, which may indicate liver injury, must be reported to the Sponsor in an expedited manner (refer to the section on AESIs [Section 8.3.9]). Clinical laboratory findings of ALT >3 ULN and bilirubin ≥2 × ULN (>35% direct bilirubin), which may suggest severe liver injury (possible Hy's Law), must be reported to the Sponsor in an expedited manner.

b Fasting glucose is preferred. Fasting/nonfasting status will be recorded at the time of blood collection for glucose assessment.

c If alkaline phosphatase is elevated, consider fractionating.

d Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. Also, lack of efficacy or failure of expected pharmacological action also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

A) Results in death

B) Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

C) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

D) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

E) Is a congenital anomaly/birth defect

F) Is a suspected transmission of any infectious agent via an authorized medicinal product

G) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
    - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
  - Development of drug dependence or drug abuse
  - ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN
  - Suicide attempt or any event suggestive of suicidality
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
  - Bullous cutaneous eruptions

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.

- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor's representative. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor's representative.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor's representative with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in Investigator Study File.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Investigator Study File.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A woman is considered a WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they want to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Women in the following categories are considered WONCBP:

1. Any female with permanent infertility due to one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
   - For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.
2. Postmenopausal female

   A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
   - A high follicle stimulating hormone (FSH) level in the postmenopausal range must be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
   - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Permanent sterilization methods include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of the study intervention, additional evaluations should be considered.

10.4.2 Contraception guidance

If locally required, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly effective methods[b] that have low user dependency *Failure rate of <1% per year when used consistently and correctly.*

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS) [c]
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or due to a medical cause)
  Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
  Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly effective methods[b] that are user dependent *Failure rate of <1% per year when used consistently and correctly.*

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - oral
  - injectable

Highly effective methods[b] **that are user dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c Male condoms must be used in addition to hormonal contraception.
Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

Note: Periodic abstinence (calendar, symptothermal, and postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. A male condom and female condom should not be used together (due to risk of failure from friction).

For male study participants whose partner is a WOCBP, they agree to the following during the study period and for at least 92 days following their last dose of IMP:

- Refrain from donating or cryopreserving sperm

  Plus, either:
- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

  OR
- Must agree to use contraception/barrier (male condom) as detailed below:

  A male condom and an additional highly contraceptive method as described above in this section, when having sexual intercourse with a WOCBP who is not currently pregnant

Female participants are eligible to participate if they are not pregnant or breastfeeding and 1 of the following conditions applies:

- Are a woman of nonchildbearing potential (WONCBP) as defined in Section 10.4.1.

  OR
- Are a WOCBP and agree to use a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described above in this section during the study intervention period (to be effective before starting the study intervention) and for at least 32 days after the last administration of the IMP and agree not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.
- WOCBP must have a negative highly sensitive pregnancy test within 24 hours before the first administration of the study intervention, see Section 8.2.6.

If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

COLLECTION OF PREGNANCY INFORMATION:

For male participants with partners who could become pregnant:

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive the IMP.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

For female participants who could become pregnant:

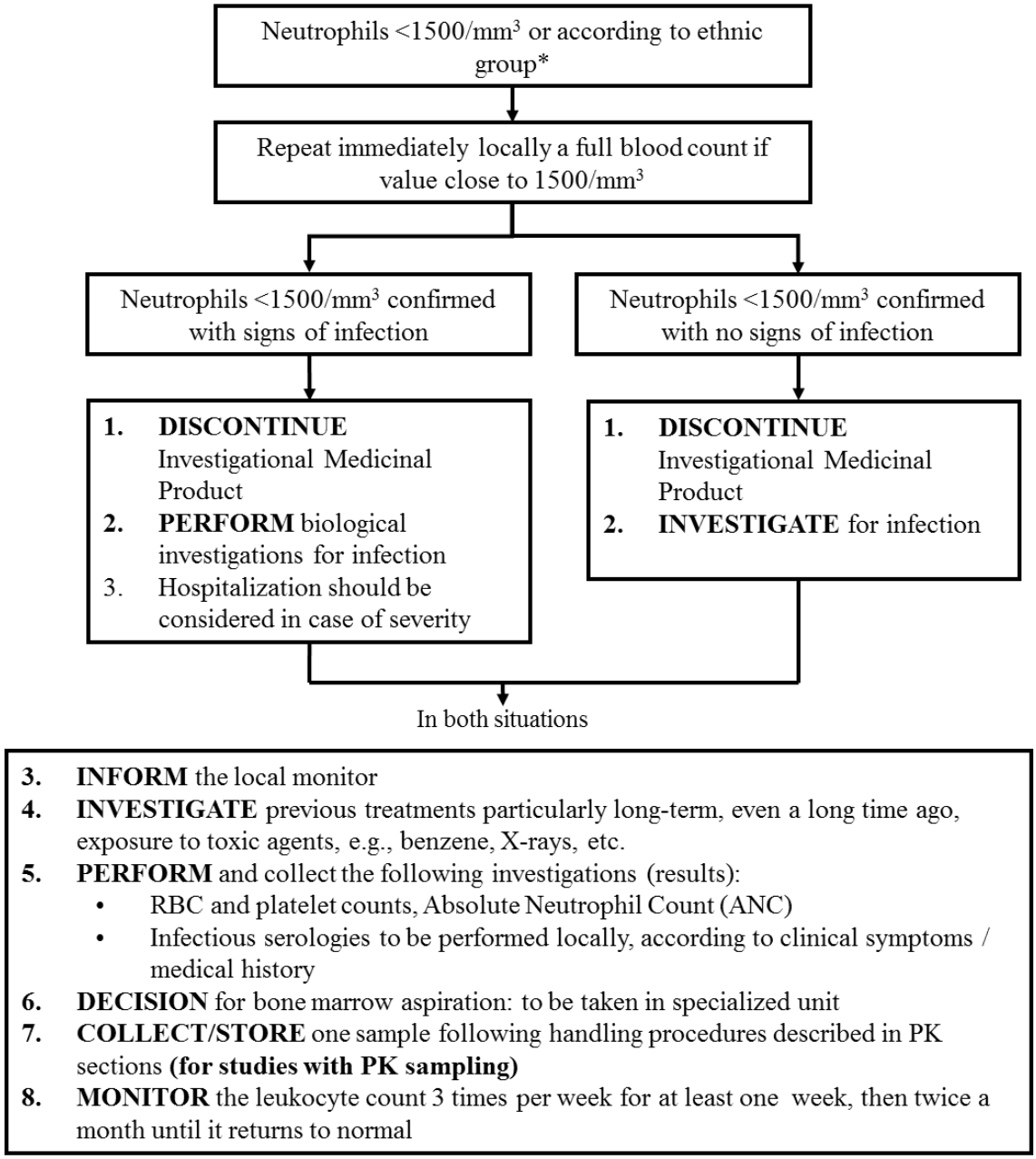
- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue the study intervention or be withdrawn from the study.

10.5 APPENDIX 5: GENETICS

Not applicable.

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: ACTIONS AND FOLLOW-UP ASSESSMENTS AND STUDY INTERVENTION RESTART/RECHALLENGE

NEUTROPENIA

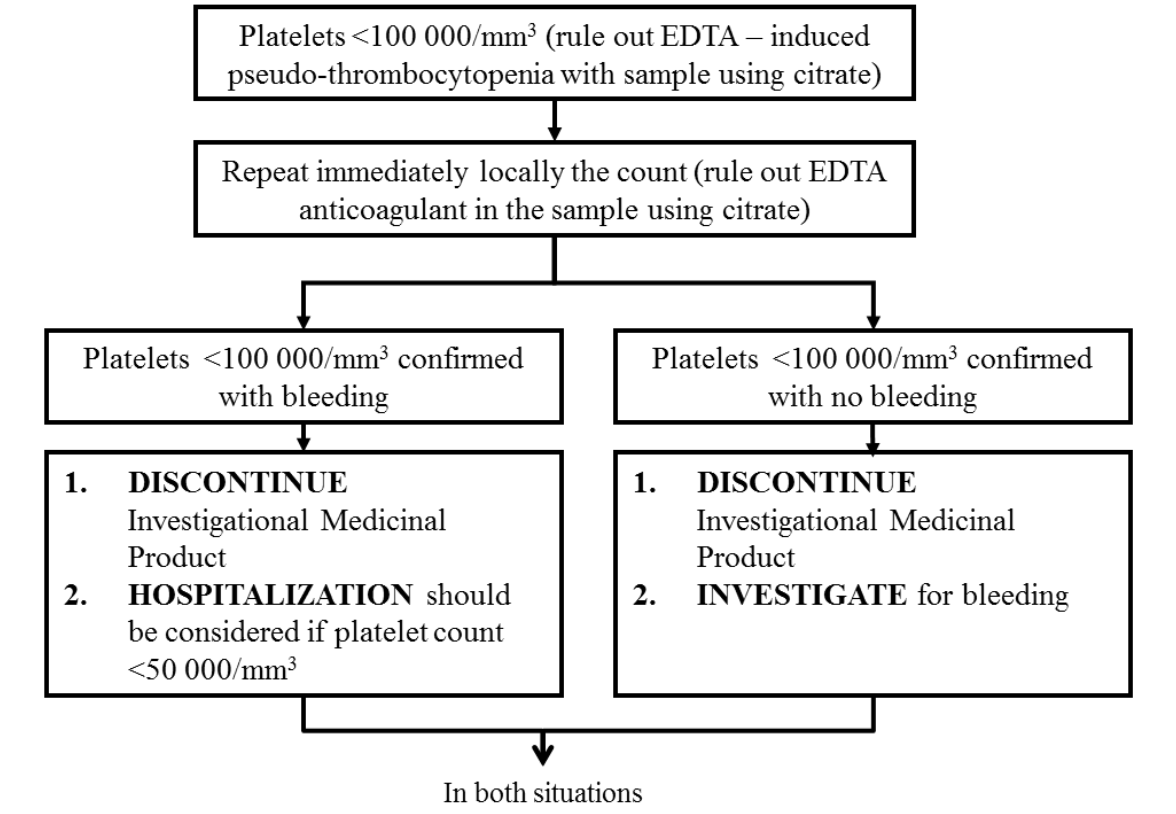


* For individuals of African descent, the relevant value of concern is <1000/mm3

Abbreviations: ANC = absolute neutrophil count; PK = pharmacokinetic; RBC = red blood cells

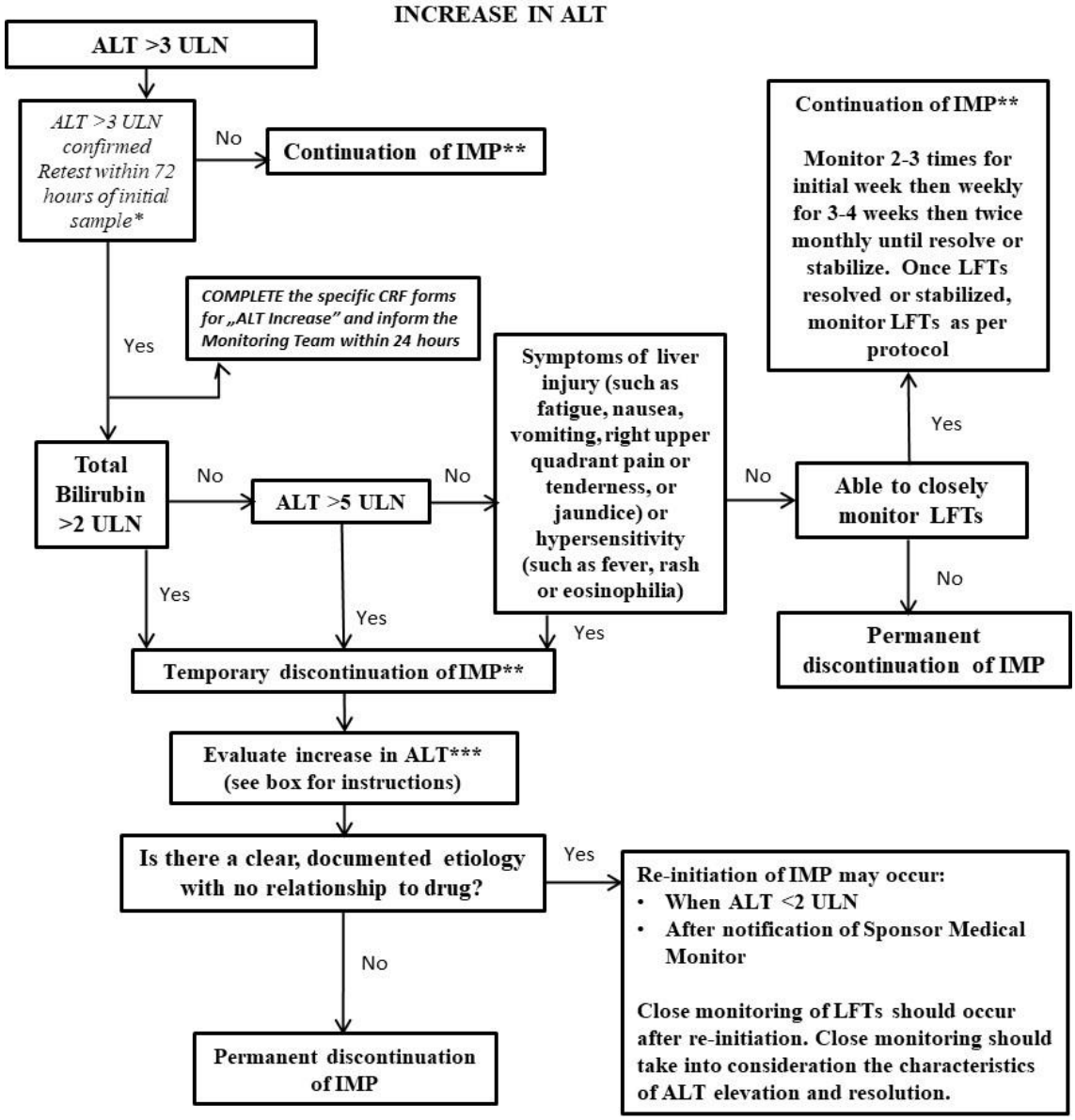
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3 is met.

THROMBOCYTOPENIA



Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3 is met.

These actions are required for ALT increase events ONLY. For all other safety events described, these are suggested per the Investigator's medical judgement.



Abbreviations: ALT = alanine aminotransferase; CRF = case report form; IMP = investigational medicinal product; LFT = liver function test; ULN = upper limit of normal

*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

** Unless a protocol-defined criterion for permanent discontinuation is met.

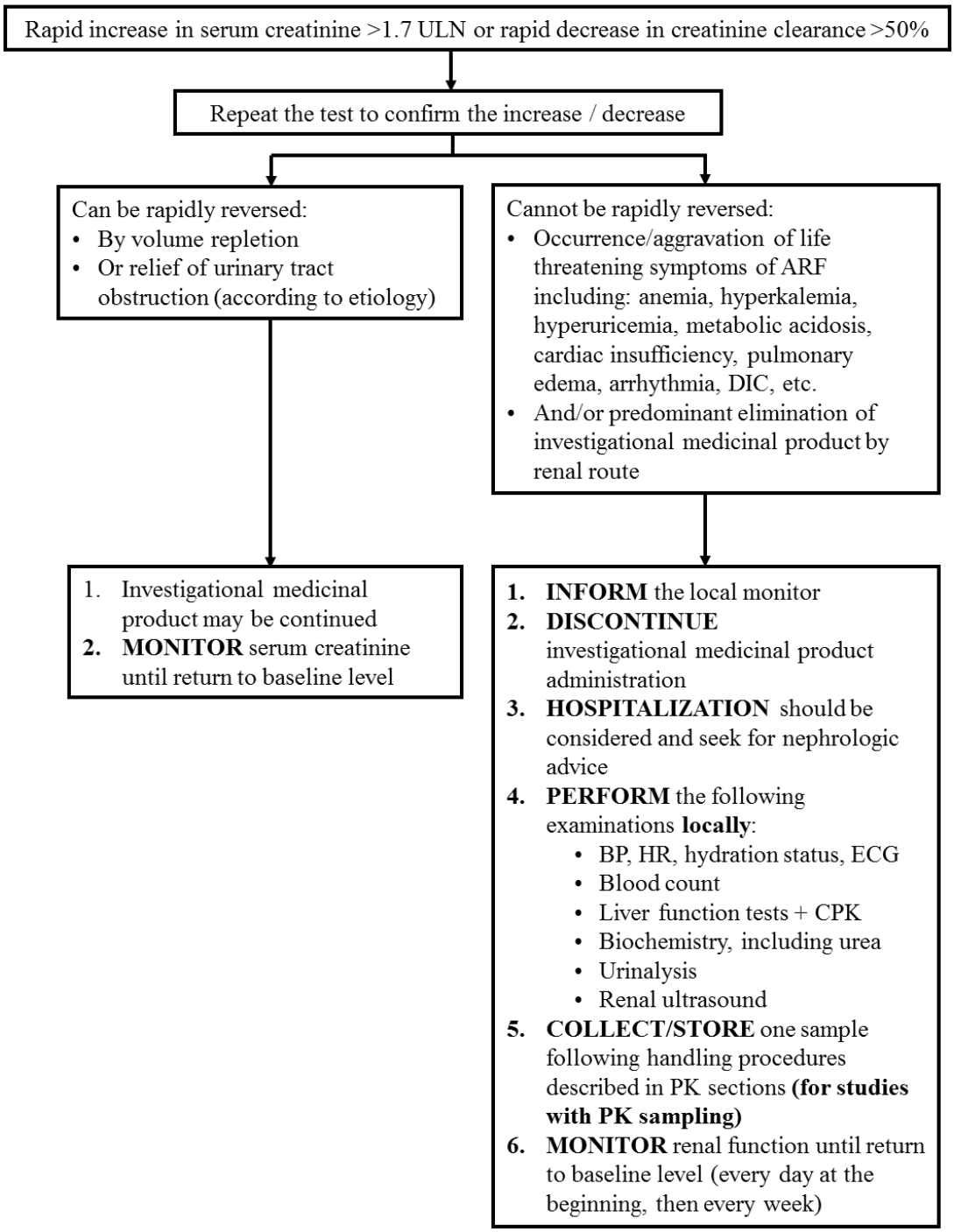
*** See box below

Note:

• "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.

• See Section 10.3 for guidance on safety reporting.

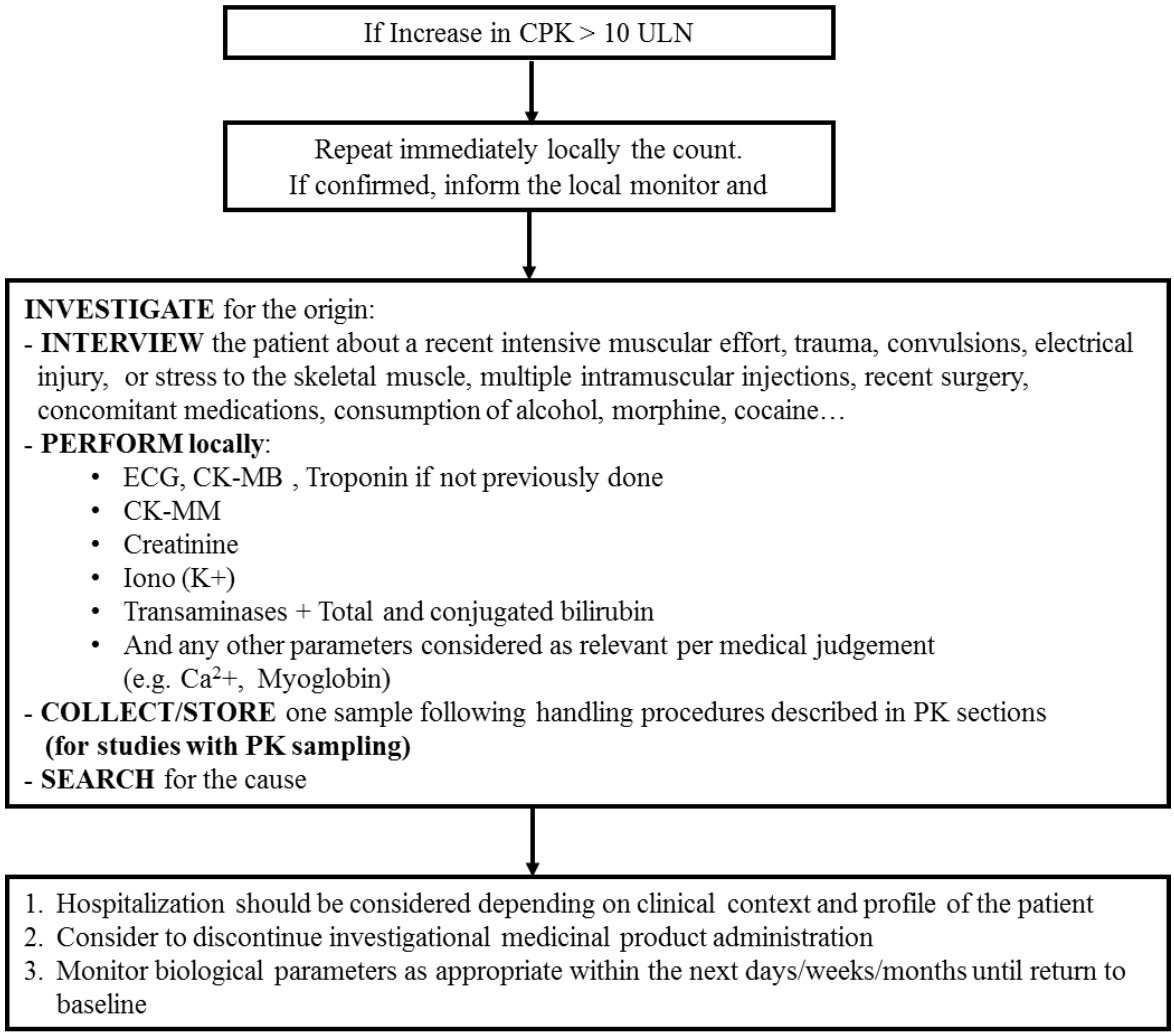
INCREASE IN SERUM CREATININE in patients with normal baseline (creatininemia between 45 µmol/L and 84 µmol/L)



Abbreviations: ARF = acute renal failure; BP = blood pressure; CPK = creatine phosphokinase; DIC = disseminated intravascular coagulation; ECG = electrocardiogram; HR = heart rate; PK = pharmacokinetics; ULN = upper limit of normal

Increase in serum creatinine is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3 is met.

INCREASE IN CPK OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



Abbreviations: CK-MB = creatine kinase myocardial band; CK-MM = creatine kinase muscle; CPK = creatine phosphokinase; ECG = electrocardiogram; ULN = upper limit of normal

Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting adverse events in Section 10.3 is met.

Abbreviations: aPTT = activated partial thromboplastin time; EDTA ethylenediamine tetraacetic acid; INR = international normalized ratio; PK = pharmacokinetics; PT = prothrombin time

10.7 APPENDIX 7: AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC/REGION REQUIREMENTS

10.8.1 China

10.8.1.1 Study objectives and endpoints

All the objectives and endpoints for both study parts in Section 3 will be unchanged for participants in China except for serum glial fibrillary acidic protein (sGFAP) assessment (no sGFAP will be analyzed for the participants from China).

Part A

Objectives	Endpoints
Primary	
• To assess the effect of SAR443820 compared to placebo on sNfL	• Week 48 sNfL levels relative to baseline
Secondary	
• To evaluate efficacy of SAR443820 compared to placebo on imaging and clinical endpoints	• Cumulative number of new gadolinium (Gd)-enhancing T1 hyperintense lesions as detected by MRI at Week 48, defined as the sum of the individual number of new Gd enhancing T1 hyperintense lesions at all scheduled visits starting after baseline up to and including the Week 48 visit • Cumulative number of new and/or enlarging T2 hyperintense lesions as detected by MRI, at Week 48, defined as the sum of the individual number of new and/or enlarging T2 lesions at all scheduled visits starting after baseline up to and including the Week 48 visit • Time to onset of 12 weeks confirmed disability progression (CDP) from baseline as assessed by the Expanded Disability Status Scale (EDSS) score • Time to onset of sustained 20% increase in 9-Hole Peg Test (9-HPT) confirmed over at least 12 weeks • Time to onset of sustained 20% increase in timed 25 foot walk test (T25-FW) confirmed over at least 12 weeks • Change from baseline in EDSS Plus at Week 48 • ARR of RMS population (relapsing SPMS and RRMS) up to Week 48

Objectives	Endpoints
• To explore effect of SAR443820 compared to placebo on brain volume and chronic lesions	• Percent change from baseline in brain volume loss (BVL) as detected by brain MRI at 48 weeks • Change from baseline in the volume, number, and intensity (T1) of slowly expanding lesions (SELs), and normalized T1 intensity in lesions at Weeks 12, 24, 36, and 48 • Change from baseline in the total number and volume of non-enhancing lesions volume at Weeks 12, 24, 36, and 48 • Change from baseline in the number of phase rim lesions (PRL) at Weeks 12, 24, 36, and 48; among participants at sites with 3T capability
• To assess the safety and tolerability of SAR443820	• Incidence of AE, SAE, TEAE, PCSA in laboratory tests
• To assess pharmacokinetic (PK) of SAR443820	• Plasma concentration of SAR443820
Tertiary	
• To assess the effect of SAR443820 compared to placebo on sNfL in subpopulations of multiple sclerosis (MS)	• Change from baseline in sNfL level in MS subpopulations (RRMS, SPMS, PPMS) over 48 weeks
• To assess the effect of SAR443820 compared to placebo on biomarkers of neurodegeneration, inflammation, and disease progression	• Change from baseline compared to Week 48 in: plasma chitinase-3-like protein 1 (CHI3L1), interleukin-1B (IL1B), IL6, IL8, Chemokine (C-C motif) ligands 3 (CCL3), and Chemokine (C-C motif) ligands 4 (CCL4)
• To assess efficacy of SAR443820 compared to placebo on patient-reported outcomes (PROs) assessing the physical and psychological impact of MS from the patient's perspective (MSIS-29v2) and the impact of MS on the individual's walking ability (MSWS-12)	• Change from baseline in MSIS-29v2 physical and psychological domains scoring at Week 12, 24, 36, and 48 • Change from baseline in MSWS-12 at Week 12, 24, 36, and 48

Part B

Objectives	Endpoints
Primary	
• To assess long-term trends in durability of sNfL	• Week 96 sNfL levels relative to baseline
Secondary	
• To explore the effect of SAR443820 on brain volume and chronic lesions	• Percent change from baseline in BVL as detected by brain MRI at Week 96 • Change from baseline in volume, number and intensity (T1) in SEL and normalized T1 intensity in lesions to Week 96 • Change from baseline in the total number and volume of non-enhancing lesions Week 96 • Change from baseline in the number of PRLs (same participants/centers from Part A) at Week 96
• To assess the long-term safety and tolerability of SAR443820	• Incidence of AE, SAE, TEAE, PCSA in laboratory tests, ECG, and vital signs during through Week 96

Objectives	Endpoints
• To evaluate long-term effect of SAR443820 on disease progression and activity assessed by other clinical and imaging measures on physical function and patient-reported outcomes (PROs)	• Cumulative number of new Gd-enhancing lesions as detected by T1-weighted MRI between 48 and 96 weeks; number of new or enlarging T2-hyperintense lesions on MRI at Week 96 relative to Week 48 • Annualized relapse rate (ARR) of RMS population (relapsing SPMS and RRMS) up to Week 96 • Time to onset of composite CDP (CCDP), confirmed over at least 12 weeks (3-month CCDP), by the EDSS Plus composite (EDSS score increase, OR 20% increase in the T25-FW test, OR 20% increase in the 9-HPT) • Time to onset of 12 weeks CDP as assessed by the EDSS score • Time to onset of sustained 20% increase in 9-HPT confirmed over at least 12 weeks • Time to onset of sustained 20% increase T25-FW test confirmed over at least 12 weeks • Change from baseline in EDSS Plus at Week 96 • Change in MSIS-29v2 physical and psychological domains scoring from baseline through Week 96 • Change in MSWS-12 from baseline through Week 96

The content of this section supersedes the content in Section 3 for the study conducted in China.

10.8.1.2 Sample storage and disposition of samples after study completion

Blood samples for storage to support additional tertiary objectives beyond those in the study protocol will not be collected for participants in China.

All samples from participants in China will be disposed of following completion of the CSR.

10.8.2 Germany

Informed consent process: All references to "legally authorized representative" are not applicable in Germany; only participants who can give written consent themselves are included in the study. References to "legally authorized representative" are found in Section 1 and Section 10.1.3.

German participant continuation into Part B will be contingent on local ethics committee acknowledgment of recommendation from global study Data Safety Monitoring Committee and continued approval. The Sponsor will provide these documents in sufficient time to limit any disruption to the participation of German enrollees and their transition into the Part Open label extension phase.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

The following contingencies may be implemented for the duration of the emergency (after Sponsor agreement is obtained).

Study intervention

The following contingencies may be implemented to make clinical supplies available to the participant for the duration of the emergency:

- DTP supply of the IMP from the PI/site/Sponsor where allowed by local regulations and agreed upon by the participant.

If a participant has to stop the IMP due to a regional or national emergency (eg, coronavirus disease-2019 [COVID-19]), reinitiation of the study intervention will be done under close and appropriate clinical/and or laboratory monitoring and following the instructions provided in Section 7.1.3.

Study assessments and procedures

During the emergency, if the site will be unable to adequately follow protocol-mandated procedures, alternative treatment outside the clinical trial should be proposed, and screening/enrollment/administration of the study intervention may be temporarily delayed.

Attempts should be made to perform all assessments in accordance with the approved protocol to the fullest extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

The following procedures are to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, a home health vendor, etc.) may be planned for the collection of possible safety and/or efficacy data, including 1) collection of samples for screening and clinical safety analyses, 2) ECG and vital signs assessments, and 3) AEs.
- If onsite visits are not possible, visit windows may be extended for assessments of safety and/or efficacy data that cannot be obtained remotely.
- Use of local site or laboratory locations may be allowed when central laboratory assessments cannot be performed due to a government declared national emergency.

Statistical analyses

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact of the emergency on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

Informed consent

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local laboratories).

10.10 APPENDIX 10: STRONG AND MODERATE CYP3A4 INHIBITORS AND STRONG CYP3A4 INDUCERS

Table 9 - Strong and moderate CYP3A4 inhibitors and strong CYP3A4 inducers

Reason for exclusion	Compound (INN)	Therapeutic class	Wash out period (day)
Strong CYP3A4 inducer	Apalutamide	Antiandrogens	21
	Avasimibe	Other antilipemics	5
	Phenobarbital	Anticonvulsant	20
	Phenytoin	Anticonvulsant	14
	Rifampin	Antibiotics	14
	Rifapentine	Antibiotics	14
	St John's wort	Herbal medicine	14
	Carbamazepine	Anticonvulsant	14
	Enzalutamide	Antiandrogens	14
	Ivosidenib	Cancer treatment	19
	Lumacaftor	Cystic fibrosis treatment	14
	Mitotane	Other antineoplastics	90
Strong or moderate CYP3A4 inhibitor	ACT-539313	Hypnotic	2
	ACT17882	Renin inhibitor	5
	Amprenavir	Protease inhibitor	3
	Aprepitant	Antiemetics	3
	Atazanavir, atazanavir/ritonavir	Protease inhibitor	2
	Berotralstat	Cardiovascular drug	20
	Boceprevir	Antiviral	1
	Casopitant	Antiemetics	4
	Ceritinib	Kinase inhibitor	10
	Cimetidine	H-2 receptor antagonist	1
	Ciprofloxacin	Antibiotics	1
	Clarithromycin	Antibiotics	1
	Cobicistat	None	1
	Conivaptan	Diuretics	2
	Crizotinib	Kinase inhibitor	9
	Danoprevir/ritonavir	Antiviral	2
	Darunavir, darunavir/ritonavir	Protease inhibitor	4
	Diltiazem	Calcium channel blocker	1
	Dronedarone	Antiarrhythmic	7
	Duvelisib	Kinase Inhibitor	2
	Elvitegravir/ritonavir	AIDS treatment	3

Reason for exclusion	Compound (INN)	Therapeutic class	Wash out period (day)
	Erythromycin	Antibiotic	1
	Faldaprevir	Antiviral	8
	Fedratinib	Kinase inhibitor	24
	FK1706	Central nervous system agent	15
	Fluconazole	Antifungal	7
	Grapefruit juice	N/A	2
	Idelalisib	Kinase inhibitor	2
	Imatinib	Antineoplastic agent	5
	Indinavir, indinavir/ritonavir	Protease inhibitor	2
	Isavuconazole	Antifungal	27
	Istradefylline	Antiparkinsonian	18
	Itraconazole	Antifungal	5
	Josamycin	Antibiotic	1
	Ketoconazole	Antifungal	1
	LCL161	Cancer treatment	2
	Lefamulin	Antibiotic	2
	Letermovir	Antiviral	3
	Lonafarnib	Other	2
	Lopinavir, lopinavir/ritonavir	Protease inhibitor	2
	Mibefradil	Calcium channel blocker	5
	Mifepristone	Antiprogestins	18
	Nefazodone	Antidepressant	1
	Nelfinavir	Protease inhibitor	2
	Netupitant	Antiemetic	20
	Nilotinib	Kinase inhibitor	4
	Posaconazole	Antifungal	7
	Ravuconazole	Antifungal	40
	Ribociclib	Kinase inhibitor	7
	Ritonavir	Protease inhibitor	2
	Saquinavir, saquinavir/ritonavir	Protease inhibitor	3
	Schisandra sphenanthera	Herbal medicine	14
	Telaprevir	Antiviral	3
	Telithromycin	Antibiotic	3
	Tipranavir/ritonavir	Protease inhibitor	2
	Tofisopam	Benzodiazepine	1
	Troleandomycin	Antibiotic	1
	Tucatinib	Kinase Inhibitor	2
	Verapamil	Calcium channel blocker	1
	Voriconazole	Antifungal	1
	Voxelotor	Hemoglobin inhibitor	8
	Voxelotor	Hemoglobin inhibitor	2
	Voxelotor	Hemoglobin inhibitor	5

10.11 APPENDIX 11: ABBREVIATIONS

9-HPT:	9-hole peg test
ADL:	Activities of Daily Living
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
AUC:	area under the curve
AUC0-24h:	area under the plasma concentration-time curve over the last 24-h dosing interval
BID:	twice daily
BMI:	body mass index
CDP:	confirmed disability progression
CI:	confidence interval
C_{max}:	maximum plasma concentration
CNS:	central nervous system
CPK:	creatine phosphokinase
CRF:	case report form
CSF:	cerebrospinal fluid
CSICF:	Core Study Informed Consent Form
CSR:	clinical study report
C-SSRS:	Columbia Suicide Severity Rating Scale
CYP:	cytochrome P450
DMC:	data monitoring committee
DMT:	disease-modifying therapy
DTP:	direct-to-patient
EAE:	experimental autoimmune encephalomyelitis
ECG:	electrocardiogram
eCRF:	electronic case report form
EDSS:	Expanded Disability Status Scale
FIH:	first-in-human
FSH:	follicle stimulating hormone
Gd:	gadolinium
GDPR:	General Data Protection Regulation
GFAP:	glial fibrillary acidic protein
GMR:	geometric means ratio
HBcAb:	hepatitis B core antibody
HBsAg:	hepatitis B surface antigen
HIV:	human immunodeficiency virus
HRT:	hormonal replacement therapy
IA:	interim analysis
IB:	Investigator's Brochure
ICF:	informed consent form

ICH-GCP:	International Council for Harmonization of Good Clinical Practice
IE:	intercurrent event
IEC:	Independent Ethics Committees
IMP:	investigational medicinal product
IRB:	Institutional Review Boards
IRT:	interactive response technology
ITT:	intent-to-treat
IV:	intravenous
MAD:	multiple ascending dose
MAR:	missing at random
MDRD:	Modification of Diet in Renal Disease
mITT:	modified intent-to-treat
MLKL:	mixed lineage kinase domain-like protein
MMRM:	mixed effect model with repeated measures
MRI:	magnetic resonance imaging
MS:	multiple sclerosis
MSIS-29v2:	Multiple Sclerosis Impact Scale-29 items version 2
MSWS-12:	Multiple Sclerosis Walking Scale 12 items
NfL:	neurofilament light chain
NIMP:	noninvestigational medicinal product
NMPA:	National Medical Products Administration
NOAEL:	no-observed-adverse-effect level
PBPK:	physiologically based pharmacokinetic
PCSA:	potentially clinically significant abnormality
PK:	pharmacokinetic
PML:	progressive multifocal leukoencephalopathy
PMS:	progressive multiple sclerosis
PPMS:	primary progressive multiple sclerosis
PRL:	phase rim lesion(s)
PRO:	patient reported outcome
QD:	once daily
RIPK1:	receptor interacting serine/threonine kinase 1
RIPK3:	receptor interacting serine/threonine-protein kinase 3
RNA:	ribonucleic acid
RRMS:	relapsing remitting multiple sclerosis
SAD:	single ascending dose
SAE:	serious adverse event
SAP:	statistical analysis plan
SEL:	slowly expanding lesion(s)
SIB:	suicidal ideation and behavior
sNfL:	serum neurofilament light chain
SoA:	schedule of activities
SOC:	standard of care
SPMS:	secondary progressive multiple sclerosis
SUSAR:	suspected unexpected serious adverse reaction
T25-FW:	timed 25-foot walk test

TE:	treatment-emergent
TEAE:	treatment emergent adverse event
TNFR1:	tumor necrosis factor receptor 1
ULN:	upper limit of normal
WOCBP:	woman of childbearing potential
WONCBP:	woman of nonchildbearing potential

10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

10.12.1 Amended protocol 01 (21 September 2022)

This amended protocol (amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The purpose of this amendment is to include the dose change in the study.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis; Objective and endpoints 3.Objectives, endpoints, and estimands 10.8.1.1 Study Objectives, endpoints	Part A: Secondary objective 2, endpoint 4, wordings updated from: 'Change from baseline in the number of phase rim lesions (PRL) subset of centers with 3T capacity, 25% of participants at Weeks 12, 24, 36, and 48' To 'Change from baseline in the number of phase rim lesions (PRL) at Weeks 12, 24, 36, and 48; among participants at sites with 3T capability" Part B: the following text was deleted from the secondary objective 1, endpoint 4 'with 3T capacity, 25% of participants' 29v2m is replaced with "29v2" and MSWS 12m is replaced with "MSWS 12".	To add consistency in objectives and endpoints. Clarification
	Part A: tertiary objective 2, endpoint 1: updated from 'serum' to 'plasma' for CHI3L1.	Clarification
1.1 Synopsis: Brief summary; Study interventions; 1.1 Schema 2.3.1 Risk assessment, Table 1 2.3.3 Overall benefit/risk conclusion 4.1 Overall design 4.3 Justification for dose 6. Table 4: Study intervention administered 9.2.1 General consideration	To change SAR443820 dose from 20 mg BID to 20 mg QD	The dose of 20 mg QD SAR443820 is selected for this Phase 2 study to strike a balance between the convenience of once-a-day dosing while maintaining robust potential treatment effectiveness in participants with MS. Target engagement close to 90% measured by pS166-RIPK at C_{trough}

Section # and Name	Description of Change	Brief Rationale
1.3 1 Part A, Schedule of Activities	Specified 'Brain' for MRI with and without Gd assessment	To add more clarity.
	Footnotes 'n' and 'o' related to brain MRI assessment was updated. Footnote 'n' updated as 'Baseline scan can be carried out within 5 to 7 day prior to Day 1 randomization but after all other screening assessment have been completed and none excluded the patient.' Footnote 'o' updated as 'to be performed only if the previous MRI was done more than 4 weeks ago.'	
	The following additional visits was added for the assessment of 12-lead ECG: Day 1 (postdose), Week 6, and Week 12	More frequent ECG monitoring required, as this is the first study to use to SAR443820 in participants with MS.
	Footnote 'j' was updated to add following wordings 'should not be older than 24 hours upon first IMP intake on Day 1'	To add more clarity.
1.3 1 Part A, Schedule of Activities 3.1.3 Pharmacodynamic assessments 8.6 Biomarkers 10.8.1. China; study objectives and endpoints	Footnote 't' and other sections were updated to specify that 'serum GFAP will not be collected from participants in China'	To add more clarity
1.3 2 Part B, Schedule of Activities	Footnote 'b' added 'The participants will attend a safety follow-up visit within 2 weeks following discontinuation of IMP, if they no longer wish to remain in the study.'	To add more clarity
2.3.1 Risk assessment	Described overlap benefit risk of concomitant medications.	To Include description to risk table about concomitant medications safety analysis.
	The wordings under mitigation strategy for convulsion/seizures was updated to include '6-month toxicology study in rat' and duration of nonhuman primate toxicology study was updated from 3 to 6-months.	To add more clarity to risk mitigation strategy.
	The following wordings under mitigation strategy for convulsion/seizures was updated from 'Also, weight <45 kg should be avoided to not exceed the cap (as per the Pop PK model).' To 'Excluding participants in whom exposure may be increased (participants weighing <45 kg, or participant with moderate or severe hepatic impairment)'	To limit risk of exposure in participants weighing <45 kg, or participant with moderate or severe hepatic impairment.
2.3.3 Overall benefit/risk conclusion	Added details from 6-month rat studies. Overall benefit/risk conclusion updated.	To add more clarity.
3.1.1 Measurement for efficacy assessment	The following sentence was updated from 'Due to the known fluctuation in EDSS scores, CDP confirmed after 3 or 6 months is used as an endpoint in clinical trials of progressive MS.' To 'Due to the known fluctuation in EDSS scores, CDP confirmed after 12 and 24 weeks is used as an endpoint in clinical trials of progressive MS'	To add consistency
4.1 Overall design	The following sentence was updated and included "up to". 'Participants who discontinue the treatment or choose not to enter Part B will have their early discontinuation or safety follow-up visit, respectively, up to 2 weeks after the last dose of IMP.'	To clarify timing of safety follow up visit (within 2 weeks of discontinuation)

Section # and Name	Description of Change	Brief Rationale
4.3 Justification for dose	Justification of dose was update in line with rat study and non-human primates toxicology study.	To add clarification.
5.1 Inclusion criteria 6.8 Concomitant therapy	Inclusion criterion 'I 04' and concomitant therapy details were updated to include allowed DTMs. 'I 04' was updated from: 'Participants who in the opinion of the Investigator are stable on their DMT (past 3 months) AND do not require a change in MS treatment for the duration of Part A (through Week 48).' To: 'Participants who are either untreated or in the opinion of the Investigator are stable on an allowed DMT (interferons, glatiramer acetate, fumarates, or teriflunomide) for at least the past 3 months, AND not anticipated to require a change in MS treatment for the duration of Part A and Part B (through Week 96; in Part B changes in dose of allowed DMTs or transition to other allowed DMTs is permitted)'	To add clarification for allowed DMT and to add duration of Part B
5.2 Exclusion criteria	New exclusion criterion 'E 01' was added: 'Participants with immunodeficiency syndromes or other autoimmune diseases requiring immunosuppressive therapy.'	Added to limit enrollment of patients with potential higher risk of infections.
	Exclusion criterion 'E 03' was updated to replace "study enrollment" with "screening".	To align with DMT stability and ensure demonstration of relapse-free requirement
	Exclusion criterion 'E 12' was updated.	To add clarification for the prohibited medications/ treatments washout period.
5.2 Exclusion criteria	Added following new exclusion criterion: 'E 24: Participant is under tutorship or curatorship; participant under safeguard of justice or deprived of his/her liberty by a court decision' and 25 added' 'E 25 Participant is unable to provide informed consent'	Added to ensure all enrolled patients are capable of providing informed consent.
6.3 Measures to minimize bias: Randomization and blinding	The following sentence was updated to add "or before if clinically required" 'In addition, in accordance with standard clinical practice, during the blinded intervention period, the Treating Investigator can access MRI reports once a year starting at Month 12, or before if clinically required, through the local radiologist.'	To add more clarity.
6.7 Treatment of overdose	Overdose definition updated to "overdose is defined as at least 40 mg IMP within 24 hours."	To align with once daily dosing
6.8 Concomitant therapy	[redacted]"	To add clarification around strong or moderate inhibitors or strong inducers of CYP3A4.

Section # and Name	Description of Change	Brief Rationale
7.1.1 Permanent discontinuation	Update the following paragraph from: "The study intervention should be continued whenever possible. In rare instances, it may be necessary for a participant to permanently discontinue study intervention." To "Compliance with and continuation of the study intervention is encouraged, while maintaining the safety of study participants and the integrity of the study. In certain instances, it may be medically necessary for a participant to permanently discontinue study intervention."	To add clarification.
	The following sentence was updated to add 'Part B': "Noncompliance with the protocol, dosing regimen and visits including switching DMT or taking a prohibited DMT in Part A"	To add clarification.
7.2 Participant discontinuation/withdrawal from the study	Removed following text "This is expected to be uncommon." From sentence 'A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or compliance reasons.' Added text "For Part A and Part B" to the following sentence: 'For Part A and Part B, if a participant no longer wishes to take the IMP, they will be encouraged to remain in the study or to attend a safety follow-up visit within 2 weeks following discontinuation of IMP.'	To add more clarity.
8.1.3 Magnetic resonance imaging	The following text was added "according to local labeling requirements". The following text was added: "Baseline MRI scans may be conducted as early as 5 to 7 days prior to first dose, but must be completed after all other screening activities have been completed, and none are deemed exclusionary."	To add more clarity
8.2.6 Pregnancy testing	The following text was added "Results should not be older than 24 hours upon intake of first dose of IMP."	To add more clarity
8.3.9 Adverse events of special interest	"[redacted] mg" replaced with "[redacted] mg" and "12 hours" replaced with "24 hours"	To align with overdose definition
8.6 Biomarkers	Added alternative name of CH13L1 as 'YKL40'.	To add more clarity
9.2.1 General consideration	"on-treatment period" was updated to add '+1 day'.	Updated for consistency
9.2.2 2 Part B	Updated primary endpoint analyses of Part B: durability of sNfL.	To add clarity, statistical methods for primary endpoint analyses of Part B updated.
9.2.6.1 Adverse events	The following text was added "all TEAEs leading to death." in sentence "An AE incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment-emergent AESI (defined with a preferred term [PT] or a prespecified grouping), all treatment-emergent SAEs, all TEAEs leading to permanent treatment discontinuation, and all TEAEs leading to death."	Updated to include all TEAEs leading to death
9.4 Sample size determination	Anticipated dropout rate was changed from 20% to 17%.	To align with the sample size of 168 participants
10.2 Appendix 2 clinical laboratory tests	Table 8 was updated to include "except local urine pregnancy test and urinalysis"	To add more clarity

Section # and Name	Description of Change	Brief Rationale
10.4.2 Contraception guidance	Updated contraceptive requirements for male and female participants.	To align appendix contraceptive requirements with Inclusion criterion 'I 06'.
11 References	'Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-52' was replaced with 'Standardised Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale Slightly modified from J.F. Kurtzke, Neurology 1983:33,1444-52©2011 Ludwig Kappos, MD, Neurology, University Hospital Basel, 4031 Basel, Switzerland; Version 04/10.2'	Update
Throughout	Minor editorial, typographical error corrections and document formatting revisions	Minor, therefore have not been summarized.

10.12.2 Amended protocol 02 (19 May 2023)

This amended protocol (amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

The main purpose of the protocol amendment 02 is to add four visits (Week 4, 9 and 16 in Part A and Week 56 in Part B) for liver chemistry monitoring at each visit.

Protocol amendment summary of changes table

Section # and Name	Description of change	Brief rationale
1.2 SCHEMA 1.3.1 Part A 1.3.2 Part B 4.1 OVERALL DESIGN	Added site visits including a liver chemistry test on Week 4, Week 9 and Week 16 in Part A and Week 56 visit in Part B respectively. Added instructions on sample collecting, testing and results reporting at Week 4, 9, 16 and Week 56 visit. Updated the study schema to add Week 4, 9 and 16 visit and Week 56 visit. Week 60 visit in Part B changed from phone visit to on site visit.	Increase liver chemistry monitoring as related to a Suspected Unexpected Serious Adverse Reaction (SUSAR) case of ALT and bilirubin increase in another Phase 2 study (ACT16970) testing 20 mg BID SAR443820 in patients with amyotrophic lateral sclerosis.
8 STUDY ASSESSMENTS AND PROCEDURES	The following text was added as a bullet: "If onsite visits are not feasible (due to disease progression, increased monitoring for AE follow-up, etc.) for visits that require sample collection only (Week 4, Week 9, Week 16, Week 56 or Week 60 visits), remote visits (eg, with home nurses, a home health vendor, etc.) may be planned for sample collection, only if the service is put in place in the country in which the study is being conducted."	To provide flexibility of assessment when it is not feasible for participants to conduct site visits.

Section # and Name	Description of change	Brief rationale
10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW UP ASSESSMENTS AND STUDY INTERVENTION RECHALLENGE GUIDELINES	Updated the appendix heading from: "Appendix 6: Liver and other Safety: Suggested Actions and Follow Up Assessments and Study Intervention Rechallenge Guidelines" To: "Appendix 6: Liver and other Safety: Actions and Follow Up Assessments and Study Intervention Restart/Rechallenge"	To clarify that it is required to follow the procedure described in this appendix.
	The following text added: "These actions are required for ALT increase events ONLY. For all other safety events described, these are suggested per the Investigator's medical judgement." Updated the algorithm graphical chart with increased frequency of ALT monitoring after ALT increase and updated the guidance text.	To ensure all listed tests for etiology analysis of ALT increase will be conducted and to increase the frequency of liver function monitoring after ALT increase.
10.8 APPENDIX 8: COUNTRY-SPECIFIC/REGION REQUIREMENTS	Section title changed from: "APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS" to: "APPENDIX 8: COUNTRY-SPECIFIC/REGION REQUIREMENTS"	To be compliant with Sanofi standards.
10.8.2 Germany	A new section added to define informed consent procedures for Germany.	To be compliant with Sanofi standards.
10.8.2 Germany	The following text added: "Informed consent process: All references to "legally authorized representative" are not applicable in Germany; only participants who can give written consent themselves are included in the study. References to "legally authorized representative" are found in Section 8.3 and Section 10.1.3. German participant continuation into Part B will be contingent on local ethics committee acknowledgment of recommendation from global study Data Safety Monitoring Committee and continued approval. The Sponsor will provide these documents in sufficient time to limit any disruption to the participation of German enrollees and their transition into the Part Open label extension phase."	Added as requested by German ethic committee.
10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY	Summary of changes table for amendment 01 is moved to appendix 12.	To describe the protocol amendment history.
Throughout	Minor editorial, typographical error corrections and document formatting revisions	Minor, therefore have not been summarized.

10.12.3 Amended protocol 03 (06 July 2023)

This amended protocol (amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

The main purpose of the protocol amendment 03 is to clarify exclusion of participants with a history of alcohol abuse and to limit consumption of alcohol during the course of the study.

Protocol amendment summary of changes table

Section # and Name	Description of change	Brief rationale
5.2 Exclusion criteria	Specifying exclusion of participants with history of alcohol abuse	Minimize the risk of liver injury caused by history of alcohol dependence/abuse
5.3.2 Lifestyle considerations, caffeine, alcohol and tobacco	Limit for daily consumption of alcohol while in the study	Minimize exposure to alcohol during the study, to not exacerbate potential liver injury risks of SAR443820
10.12 Appendix 12: Protocol amendment history	Updated to reflect current amended protocol.	Update.
Throughout	Minor editorial, typographical error corrections and document formatting revisions. Updates according to Sponsor's style guide.	Minor, therefore have not been summarized.

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